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Homogeneous Gold Catalysis: Ligand Design and Reactions of Alkynes

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Chemistry

by

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June 2014

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BOOK CHAPTERS

1. Wang, Y.; Zhang, L. "Gold-Catalyzed Cascade Reactions" in *Catalytic Cascade Reaction*s, Wiley-VCH, ISBN: 978-1-118-01602-2

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1. Wang, Y.; Zhang, L. "The use of Br/Cl to promote regioselective gold-catalyzed rearrangement of propargylic carboxylates: an efficient synthesis of (1*Z*, 3*E*)-1-bromo/chloro-2-carboxy-1,3-dienes" *Poster at the 239th ACS National Regional Meeting, San Francisco, CA, Mar. 2010*
2. Wang, Y.; Zhang, L.; Wu, G.; Cao, Z. "Designed Ligand-Directed *anti*-Attack of Gold Alkyne complex: A New Paradigm for Efficient Gold Catalysis" *Poster at the 17th IUPAC International Symposium on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS 17), Fort Collins, CO, Aug. 2013*

ABSTRACT

Homogeneous Gold Catalysis:

Ligand Design and Reactions of Alkynes

by

Yanzhao Wang

In the past two decades, great progress has been made in developing efficient homogeneous gold catalysis. As soft "π" Lewis acids, cationic gold(I) complexes are particularly powerful in terms of activating alkyne/allene/alkenes towards nucleophilic attack, leading to a variety of synthetically versatile. In my dissertation study, several novel synthetic methodologies have been developed, including: (1) Au-catalyzed ligand-directed a*nti* nucleophilic attack of alkynes; the new ligands I developed enable highly efficient gold-catalyzed nucleophilic additions of acids, anilines and water to the alkynes; and catalyst loadings could be lowered to ***10 parts per million***; (2) rapid access of chroman-3-ones via gold-catalyzed oxidation of propargyl aryl ethers; this atom-economic and step-efficient transformation was enabled by a bulky gold catalyst, Me_4tBuXPhosAuNTf_2 and bulky electron-deficient pyridine *N*-oxides derived from Hantzsch esters; (3) Au-catalyzed novel indole synthesis via a key [3,3] sigmatropic rearrangement; 2-alkylindoles were produced

with high regioselectivity and efficiency from easily accessed *N*-arylhydroxylamines under mild conditions; an improved approach involved cooperative dual catalysis of Zn and Au was developed; much broader substrate scope, shorter reaction time and good to excellent yields were achieved with good control of regioselectivity.

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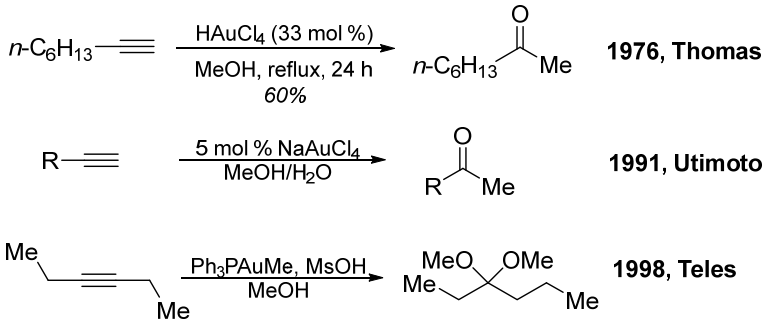
1. Homogeneous Gold Catalysis *via* Carbophilic Activation

1.1. Introduction

One of the exciting thrusts in organic synthesis in the past two decades is homogeneous gold catalysis.[1-7] As early as in 1976, Thomas et al.[8] reported the first homogeneous gold-catalyzed reaction: hydration of alkynes promoted by chloroauric acid; fifteen years later, a similar transformation catalyzed by $NaAuCl_4$ was reported by Utimoto et al.;[9] surprisingly, not much attention was attracted to this area until 1998, when Teles' group described an analogous reaction catalyzed by a cationic Au(I) species instead of Au(III), providing ketones, enol ethers and ketals for different substrates (Scheme 1).[10] Demonstrating a mild and efficient method to build up C–O bond, this article marked the beginning of a rising tide of homogeneous gold catalysis.

Scheme 1. Gold-Catalyzed Hydration and Alcohol Addition to Alkynes



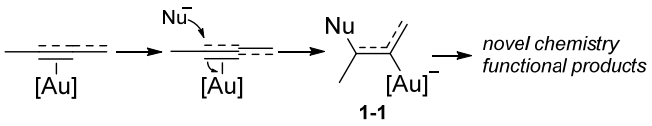
Some of the key advantages to employing gold as a catalyst rapidly became clear. First, as a soft Lewis acid, gold presents extremely great reactivity in terms of activating π bonds, including alkynes, allenes and alkenes. Second, due to it oxidative

stability, gold-catalyzed reactions are typically performed under ambient conditions, without precautions against oxygen or moisture. Third, as an environmentally benign alternative to conventional stoichiometric π-acids, such as Hg.[11,12] gold is often tolerant to many functional groups and protecting groups that would otherwise be detrimental.

1.2. Modes of Reactivity in Homogeneous Gold Catalysis

The cationic Au-complexes are susceptible to a wide spectrum of nucleophilic attacks as the initial step (Scheme 2) and it is well established that in this step, the nucleophile and gold add to the alkynes/allenes in a *trans* manner. The subsequent versatile transformations such as isomerization, rearrangement, and cross-coupling allow rapid access to various synthetically useful molecules and building blocks.

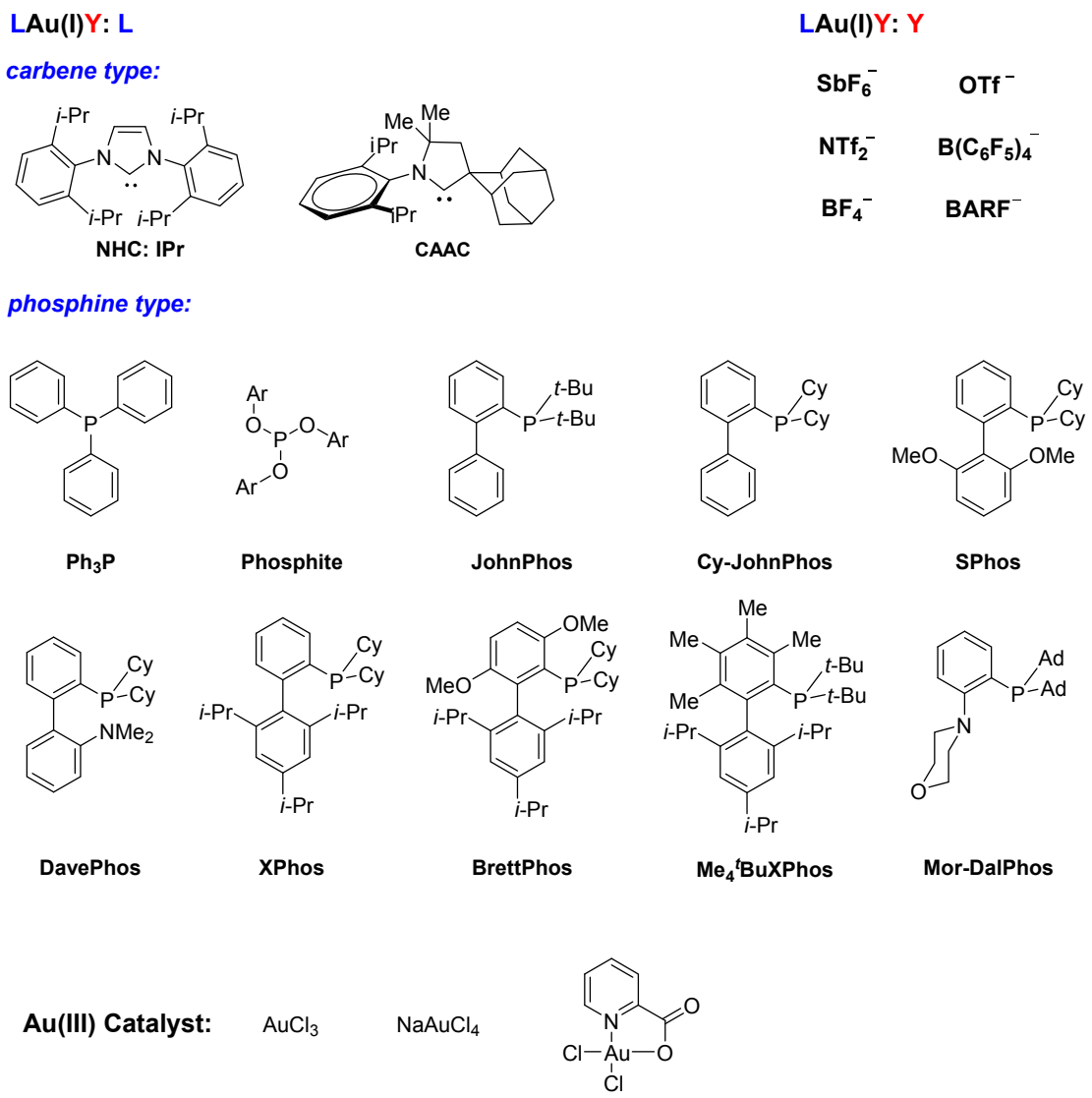
Scheme 2. Initial Nucleophilic *anti*-Attack



In gold-catalyzed reactions, ligands play a crucial role in terms of stabilizing the cationic gold center. They can significantly modulate the catalytic reactivity of the metal center. The high efficiency, excellent chemo-, regio- and stereoselectivity demonstrated in reactions largely relies upon choosing the appropriate ligands. A

recent review summarized the ligand effects in homogeneous gold catalysis.[13] Currently, the popular Au(I) and Au(III) catalysts employed in laboratories worldwide are illustrated in Figure 1.

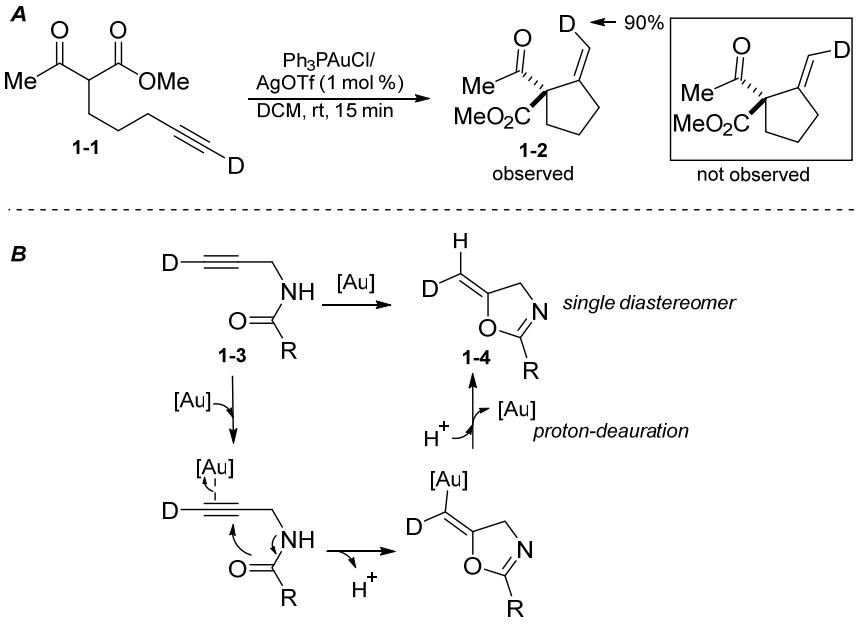
Figure 1. Common Gold Catalysts



In early 2004, Toste et al.[14] reported a gold(I)-catalyzed Conia-ene reaction of α-ketoesters with tethered alkynes to give β-vinylated ketones in good to excellent yields. No reaction occurs with diester substrates and poor reactivity is observed with

internal alkynes. The authors proposed a mechanism involving the attack of 1,3-dicarbonyl nucleophiles on a Au(I) activated alkyne, which is supported by deuterium labeling experiments. At the same time, the trans-manner of addition to alkynes was also demonstrated (Scheme 3-A). Using the terminally deuterated α-ketoester **1-1**, the authors observed only one isomer **1-2**, indicating that the nucleophile attacks the gold-alkyne complex in a trans-manner.

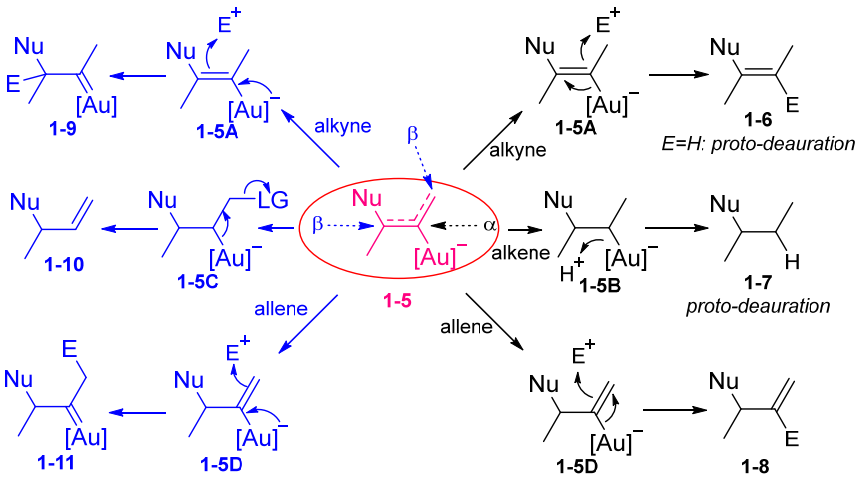
Scheme 3. Evidence of Nucleophilic anti-attack to Gold-activated Alkynes



Eight months later, Hashmi et al.[15] accomplished a Au(III)-catalyzed synthesis of 2,5-disubstituted oxazoles synthesized from the corresponding propargyl carboxamides. In this work, the *anti*-addition was also supported. Only one single diastereomer **1-4** was observed during the conversion of deuterated amide **1-3**, which means the activation of the alkyne and the subsequent addition of the oxygen nucleophile is strictly stereospecific (Scheme 3-B). This suggests that the

carbonyl-oxygen stereoselectively attacks the Au-coordinated alkyne from the backside and the intermediate, aurated enolether species, is then stereospecifically proto-demetalated to yield oxazole **1-4**.

Figure 2. General Reaction Patterns of Gold Catalysis



After the initial *anti*-attack, the intermediate **1-5** is ready to further go through α or β proto-deauration/functionalization to deliver different products. In terms of the reaction happening at α position, when the substrate is alkyne or allene, as the Au-C(sp2) bond in intermediate **1-5A** or **1-5D** is labile and possesses weak nucleophilicity, alkenyl gold can be protonated or react with an electrophile (E^+) in a manner similar to vinylsilane, thus leading to bifunctionalized alkenes **1-6** or **1-8** under mild reaction conditions; when the substrate is alkene, normally the Au-C(sp3) bond (**1-5B**) goes through proto-deauration and affords the adduct **1-7**. In terms of the β approach, for the substrate of alkyne and allene, Au of **1-5A** or **1-5D** donates electrons back from its filled d-orbital, forming a reactive carbenoid

1-9 or **1-11** respectively with the electrophile picked up at β position; for the allene substrate with a leaving present at β position, **1-5C** would generate functionalized olefin **1-10** as the final product.

The diverse range of transformations that have resulted from the π-acid activation of alkynes, allenes and alkenes discussed in the following sections. Based on the considerations and processes discussed above, subsequent transformations are best considered by grouping them according to the substrate type and nucleophilic component of the reaction.

1.3. Gold-Catalyzed Reactions of Alkynes

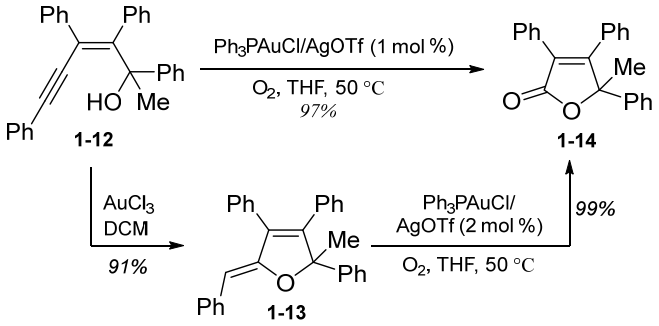
1.3.1. Simple Nucleophilic Addition to Alkynes

The simple nucleophiles could be hydroxyl group, free amino group, carboxylic acid, amide, and carbamate, etc. Valuable functional structures including ketone, acetal, enol ethers or enol esters, imines, enamine and enamide can be accessed.[1,2]

1.3.1.1. C–O Bond Formation

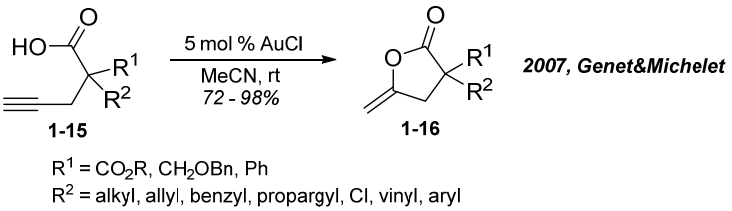
In 2005, Liu et al.[16,17] reported a butenolide synthesis via a gold-catalyzed cascade cyclization/oxidative cleavage reactions of (*Z*)-enynols with molecular oxygen. The dihydrofuran **1-13** was initially formed from direct cyclization of substrate **1-12**, in the presence of molecular oxygen, underwent gold-catalyzed aerobic oxidation to give the corresponding butenolide **1-14** (Scheme 4).

Scheme 4. Synthesis of Butenolides



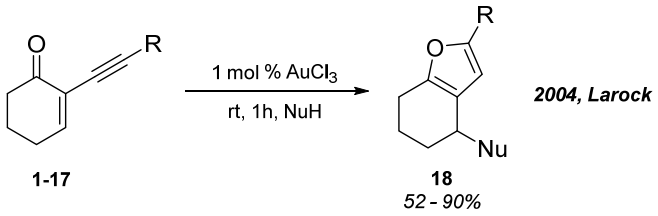
Geneˆt et al.[18] reported the AuCl-catalyzed transformation of substrates **1-15** to afford vinyl lactones **1-16** in good to excellent yields (Scheme 5). Remarkably, $AuCl_3$ is also able to catalyze this intramolecular addition of carboxylic acids to alkynes which leads to lactones.

Scheme 5. Lactones from Intramolecular Acid Addition



Larock et al.[19] used α-alkynyl enones **1-17** as substrates that undergo tandem intramolecular carbonyl addition, followed by intermolecular nucleophilic attack to generate highly substituted furan compounds **1-18**. Notably, a variety of nucleophiles add successfully, including alcohols, anilines, 1,3-diketones, indoles, and even arenes (Scheme 6).

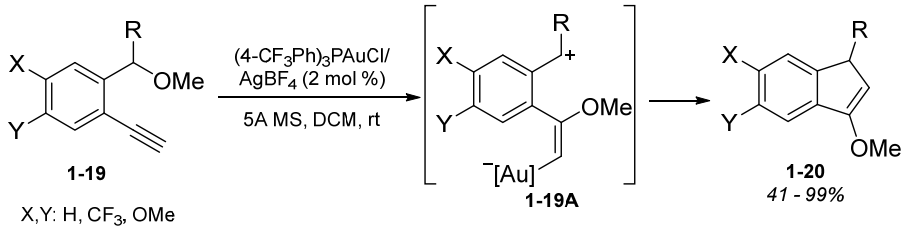
Scheme 6. Synthesis of Highly Substituted Furans from Alkynyl Enones



1-17 **18** *52 - 90%*

A benzylic ether group is also suitable as a nucleophile towards gold-activated alkynes. Toste et al.[20] were able to convert benzyl methyl ethers **1-19** to indenyl methyl ethers **1-20** in moderate to excellent yields (Scheme 7). Crossover experiments with deuterated substrates indicated an alkyne activation to deliver intermediate **1-19A**. Even a chirality transfer was observed, indicating a "memory effect" in the intermediate.

Scheme 7. Synthesis of Indenyl Ethers by Gold(I)-Catalyzed Intramolecular Carboalkoxylation of Alkynes



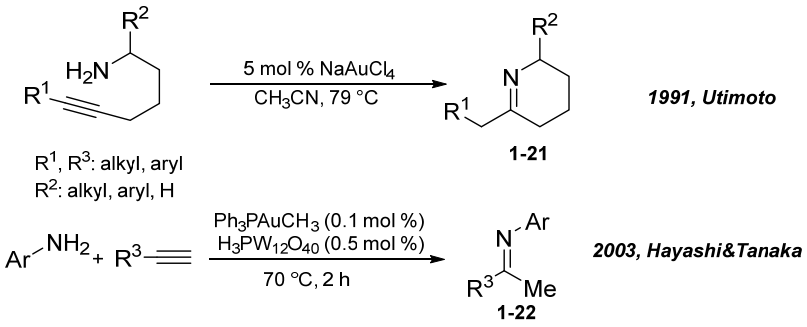
1-19 X,Y: H, CF_3, OMe; R: aryl, vinyl **1-19A** **1-20** *41 - 99%*

1.3.1.2. C–N Bond Formation

Utimoto et al.[21] investigated the intramolecular hydroamination reaction of

alkynes under mild and neutral conditions, where sodium tetrachloroaurate catalysts were superior for the 6-*exo*-*dig* cyclization compared to Pd(II) catalysts. After the initial enamine formation, a subsequent tautomerization led to the thermodynamically more stable imine **1-21** as the final product. The first intermolecular reactions of alkynes and anilines were reported by Tanaka et al.[22] in 2003. The reactions were performed under solvent-free conditions (Scheme 8). With catalyst loadings as little as 0.01 mol % of $(Ph_3P)AuMe$ and 0.05 mol % of $H_3PW_{12}O_{40}$ as acidic promoter, a TON of 9000 could be achieved for 4-bromo and 4-cyanoaniline. Aryl, alkyl, and dialkyl acetylenes reacted, and aliphatic amines could not be used as nucleophilic partners potentially due to their much stronger basicity.

Scheme 8. Au-Catalyzed Hydroamination of Alkynes

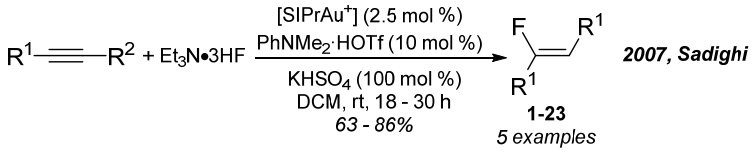


1.3.1.3. C–F Bond Formation

While the first gold-catalyzed hydrochlorination of alkynes was reported as early as 1976, [23] it was not until 2007 that the first hydrofluorination of alkynes was realized through gold catalysis.[24] Sadighi et al. found that (NHC)gold(I) fluoride

reversibly added to internal alkynes, demonstrating the first gold-mediated C–F bond formation. Replacing fluoride ion with the less coordinating BF_4 ion enables catalysis with $Et_3N{\cdot}3HF$ as a source of HF to give good yields of vinyl fluorides **1-17**. Additions across the alkyne are always in an *anti*-fashion, giving a mixture of regioisomers which depends on the electronic nature of R^1/R^2. It should be noted that $KHSO_4$ additive and catalytic amount of $PhNMe_2{\cdot}HOTf$ remarkably increase the reaction yields (Scheme 9).

Scheme 9. Hydrofluorination of Internal Alkynes

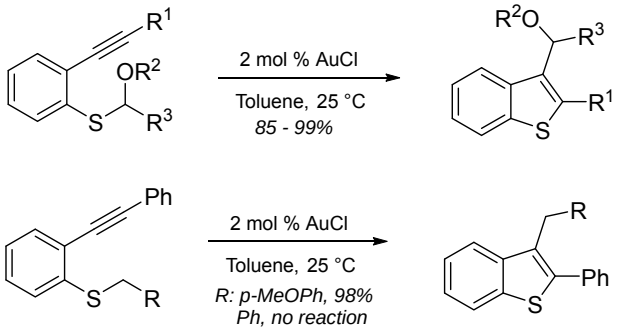


1.3.1.4. C–S Bond Formation

C–S bond formation is one of the fundamental transformations in organic synthesis. Nakumura et al. successfully employed Pd, Pt, and Au salts in the cyclization-isomerization of *o*-alkynylanilines as well as *o*-alkynylphenols, given that a suitable migratory group is available (e.g., allyl, acyl, etc.), but the corresponding cyclizations for *o*-alkynylthiophenols are not feasible for Pd due to catalyst poisoning. However, AuCl and $AuCl_3$ were found out to be ideal for promoting the cyclization,[25] which is the first protocol for directly synthesizing 2,3-disubstituted benzothiophenes. Although the reaction is sensitive to the electronic requirements of the migrating

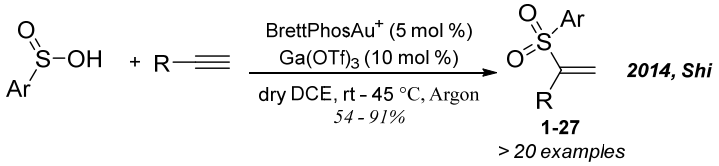
group, it is remarkably tolerant of the sterics of the substrate. The reaction conditions are mild and all yields are good to excellent (Scheme 10).

Scheme 10. Synthesis of 2,3-disubstituted benzothiophenes by Gold Catalysis



Due to its coordinating feature and reducing property, thiol is not a good nucleophilic partner for direct intermolecular addition to alkynes via gold catalysis. Early this year, Shi et al.[26] showed an alternative method to build up C–S bond by the synthesis of vinyl sulfones **1-18** from sulfinic acids and terminal alkynes making use of a combination of a triazole BrettPhosAu(I) complex and gallium triflate (Scheme 11). Moderate to excellent yields were achieved under mild conditions. Alkyl and aryl acetylenes reacted, but internal alkynes were not suitable for this methodology due to their relatively low reactivity compared with terminal alkynes.

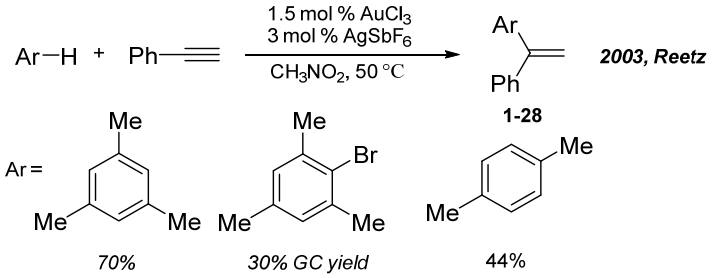
Scheme 11. Gold-Catalyzed Intermolecular C–S Bond Formation



1.3.1.5. C–C Bond Formation

The intermolecular hydroarylation of alkynes was investigated by Reetz and Sommer in 2003.[27] For phenylacetylene, a combination of $AuCl_3$ and $AgSbF_6$ was optimal, leading to 1,1-disubstituted alkenes (Scheme 12); for ethyl propiolate, gold(I) catalysts gave best performance, giving 1,2-disubstituted derivatives.

Scheme 12. Intermolecular Hydroarylation of Alkynes

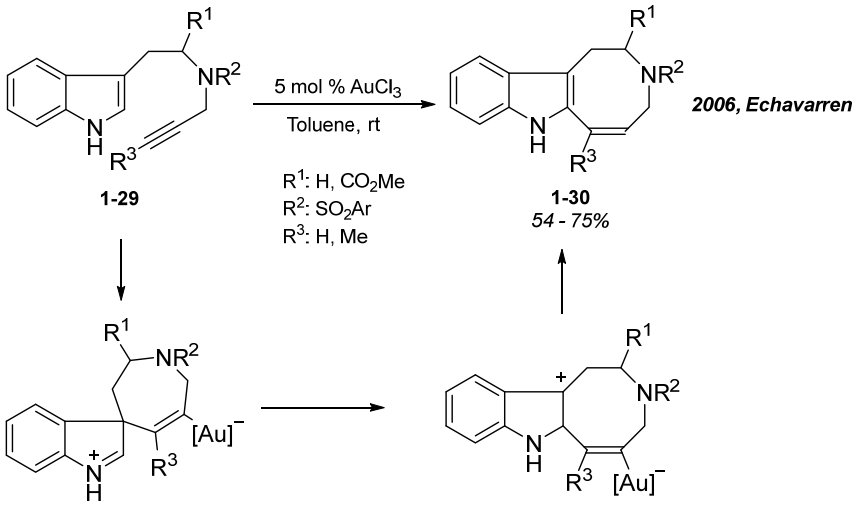


The corresponding intramolecular versions were reported by Echavarren [28] in 2005. One year later, with indoles in **1-29** as the intramolecular nucleophilic partner, Ferrer and Echavarren[29] obtained up to eight-membered ring fused indole derivatives **1-30**. These are formed by a 7-*endo-dig* cyclization followed by a ring expansion (1,2-shift) and not by a direct 8-*endo-dig* cyclization (Scheme 13).

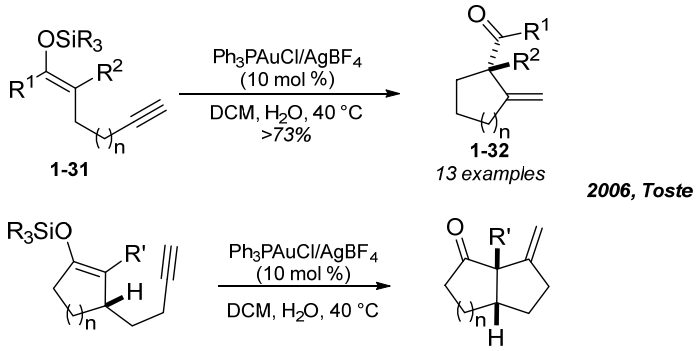
In 2006, Toste et al.[30] were able to utilize silyl enol ethers as the nucleophile to realize the intramolecular addition to alkynes. The reaction allows for the diastereoselective synthesis of a variety of bicyclic frameworks containing all-carbon quaternary centers. Taken together, the gold(I)-catalyzed 5-*exo-dig*, 5-e*ndo-dig*, and

5-*endo-trig* pentannulation reactions provide access to cyclopentenes with control of the double bond position. The synthetic utility of these reactions was demonstrated by an efficient total synthesis of (+)-lycopladine A (8 steps, 17% overall yield).

Scheme 13. Gold-Catalyzed Intramolecular Reaction of Indoles with Alkynes



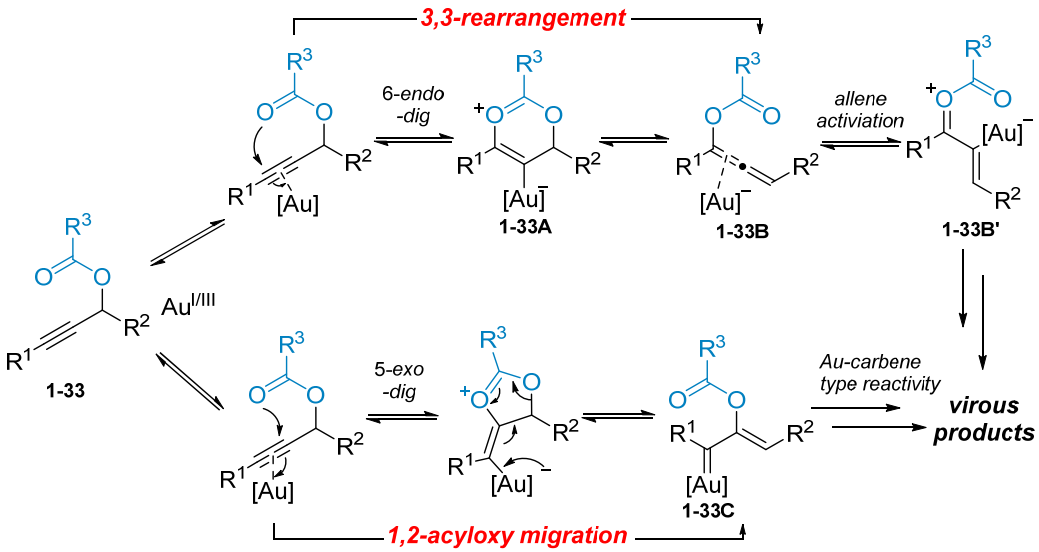
Scheme 14. Cyclization of Silyl Enol Ethers



1.3.2. Rearrangement of Propargylic Carboxylates

Propargylic carboxylates are versatile substrates that have been studied comprehensively in gold catalysis, allowing access to a variety of functional structures. With more and more experimental evidence, two divergent initial pathways in gold-catalyzed reactions of propargylic carboxylates have been proposed: 3,3-rearrangement and 1,2-acyloxy migration (Scheme 15).

Scheme 15. Rearrangement of Propargyl Carboxylates

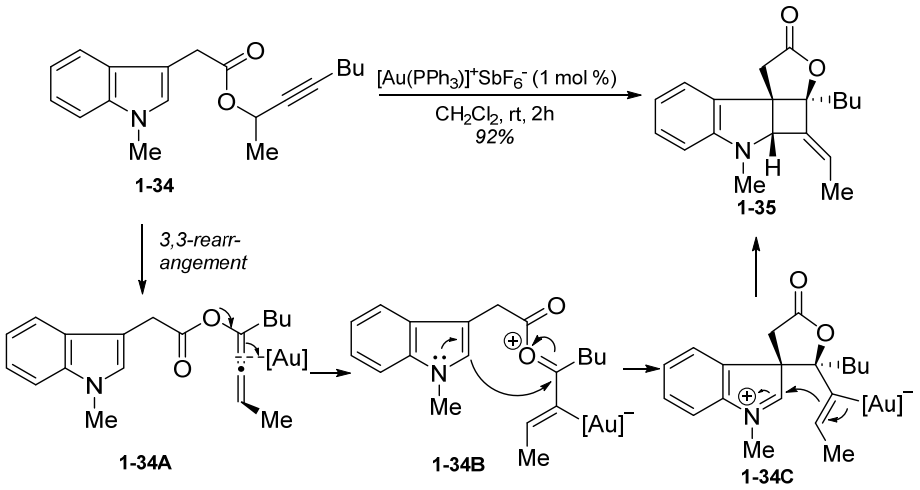


An initial 6-*endo*-dig cyclization of the ester carbonyl group results in the formation of a six-membered, gold-containing oxocarbenium intermediate **1-33A**, which can undergo ring opening to form carboxyallene **1-33B** or **1-33B'** via further activation of gold on the allene motif. In the case of 1,2-acyloxy migration, an initial 5-*exo*-dig cyclization of the ester carbonyl group to the gold-activated alkyne leads to the formation of alkenyl gold carbene **1-33C** upon heterolytic fragmentation of the

original ester bond. The reaction outcome drastically depends on the reaction pathways, which is mostly controlled by the substitution patterns on the propargyl moiety: in general, sterically and/or electronically unbiased substrates undergo reactions via 3,3-rearrangement, while electronically and/or sterically biased substrates prefer 1,2-acyl migrations.

Our group reported a cascade reaction of sequential 3,3-rearrangement and [2 + 2] cycloaddition in 2005.[31] When indole-3-acetate **1-34** was treated with $Ph_3PAuSbF_6$ (1 mol %), highly functionalized tetracyclic indole-derived cyclobutane **1-35** was formed highly diastereoselectively in excellent yield (Scheme 16).

Scheme 16. Gold-Catalyzed Formation of Tetracyclic Cyclobutanes

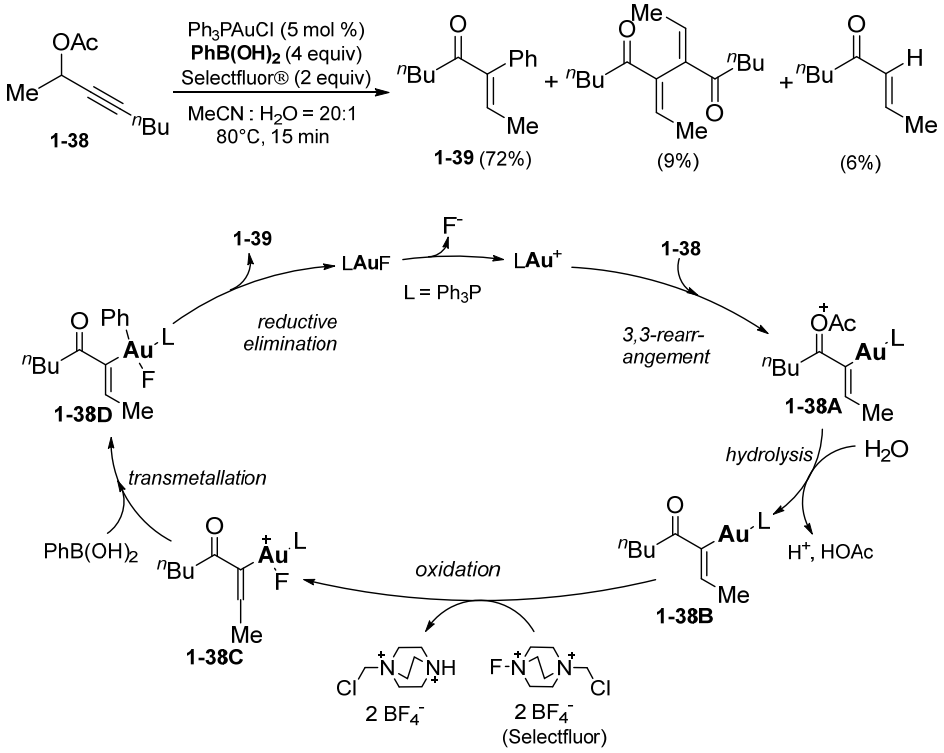


Activation of the alkyne motif in propargylic ester **1-34** by $[Au(PPh_3)]^+$ promotes a 3,3-rearrangement of the indole-3-acetoxy group, which leads to the formation of allenylic ester **1-34A**. The allene moiety of **1-34A** is further activated by the cationic Au(I) complex, resulting in the formation of oxonium **1-34B**. Cyclobutane **4** with an

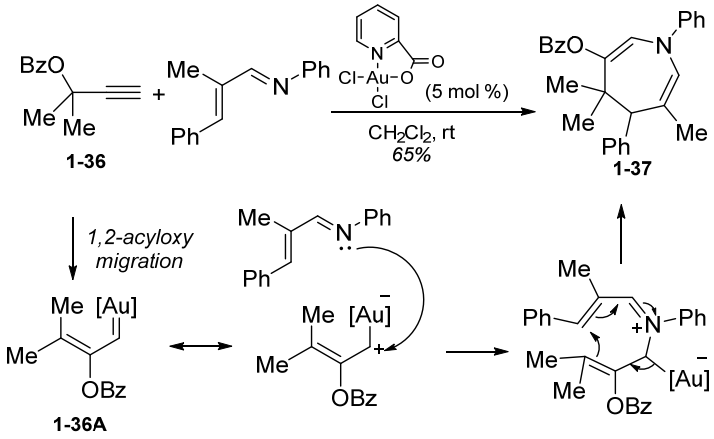
exocyclic *E*-double bond is then formed via cyclization of the oxonium group in **1-34B** to the 3-position of the indole ring, followed by intramolecular trapping of the iminium with the alkenylgold(I).

An unprecedented Au-catalyzed homogeneous oxidative cross-coupling of propargylic acetates and arylboronic acids was developed by our group[32] in 2009, offering a one-step synthesis of α-arylenones. This cross-coupling reaction reveals for the first time the synthetic potential of incorporating a Au(I)/Au(III) catalytic cycle in homogeneous gold catalysis. As shown in Scheme 17, tandem gold-catalyzed 3,3-rearrangement of the propargylic acetate **1-38** and further Au activation of the thus-formed allene moiety generates the oxocarbenium **1-38A**, which can be readily hydrolyzed into the intermediate **1-38B**. By using Selectfluor as a uniquely effective oxidant, the Au(I) center can be oxidized into Au(III) in the intermediate **1-38C**. Transmetallation from phenylboronic acid to **1-38C** then provides the Au(III) complex **1-38D**, which undergoes reductive elimination to yield the cross-coupling product **1-39**. The enone dimer side product is due to a competing transmetallation by Au(I) intermediate **1-38B** and the enone **87** is due to competitive protodeauration of **1-38B**.

Scheme 17. Au-catalyzed Homogeneous Oxidative Cross-coupling of Propargylic Acetates and Arylboronic Acids



Scheme 18. Gold-Catalyzed 1,2-Acyloxy Migration of Propargyl Carboxylate and Subsequent Intermolecular [4+3] Annulation

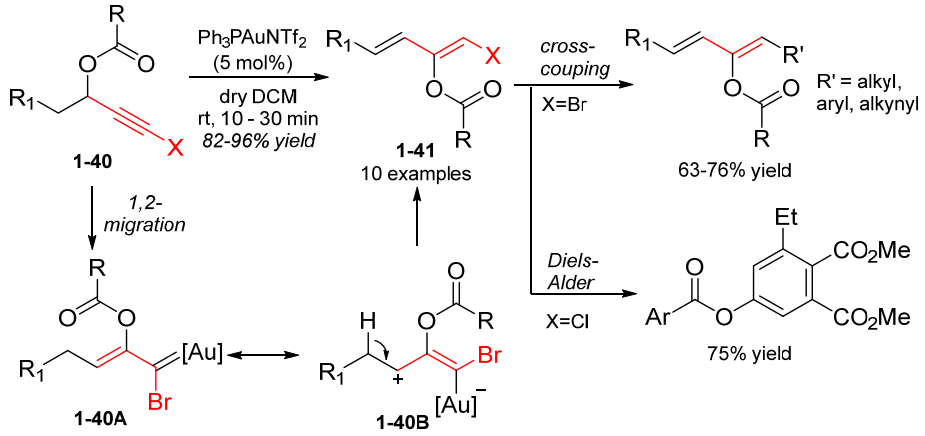


An example of Au-catalyzed 1,2-acyloxy migration of propargyl carboxylate

followed by [4+3] annulation was reported by Toste and co-workers.[33] The propargyl benzoate **1-36** has a gem-dimethyl group at the propargyl position but none at the alkyne terminus. As a result of this drastic steric difference, it undergoes 1,2-benzoxy migration selectively to form the gold carbene **1-36A**, which is a Fischer-type carbene and electrophilic. The subsequent stepwise annulation with the enimine affords the azepine product **1-37** in a synthetically useful yield.

In 2010, with the help with Dr. Biao Lu, I accomplished an efficient synthesis of (1*Z*, 3*E*)-1-bromo/chloro-2-carboxy-1,3-dienes **1-41** from terminally halogenated propargyl carboxylates **1-40** (Scheme 19).[34] The reaction were highly diastereoselective, high yielding and typically finished in 10 – 30 min.

Scheme 19. Synthesis of (1*Z*, 3*E*)-1-Bromo/Chloro-2-Carboxy-1,3-Dienes



Attaching a Br or Cl group at the alkyne terminus could efficiently promote its participation selectively in gold-catalyzed 1,2-acyloxy migra tion, generating carbene intermediate **1-40A** and its resonance form **1-40B**, which undergoes deprotonation

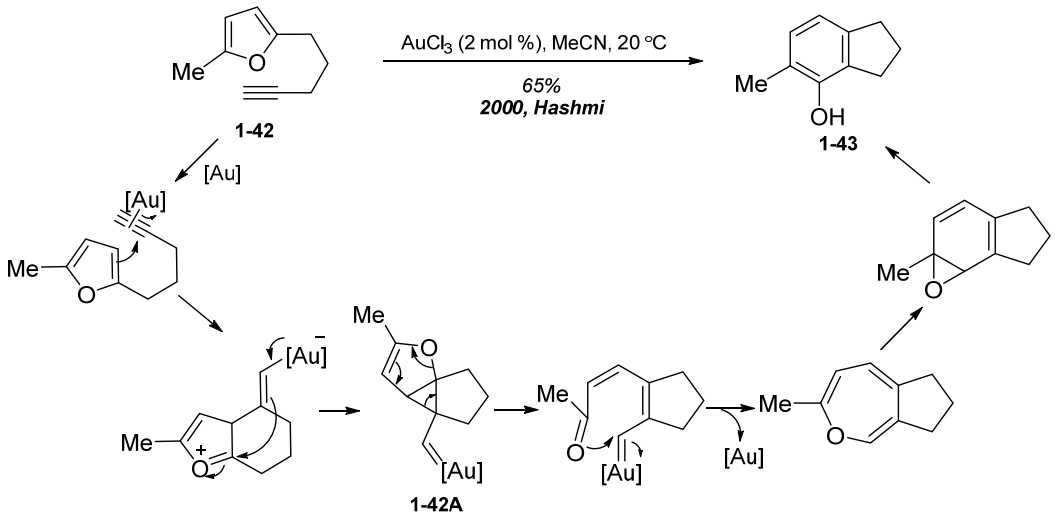
and protodeauration to afford the final diene product **1-41**. A chlorodiene product was suitable for the Diels-Alder reaction, and bromodiene products readily participated in transition metal-catalyzed cross-coupling reactions, including Kumada, Suzuki and Sonogashira reaction, offering efficient and flexible access to a much broader scope of functionalized dienes.

1.3.3. Gold-Catalyzed Cycloisomerization of Enynes

1.3.3.1. 1,6-Enynes

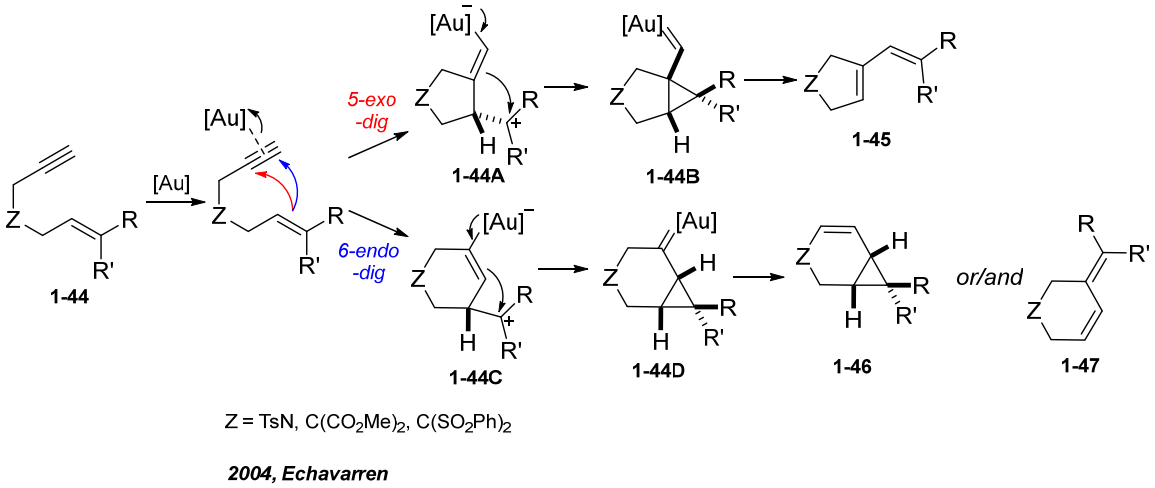
Enynes are highly versatile substrates for gold catalysis. The pioneer work by Hashmi et al.[35] on homogeneous gold-catalyzed reactions of enynes offers an excellent example of the potent coupling between alkynes and alkenes. As shown in Scheme 20, the alkynylfuran **1-42** can be considered as a specially functionalized 1,6-enyne. In the presence of $AuCl_3$ at the ambient temperature, it undergoes cascade transformations, yielding the synthetically useful highly substituted phenol **1-43**. The first step upon gold coordination is the reaction between the 'en' from the furan ring and the 'yn' moiety, leading to a reactive gold carbene intermediate **1-42A**, which undergo a series of skeleton rearrangements, eventually leading to the aromatized phenol product **1-43**.

Scheme 20. Synthesis of Polysubstituted Phenols from Enyne



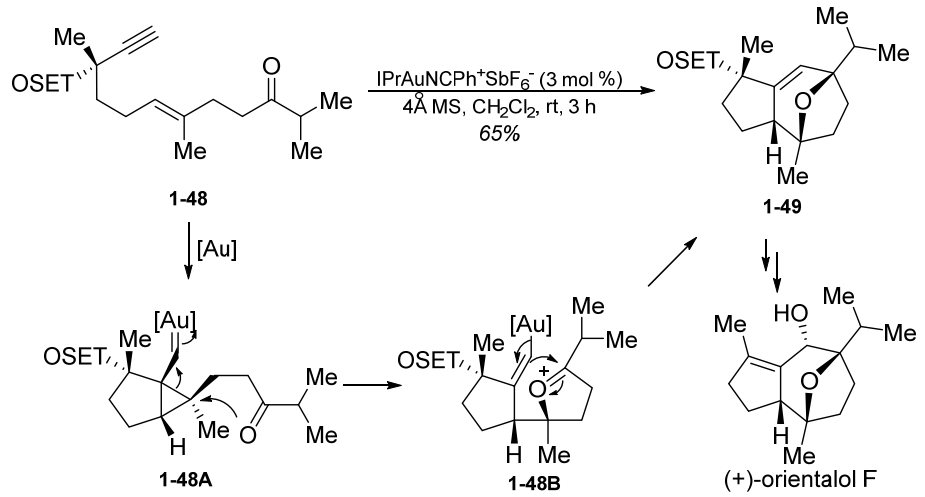
In 2004, Echavarren and co-workers published a seminal study which demonstrated that Au-based catalysts (2 mol % of PPh_3AuCl with $AgSbF_6$) were very effective for accomplishing a series of 1,6-enyne cycloisomerizations (Scheme 21).[36] There are two pathways for this reaction: one pathway was similar to that observed for Pt-based catalysts, which was initiated by a 5-*exo-dig* cyclization, followed by propanation and then generated highly reactive gold carbene intermediate **1-44B**, leading to the final diene product **1-45**. Notably, the reaction proceeded at room temperature, indicating a significantly more reactive nature of the gold catalyst compared to the Pt counterpart. The other pathway started from a 6-*endo-dig* cyclization, forming alkenyl gold intermediate **1-44C**, which generated another carbene intermediate **1-44D** by propanation. The subsequent 1,2-hydrogen migration afforded cyclopropane **1-46**, while diene **1-47** resulted from further skeleton reorganization.

Scheme 21. Skeletal Rearrangement of 1,6-enynes



By engaging a ketone tethered on the alkene side, Echavarren reported that this enyne cycloisomerization could provide a rapid access to a tricyclic skeleton in a [2+2+2] cycloaddition of ketoenynes.[37] Mechanistically, an initial enyne cyclization of **1-48** promoted by gold leads to the cyclopropyl gold carbene **1-48A**, which is then attacked by the proximal carbonyl group to give the intermediate **1-48B**. The following stereoselective cyclization of the alkenylgold moiety on the oxocarbenium in **1-48B** thereby yields the tricyclic product **1-49**. Notably, this [2+2+2] cycloaddition is highly diastereoselective, and the newly formed chiral centers in **1-49** are controlled by the chiral propargyl carbon center and the double bond geometry. This chemistry was later applied to the first total syntheses of (+)-orientalol F by the same author (Scheme 22).[38]

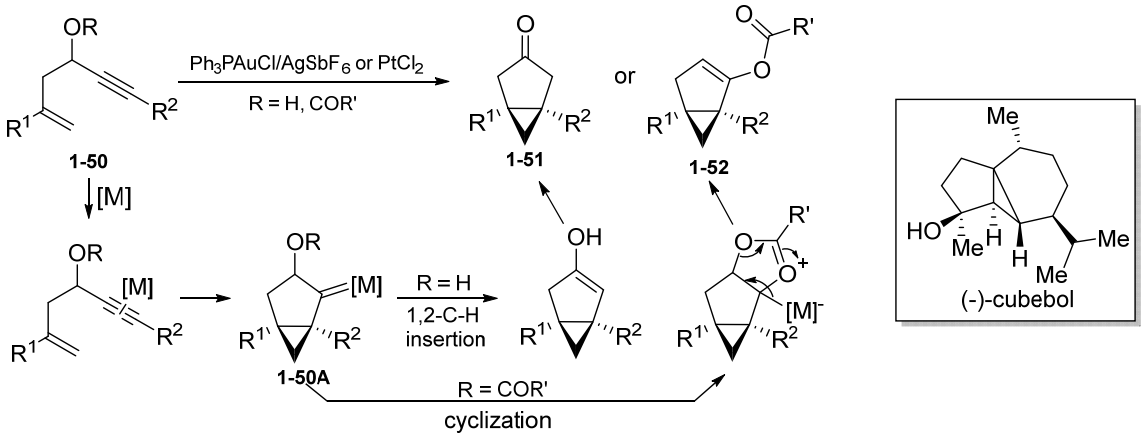
Scheme 22. Enynone Cycloisomerization en Route to the Total Synthesis of (+)-Orientalol F.



1.3.3.2. 1,5-Enynes

Besides 1,6-enynes, 1,5-enynes are also extensively studied in gold catalysis. The early independent reports by Fürstner et al.[39] and Malacria et al.[40] established that cycloisomerizations of this type of enynes proceed with an initial formation of the metal carbene **1-50A** in the presence of either LAu(I) or $PtCl_2$. This carbene can undergo either 1,2-C–H insertion to eventually afford isomeric bicyclic ketones **1-51** if R group is H, or a 1,2-acyloxy migration to yield enol esters **1-52** when R group is carbonyl. (Scheme 23). Fürstner has applied this chemistry in the total synthesis of sesquiterpenes such as (-)-α-cubebene and (-)-cubebol.[41]

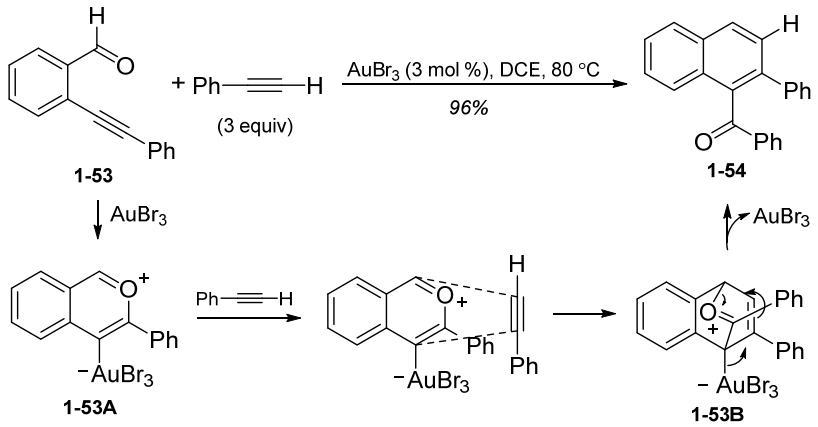
Scheme 23. Cycloisomerizations of 1,5-enynes



1.3.4. Reactions of ortho-Substituted Arylalkynes

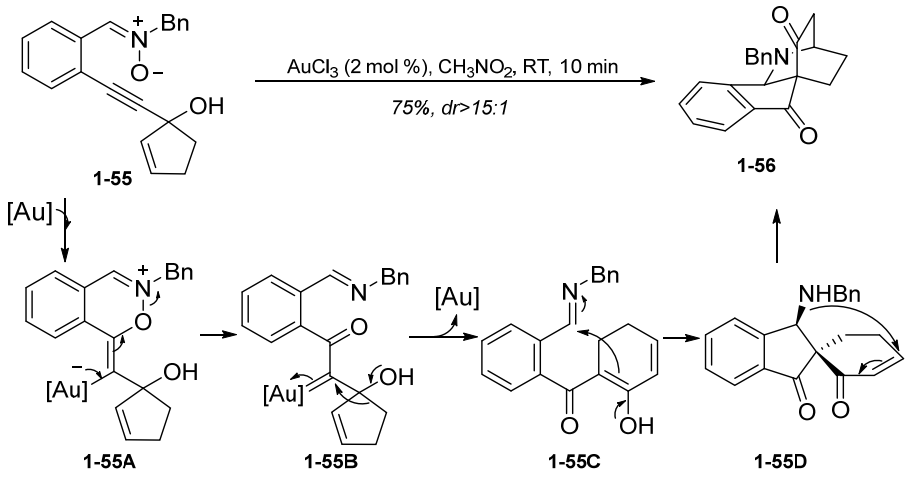
Arylalkynes with nucleophilic groups *ortho* to the C–C triple bond often serve as 'privileged' substrates for gold catalysis due to the forced proximity of reacting partners and often beneficiary conjugation between them. In a pioneer work by Yamamoto in 2004,[42] a carbonyl group is used as the *ortho* nucleophilic group, and its cyclization to the proximal gold-activated alkyne generates the benzo[*c*]pyrylium salt **1-53A**, which acts as a reactive and electron-deficient diene and undergoes [4+2] cycloaddition with phenylacetylene readily. The thus-formed intermediate **1-53B** rearranges readily to yield the synthetically useful naphthyl ketone **1-54** in an excellent yield (Scheme 24).

Scheme 24. $AuBr_3$-Catalyzed Benzannulation Reaction.



In their continued study using *ortho*-tethered nitrone as the internal oxidant, Shin et al.[43] reported the coupling of this intramolecular redox process with a pinacol-Mannich-Michael cascade in 2010.

Scheme 25. Stereoselective Gold-catalyzed Redox-pinacol-Mannich-Michael Cascade Reaction.



As shown in Scheme 25, an initial attack at the gold-activated C–C triple bond by the tethered nitrone generates the alkenylgold **1-55A**, which can fragment the N-O

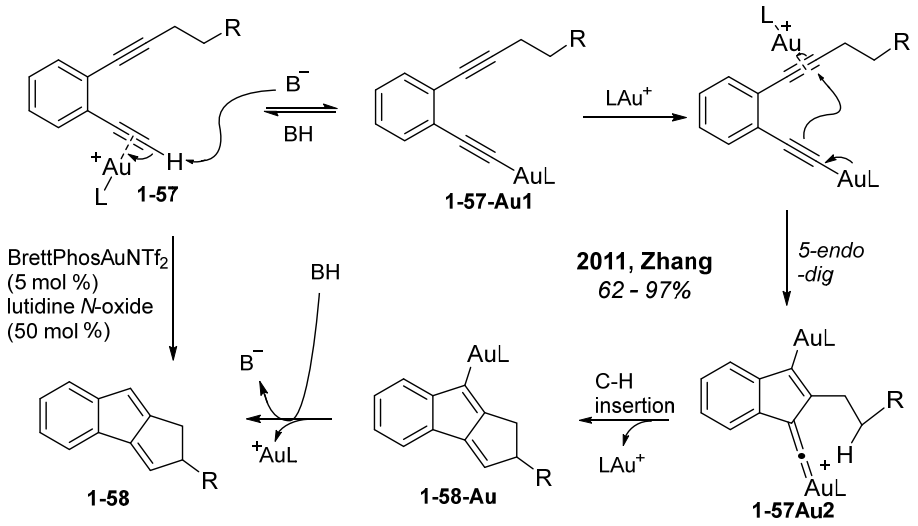
bond, and generate a reactive α-oxo gold carbene intermediate **1-55B**. With a tertiary alcohol proximate to the electrophilic carbene center, a pinacol-type rearrangement occurs immediately, leading to the β-diketone **1-55C**. Notably, this type of pinacol rearrangement was previous realized by our group in 2007.[44] Subsequent tandem Mannich reaction and Michael addition yields a complex tetracycle **1-56** in a good yield and with a good diastereoselectivity.

1.3.5. Gold Vinylidene and Related Intermediates

Vinylidenes complexes of various metals, such as Ru, Rh and W, are versatile intermediates that mediate the formation of various carbon-heteroatom and carbon-carbon bonds in a range of powerful catalytic reactions. However, little has been known about gold vinylidenes till recently. In 2011, our group reported the first case of gold vinylidene formation from cycloisomerization of benzene-1,2-diynes (Scheme 26).[45] Based on both mechanistic studies and theoretical calculations, we proposed the following mechanism: firstly, the *N*-oxide acts as a base to extract the proton from the terminal alkyne active by BrettPhosAu(I), affording alkynylgold complex **1-57-Au1**; while likely the reversed process, i.e., protodeauration, occurs, the presence of a base should help shift the equilibrium toward **1-57-Au1**. Another cationic gold(I) can then activate the other C–C triple bond of **1-57-Au1**; followed by a *5-endo-dig* cyclization, a gold vinylidene intermediate **1-57-Au2** would be generated. This novel species, in contrast to its Ru or Rh counterparts, is highly

reactive and undergo a facile C–H insertion, leading to **1-58-Au**; the subsequent protodeauration affords the observed tricyclic indenes product **1-58**. Three month later, Hashmi and co-workers reported very similar work independently.[46]

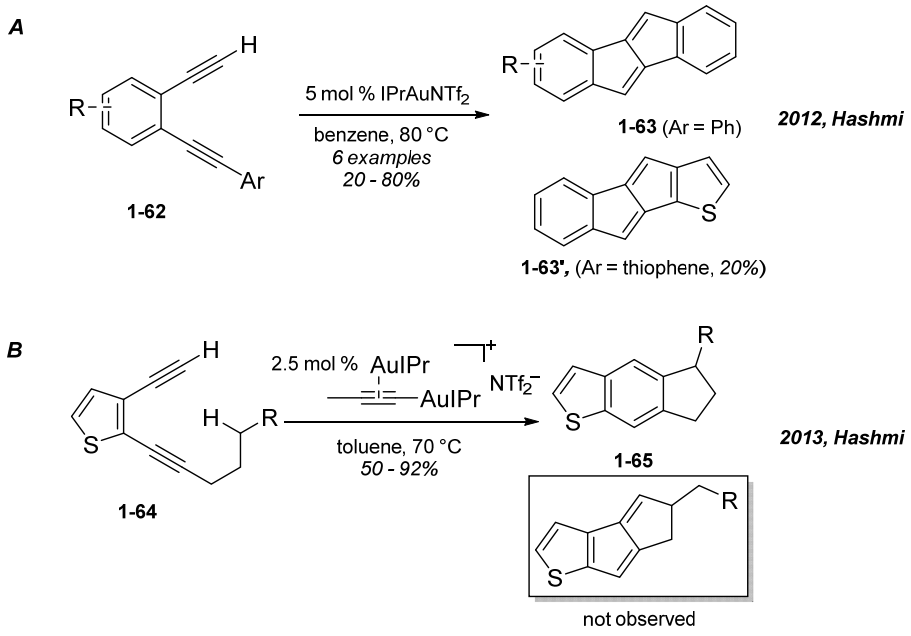
Scheme 26. First Example of Gold Vinylidene Formation from Endiynes



Later, Hashmi and co-workers explored a serious of diyne compound and reported some interesting results.[47-49] One terminal and one aryl-substituted alkyne **1-62** afforded dibenzopentalene compound **1-63** in moderate yield via the gold vinylidene pathway, which offers a straightforward and relatively efficient access towards this class of molecules which are of interest in the context of materials science.[50] However, the substrate scope is very limited: only those substrates with electron-donating/neutral substituted group on the phenyl ring were shown to work, and an interesting benzo[4,5]pentaleno[1,2-b]thiophene **1-63a** can be obtained in only 20% isolated yield (Scheme 27-A).

Interestingly, for thiophene fused diyne substrates **1-64**, the tricyclic pentalene compound, which was supposed to be formed from the gold vinylidene intermediate, was not observed by the authors; instead, indanothiophenes **1-65** were afforded in good efficiency through σ, π-dual activation and a 6-endo diyne cyclization when a dual-activation IPrAu(I) based catalyst was utilized (Scheme 27-B). Efficient synthesis of fluorenothiophenes was also demonstrated in this work, which makes this chemistry more interesting.

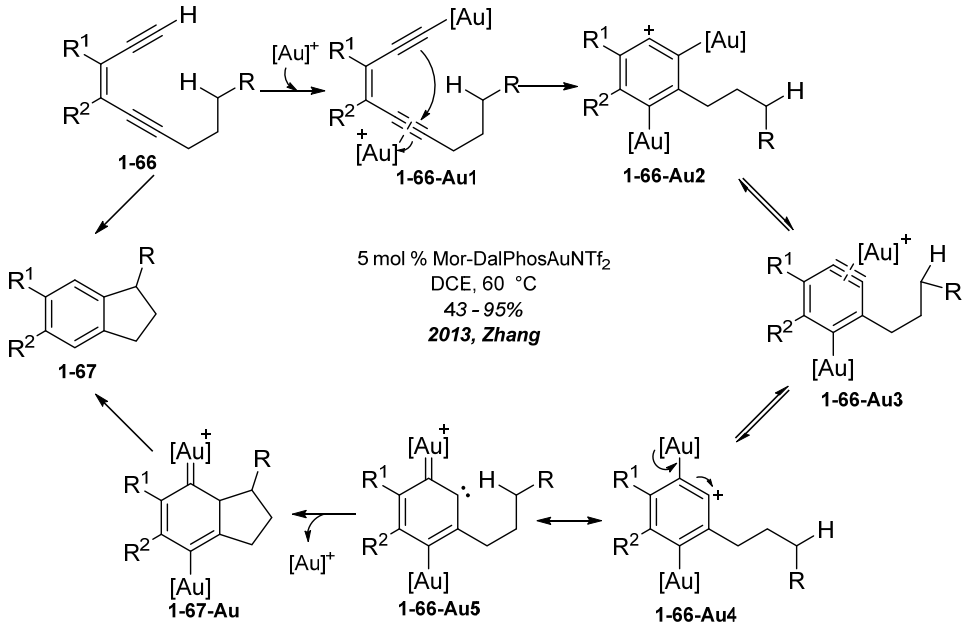
Scheme 27. Different Pathways for Different Substrates



After our group successfully generated gold vinylidene from benzene-dialkyne substrates via a 5-*endo-dig* cyclization, no success was achieved in terms of switching to the 6-*endo-dig* pathway for the same substrates. As a result, cis-enediyne, another type of substrate, was then tested. Pleasantly, the C–H insertion product, substituted

benzene **1-67**, was indeed generated and Mor-DalPhosAuNTf$_2$ served as the best catalyst. The reaction was initiated by 6-*endo-dig* cyclization to generate α-auronaphthyl cation **1-66-Au2** after gold acetylide **1-66-Au1** was formed. Moreover, cation **1-66-Au2** rearranges to its more stable structural isomer **1-66-Au4** through a low-energy-barrier gold migration, the transition state of which is in the form of an aryne-coordinated gold complex **1-66-Au3**. In the next step, the resonance form of **1-66-Au4** then generate gold carbene intermediate **1-67-Au**, which leads to the final product **1-67** upon carbene C(sp3)-H insertion.

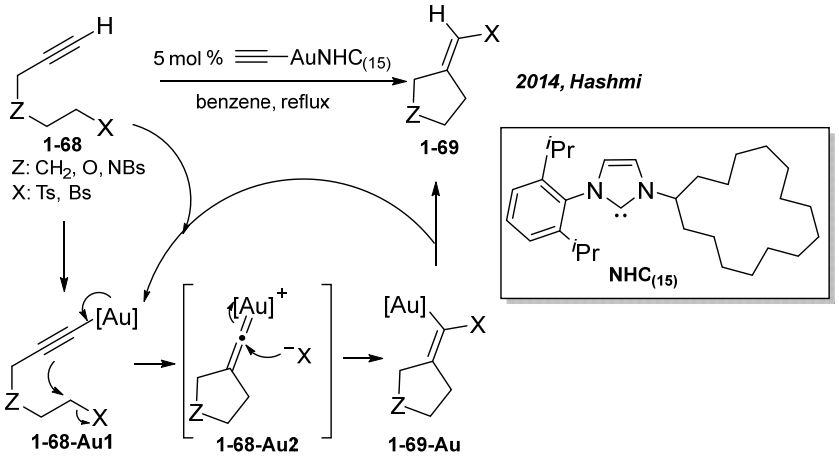
Scheme 28. Gold-Catalyzed Cyclizations of cis-Enediynes



The difference between the pathways of benzene-dialkynes and cis-enediynes can be explained by considering the difference in gained aromatic stabilization: when the substrate is benzene-dialkyne, the additional resonance energy gained upon the

6-*endo-dig* cyclization is 28 kcal/mol (64 kcal/mol for naphthalene and 36 kcal/mol for benzene).[51] However, when the substrate is cis-enediynes, the aromaticity gained by the newly formed benzene ring would be 8 kcal/mol greater (36 kcal/mol). Our DFT calculations confirmed this idea, which was also agreed by the work of Hashmi et al. reported early this year.[52]

Scheme 29. Synthesis of Vinyl Sulfonates via Gold Vinylidene Complexes



Very recently, Hashmi et al.[53] utilized terminal alkynes that bear sulfonate leaving groups at an appropriate distance to generate gold vinylidene and afford vinyl sulfonates as the final products (Scheme 29). The alkyne **1-68** was converted a gold acetylide **1-68-Au1** in the presence of a propynyl gold(I) precatalyst, after which a cyclization takes place and generates a gold vinylidene complex forming a tight contact ion pair with the sulfonate group (i.e., **1-68-Au2**), and the following recombination of the two parts eventually delivers vinyl sulfonates **1-69**. A new type of carbene ligand, $NHC_{(15)}$ seemed to perform slightly better than biaryl phosphine

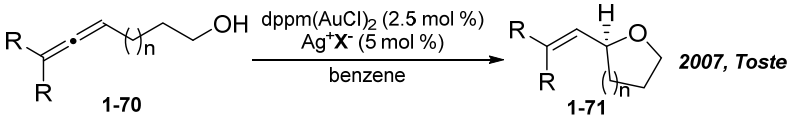
ligand XPhos (81% *vs* 79% with 2.5 mol % Au catalyst loading). In spite of the low to moderate yields and limited substrate scope, it's still a novel way to generate gold vinylidene with only one alkyne group and solo gold activation.

1.4. Gold-Catalyzed Reactions of Allenes

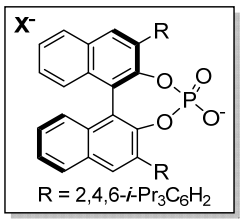
Allenes are highly valuable synthetic precursors in preparative organic chemistry because of their ability to undergo a variety of transformations. Because of their soft and carbophilic character, gold catalysts are particularly well suited for the selective activation of allenes in the presence of other reactive functionalities.

In 2007, an interesting catalytic system reported by Toste et al.[54] takes advantage of a chiral counterion, which was introduced into the catalyst by a silver phosphate salt (Scheme 30). Thus, treatment of γ- or δ-allenols **1-70** with catalytic amounts of an achiral gold precatalyst dppm$(AuCl)_2$ and the chiral silver salt afforded heterocycles **1-71** with high yield and excellent enantioselectivity in most cases. For the terminal allene (R = H), the enantiomeric excess could be improved from 80 to 92% by using a chiral gold catalyst together with the chiral silver salt. Application of this method to allenic carboxylic acids afforded chiral γ-lactones with up to 82% ee.

Scheme 30. Chiral Counterion in the Enantioselective Cycloisomerization of Allenols



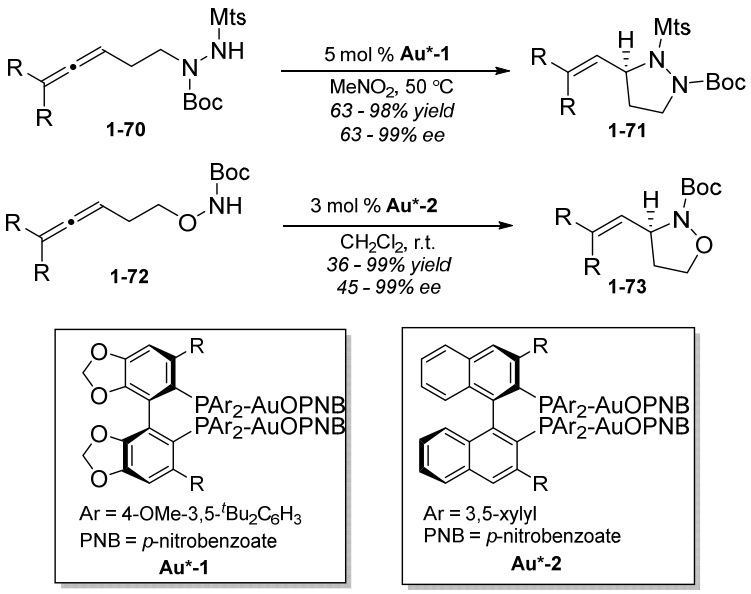
n	R	yield (%)	ee (%)
1	-$(CH_2)_4$-	90	97
1	Me	91	95
2	Me	81	90
2	H	96	80



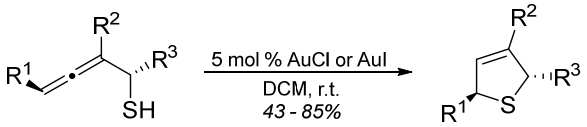
In 2010, Toste and co-workers expanded the scope of gold-catalyzed intramolecular *exo*-selective hydroaminations to allenic hydrazines **1-70** and hydroxylamines **1-72**.[55] The former substrates afforded pyrazolidines **1-71** in the presence of Segphos-Au complex **Au*-1**, whereas the binap-gold catalyst **Au*-**2 gave the best results in the cyclization of the hydroxylamine derivatives to isoxazolidines **1-73** (Scheme 31). Moderate to excellent yields and enantioselectivities were obtained in most cases, and the methodology was also applied to the synthesis of chiral tetrahydrooxazines.

Despite the propensity for thiols to bind to gold, which would be expected to nullify its ability to act as a catalytic candidate, in 2006 Krause et al.[56] found that an intramolecular hydrothiolation of allenes could take place. This is the first example of gold-catalyzed C–S bond formation and the authors posited that the gold-thiol complex should be the preferred species *in situ* with the perfect chirality transfer observed. Besides AuCl, AuI is also efficient in some cases (Scheme 32).

Scheme 31. Cycloisomerization of Allenic Hydrazines and Hydroxylamines



Scheme 32. Intramolecular Thiol Addition to Allenes



1.5. Gold-Catalyzed Reaction of Allenes

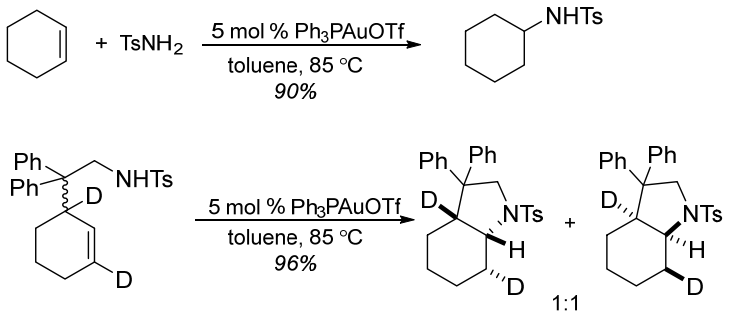
Alkene activation has attracted lots of attention in the past ten years and much progress has been made in this research area. In this segment, gold-catalyzed addition of carbon- and heteroatom-based nucleophiles to inactivated alkenes are widely recognized as “capricious” transformations due to alkyne and allene counterparts. However, tremendous developments have been made over the past few years.

1.5.1. Nucleophilic Addition Reactions

1.5.1.1. C–O Bond Formation

He et al.[57] first demonstrated that Au(I) promoted the hydroamination of alkenes in 2006. With 5% $Ph_3PAuOTf$ at 85 °C, both inter- and intramolecular additions of tosylamide occur in good to excellent yields (Scheme 33). A mechanistic analysis confirmed that a *trans*-addition mechanism was operative. As a control experiment, they also studied the ^{31}P NMR of $Ph_3PAuOTf$ at 85 °C and found that the PPh_3Au^+ species does not interact with $TsNH_2$ and indeed interacts with norbornene or cyclohexene.

Scheme 33. Hydroamination of Alkenes

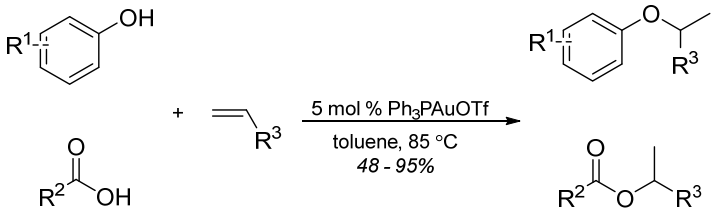


1.5.1.2. C–N Bond Formation

In 2005, He and co-workers first reported the intermolecular addition of both phenols and carboxylic acids to simple olefins with $Ph_3PAuOTf$.[58,59] Some terminal olefins eventually migrate to an internal position to give mixed products, but further migration does not take place. Allylic benzenes, however, do not migrate to more

stable styrenes. Different functional groups are tolerated (Scheme 34). One year later, the same group reported the same transformation but catalyzed by HOTf at room temperature with good to excellent yields.

Scheme 34. Phenol and Carboxylic Acid Additions to Alkenes

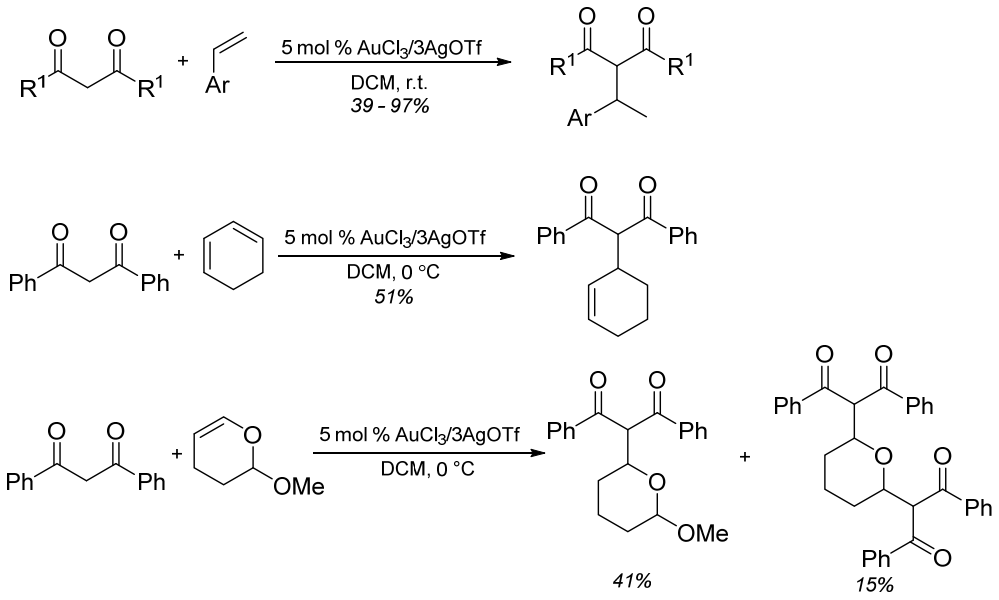


1.5.1.3. C–C Bond Formation

Li et al.[60] reported a gold(III)-catalyzed intermolecular addition of 1,3-diketones to olefins in 2004. Because of the high Lewis acidity of the $AuCl_3$/3AuOTf catalyst system, substrates like dimethyl malonate and β-ketoesters decomposed and did not undergo the reaction.

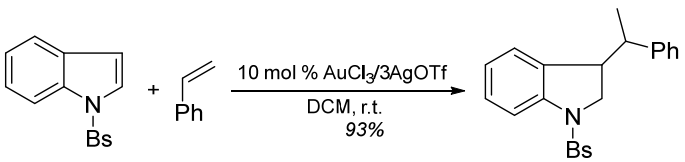
There is no detectable diastereoselectivity with the gold(III) system at room temperature. Shortly after, they found by lowering the reaction temperature to 0 °C, dienes, trienes, and cyclic enol ethers also react with diketones to give moderate to good yields.[61] Sterically hindered dienes give lower yields (Scheme 35).

Scheme 35. Intermolecular Addition of 1,3-Diketones to Olefins



Reports of direct hydroarylation of simple olefins by gold are rare. In 2007 Liu et al.[62] found that $AuCl_3$/3AgOTf can catalyze addition of *N*-protected indoles to vinyl arenes and trisubstituted olefins using the DNA-encoding and DNA-programed assembly of substrate pairs. Notably most reactions above could also be catalyzed by a catalytic amount of strong acids like HOTf (Scheme 36).

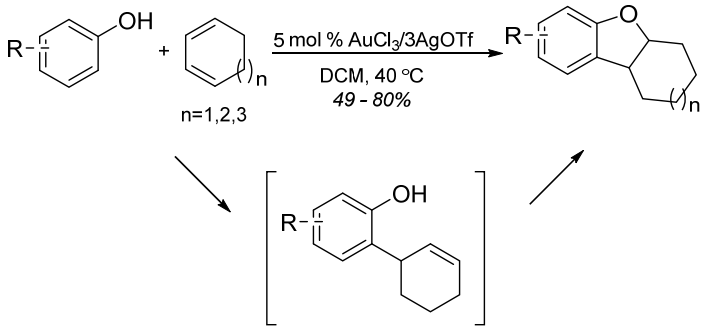
Scheme 36. Hydroarylation of Alkenes



Li et al.[63] reported that the same catalyst system, $AuCl_3$/3AgOTf, catalyzes an efficient annulation of phenols and dienes to give various benzofuran products (Scheme 37). Cationic $Ph_3PAuOTf$ shows no product formation, perhaps due to

degradation of dienes accelerated by cationic gold(I). The authors proposed that the intermolecular Friedel-Craft reaction occurs first and then the subsequent intramolecular addition of the phenol O-H bond leads to the final benzofuran products.

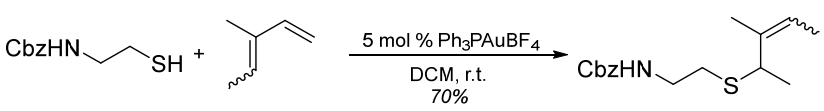
Scheme 37. Annulation of Phenols and Dienes



1.5.1.4. C–S Bond Formation

In 2007, He et al.[64] found that Ph_3PAuBF_4 to be a highly active catalyst for the addition of a wide variety of sulfur nucleophiles to conjugated dienes. A number of functional groups are tolerated including NO_2, OMe and even free OH. While free NH_2 is not tolerated, it can be protected as Cbz to permit the addition to occur. Unfortunately, attempts to add simple thiols to simple olefins failed, even at 100 °C (Scheme 38).

Scheme 38. Thiol Addition to Dienes

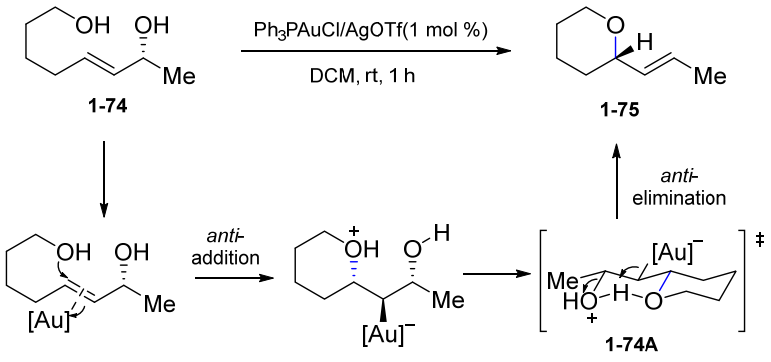


1.5.2. Allylic Substitution Reactions

From a synthetic, environmental and economic point of view, it's highly desirable to use simple allylic alcohols as alkylating reagents in place of more activated analogues (i.e. halides, acetates, carbonates and phosphates), since the only side-product is water. Late transition metal catalysts proved to be efficient in addressing the poor reactivity of these substrates.[65] Due to the ability of gold complexes to act as both σ- and π-acids, gold catalysis gained an exceptional role in the activation of allylic alcohols.

In 2011, Ess and Aponick reported a mechanistic study on the intramolecular hydroalkoxylation of hydroxy allylic alcohols **1-74**, pointing out the key role of intramolecular hydrogen bonding interactions for both reactivity and stereoselectivity. *Anti*-addition followed by *anti*-elimination was energetically favored by DFT calculation.[66]

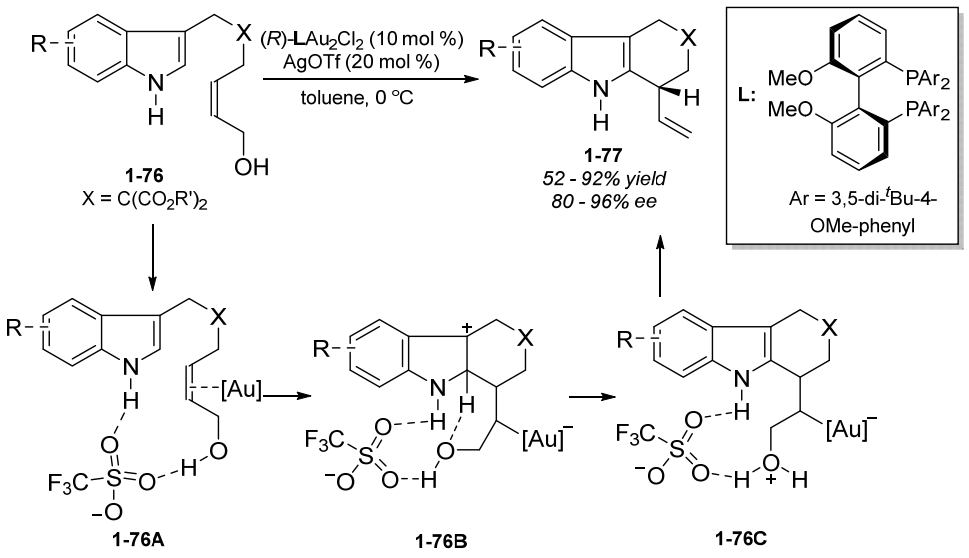
Scheme 39. Mechanistic Investigation on the Intramolecular Au(I)-catalyzed Hydroalkoxylation of Allylic Alcohols



Interestingly and also importantly, a strong hydrogen bond was established during the catalytic cycle between the hydroxy groups. The H-bond turned out to be a key interaction for the high reactivity of **1-74** toward cyclization, leading to an intramolecular proton transfer resulting into an intermediate with better leaving group **1-74A**. Furthermore, as the H-bond was conserved during the entire process of the reaction, it also determined the *E* geometry of the newly formed C–C double bond (Scheme 39).

The importance of the H-bond network in gold-catalyzed reactions of allylic alcohols is also highlighted by the intramolecular enantioselective allylic alkylation of indoles, which was documented by Bandini and Miscione.[67, 68] Combined experimental and computational studies revealed the presence of a complex H-bond network between the indole ring, the counterion OTf^- and the leaving group OH along all the reaction profile (Scheme 40). Multiple functions were recognized in these interactions. Firstly, all the strong H-bonds conferred a constrained conformation to the substrates (U-fold*)* placing the two reacting partners in close proximity (**1-76A**). Secondly, after the initial nucleophilic attack of the indole ring, the counterion, trifluoromethanesulfonate, facilitated the elimination of water from **1-76C** by shuttling one proton atom from the indolyl ring to the leaving hydroxy group. This proposed catalytic cycle also accounted for the observed stereochemistry of the product **1-77** (*R*) when the chiral gold complex (*R*)-DTBM-MeO-biphep was employed.

Scheme 40. Intramolecular Enantioselective Au(I)-Catalyzed Alkylation of Indoles with Allylic Alcohols.

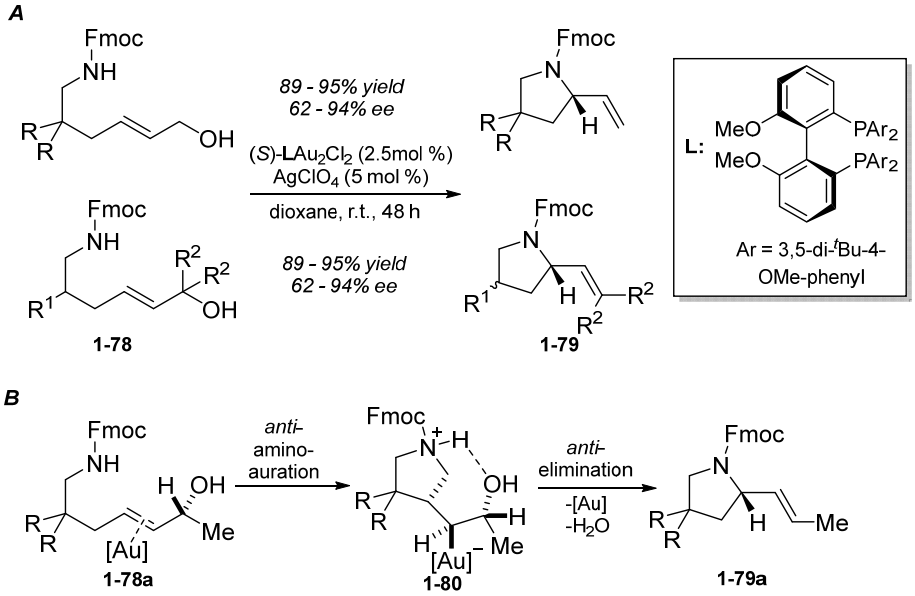


In early 2012, Widenhoefer et al.[69] were able to demonstrate an enantioselective dehydrative amination of allylic alcohols with carbamates, emphasizing what an essential role the H-bond network played in this type of allylic substitution reactions, once again. Pyrrolidines and piperidines **1-79** were obtained with enantiomeric excesses up to 94% by using a chiral gold complex based on (*S*)-DTBM-MeO-biphep (Scheme 41-A).

Mechanistic investigation suggested that the configuration of the newly formed stereocenter was completely controlled by the catalyst. On the contrary, studies on stereochemically defined secondary allylic alcohols revealed that the configuration of the allylic carbon atom affected the configuration of the newly formed C–C double bond. The *E* configuration of the carbon-carbon double bond from the starting

material turned out to be essential to achieve high enantioselectivity. Also in this case, it's worthy to mention that a mechanism consisting of an initial *anti*-aminoauration followed by *anti*-elimination accounted for the observed experimental results (Scheme 41-B).

Scheme 41. Intramolecular Enantioselective Dehydrative Amination of Allylic Alcohols Catalyzed by Chiral Au(I)-complexes.



Metal catalyzed electrophilic activation of isolated alkenes is often considered one of the most challenging metal-assisted nucleophilic manipulations of inactivated unsaturated hydrocarbons by far. Relative inertness of C=C with respect to alkynes or allenes leads to this trend. In this scenario Au(I) and Au(III) catalysis is playing a major role leading to tremendous developments

1.6. References

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2. A General Ligand Design for Gold Catalysis Allowing Ligand-Directed *anti* Nucleophilic Attack to Alkynes

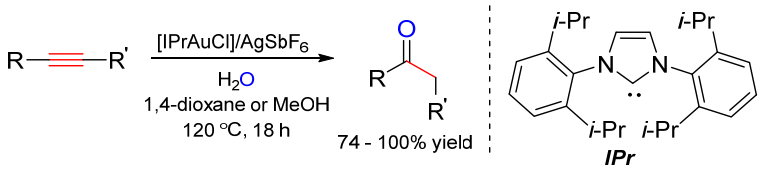
2.1. Introduction and Design

Numerous powerful synthetic methodologies, allowing efficient and rapid access to a broad series of functional structures and compounds, have been developed based on an initial *anti* nucleophilic attack at the LAu(I) coordinated C–C triple bond. However, most homogeneous gold catalyses require 1–5 mol % catalytic loading, which means it's highly unlikely for these reactions to be applicable in medium or large scale applications due to the expensive nature of metal gold, not mentioning the industrial scale processes.

The above general shortcoming in gold catalysis is mainly due to the low turnover numbers (TONs) of the catalysts: Au(I) complexes based on phosphine ligands offers good reactivities but generally short life time, while Au(I) complexes based on NHC ligands are typically more stable due to its stronger coordination nature than phosphine ligands but less reactive at the price of stability. To overcome this limitation, we need substantially improve the TONs of the catalysts and hence dramatically lowering their loadings. To realize this target, two solutions might come to play: 1) higher temperature with NHC-based catalyst to increase turnover frequency (TOF); 2) designed (phosphine) ligands to achieve higher TOF and longer lifetime.

2009, Nolan et al.[1] reported the first example of gold catalysis at part-per-million catalytic loadings: [(NHC)Au(I)]-catalyzed alkyne hydration. Due to the high thermal stability of IPrAu(I), the reactions could be heated to 120 °C for long time so that only ppm catalyst loading was required to convert alkynes to ketones in good to excellent yields (Scheme 42). However, there are a few questions marks and limitations remaining for this chemistry: large excess of $AgSbF_6$ was needed in most cases, which also potentially catalyzed this reaction, but no control reaction was done; the tolerance of functional groups or protecting groups was not demonstrated and the regioselectivity for internal alkynes were bad (2.2:1 to 4.4:1). Clearly higher temperature with NHC-based catalyst was able to increase TON, but suffer from the bad selectivity and relatively harsh conditions at the same time.

Scheme 42. [(NHC)Au(I)]-Catalyzed Alkyne Hydration at PPM Catalyst Loadings

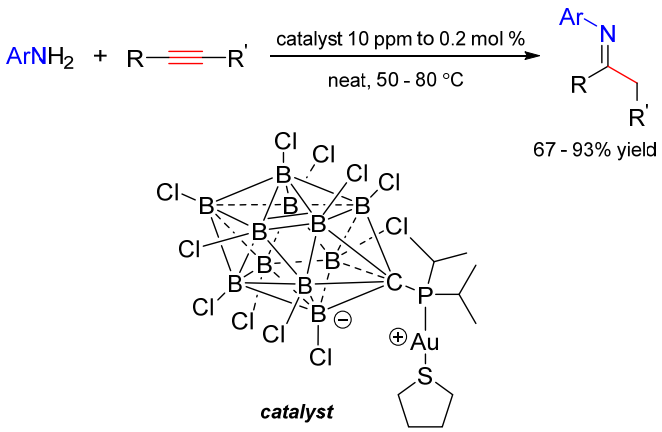


Ligand tuning[2] is a well-practiced strategy in transition metal catalysis to achieve high catalyst TONs, but little success has been reported in this regard in homogeneous gold catalysis. Recently LaVallo et al.[3] reported a new type of gold catalyst to be very efficient when catalyzing hydroamination of alkynes with primary amines; the highest

turnover number observed for hydroamination with this catalyst exceeded a stunning 95, 000. This single-component zwitterionic gold complex formed by the coordination of a phosphine ligand bearing an inert and noncoordinating carborane substituent, $CB_{11}Cl_{11}^{-}$, to an Au(I) ion (Scheme 43).

The authors postulate that the proximity of the anionic $CB_{11}Cl_{11}^{-}$ group to the Au center may lead to electrostatic stabilization of the positively charged reaction intermediates.[3] Analogously, the charge on the carborane substituent may also act as an electrostatic tether to prevent phosphine dissociation and subsequent catalyst decomposition.

Scheme 43. Hydroamination of Alkynes with Primary Anilines



Those two simple and typical but also classical and useful transformations are both based on an initial coordination of a C–C triple bond to a LAu(I), a cationic gold(I) species with one coordinating ligand, and a subsequent anti attack by a nucleophile at the alkyne (Figure 3-A). Due to the linear nature of the L-Au-alkyne complex and the

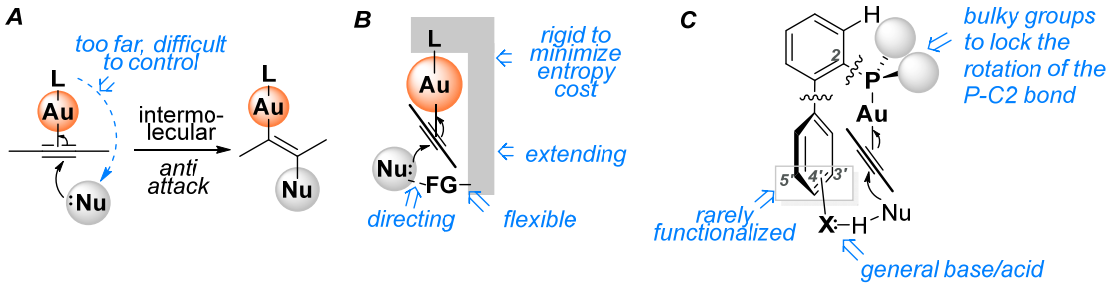
anti approach of the nucleophilic attack, it is highly challenging to introduce bonding interaction between the ligand and the nucleophile due to apparent spatial constrain. As a result, it's not surprising that there is no reported reaction of this nature before this work. Even though in the research of enantioselective gold catalysis,[4,5] ligands and/or counter anions to the metal center could impose a chiral environment in the approaching path of nucleophiles (often with allene and allylic alcohol substrates), the controls are unvaryingly from the sterics and offer little, if not to the opposite effect, rate acceleration or efficiency improvement.

Figure 3. A Novel Ligand Design for Highly Efficient Gold Catalysis

(A) anti attack at gold(I)-activated alkyne by a nucleophile

(B) a general concept to achieve *quasi*-intramolecular, ligand directed nucleophilic attack

(C) a design based on biphenyl-2-ylphosphine framework



It is envisioned that a ligand with a rigid and extending framework could project a functional directing group farther enough to reach to the approach nucleophile (Figure 3-B).[6] The functional group could be designed in such a way that it could have

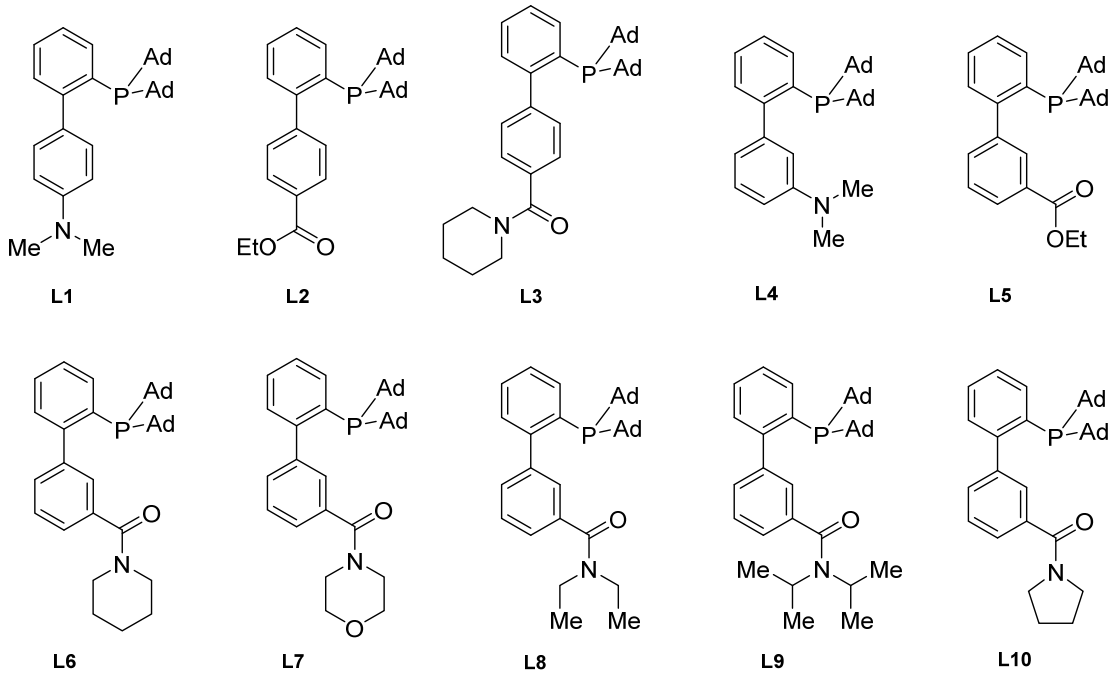
attractive interaction with the nucleophile and hence be capable of directing its attack at the gold-activated triple bond. The rigidity of the backbone would minimize the entropy cost for organizing transition states, and the directing group should be flexible enough to accommodate a broad substrate scope. This strategy is expected to facilitate the initial nucleophilic attack drastically by converting it from an intermolecular process to a *quasi*-intramolecular event and may also accelerate subsequent transformations. As a result, higher catalyst TONs and hence more efficient catalysis could be expected.

Bulky and electron-rich biphenyl-2-ylphosphines belong to a privileged class of phosphorus-based ligands that are developed by Buchwald's group[7-9] for various versatile Pd catalyzed cross-coupling reactions.[10,11] Lately, these ligands have been borrowed to apply in gold catalysis with much success,[12-19] but modification of them for gold catalysis is rare.[20] Perhaps due to the nature of Pd catalysis, the lower half of the bottom phenyl ring of these ligands (i.e., C3', C4' and C5') has seldom been substituted with functional groups. The only exceptions are a 3'-sulfonate ligand derived from SPhos and a 4'-sulfonate ligand based on XPhos for the purpose of increasing catalyst aqueous solubility so that the coupling reactions could be performed in water, a very green solvent.[21] In contrast to square planar Pd(II) complexes, bis-coordinated gold(I) complexes exhibit linear structures, which stands a ligand design philosophy different from that for Pd catalysis. In the context of biphenylphosphine ligands (Figure 3-C), by fixing the P-C2 rotation using bulky substituents on the phosphorus, the linear P-Au-alkyne axis should be parallel to and

bisect the pendant phenyl ring, thus forcing the Au-coordinated alkyne to stay right on the top of the lower half of that pendant ring. We think that if these remote positions on that part of the phenyl ring, with the activated alkyne lying above, were to be functionalized with H-bond acceptors, these functional groups could extend further enough to direct certain neutral nucleophiles via H-bonding interactions and/or proton stabilization to attack the activated alkyne in a *quisi*-intramolecular *anti* approach. Those directing groups can not only act as bases to speed up the process of the initial nucleophilic attacks, but also serve as the proton-supplier to accelerate the course of proton-deauration after the attack. In this manner the design concept shown in Figure 3-B could be implemented.

To put this concept into practice, I designed and synthesized a series of 2-biphenyldi-(1-adamentyl)phosphine ligands **L1** – **L10** (Figure 4) with either C3' or C4' functionalized. They can be readily synthesized via consecutive cross-coupling reactions and then followed by coupling of di(1-adamentyl)phosphine (Ad_2PH). Its ease of installation does make Ad_2P very temping at the first place,[22] but more importantly, its electron-rich nature makes the corresponding Au complex more stable, and the steric bulkiness of the Ad groups would protect the Au from the intermolecular deactivation. As a result, it helps to sustain the catalyst for longer life time to realize a high TOF.

Figure 4. 2-Biphenyldi-(1-adamentyl)phosphine Ligands L1 – L10

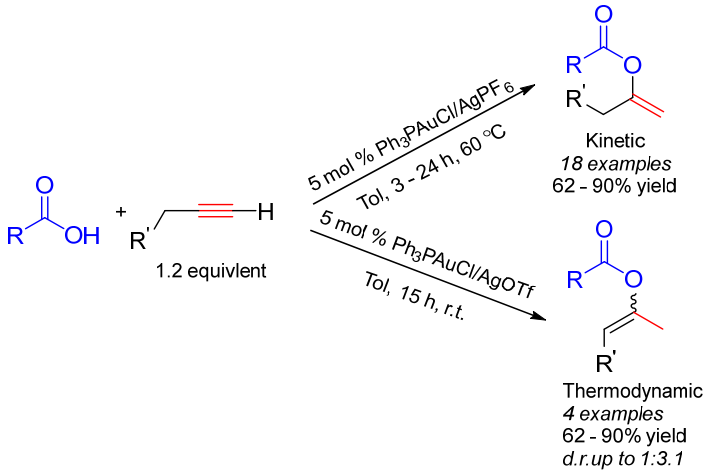


2.2. Au-Catalyzed Ligand-directed Nucleophilic Additions to Alkynes with Part-Per-Million Catalyst Loading

The addition of a carboxylic acid to an alkyne is chosen as the model reaction to exam our design and this reaction was firstly reported by Kim[23] in 2010. Interestingly, $PPh_3AuCl/AgPF_6$ catalyst afforded the Markovnikov addition products, whereas $PPh_3AuCl/AgOTf$ catalyst gave the more stable isomerized products via the Markovnikov products (Scheme 44). TONs of this transformation was up to 18, and the best catalyst TON (i.e., 124) of this type of reaction was achieved via Ru catalysis.[24] Notably, the products enol esters are versatile substrates of broad synthetic utilities; they possess not only mildly activated acyl groups which make themselves better acylation reagents than alkyl esters, but also relatively stable enol motifs that would

afford α-functionalized ketones.

Scheme 44. Gold(I)-Catalyzed Addition of Carboxylic Acids to Alkynes



2.2.1. Conditions Study

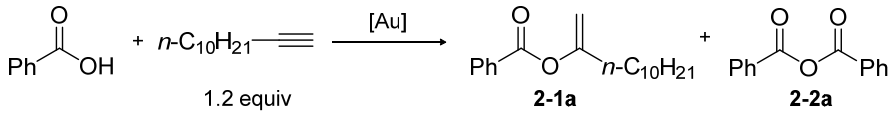
Benzoic acid and 1-dodecyne were used to optimize the reaction conditions because their non-volatile property makes it easier to detect the reaction products. I started the screening with 1 mol % Au catalyst at 40 °C using DCE as the solvent and the concentration of limiting benzoic acid was 0.5 M.

As shown in Table 1, with IPrAuNTf$_2$, a catalyst only different by the counter anion from the previously reported ppm-level IPrAuCl/AgSbF$_6$ for alkyne hydration in 1,4-dioxane/H_2O, [1] there was only trace amount of the desired 2-dodecenyl benzoate **1a** detected after 8 hours and most starting materials remained unreacted (entry 1). Gold catalysts based on biphenyl monophosphine ligands JohnPhos and bulkier

BrettPhos gave similarly low reactivity too (entries 2 and 3). Mor-DalPhosAuNTf$_2$ with a *P,N*-type ligand which showed interesting ability in terms of stabilizing α-gold carbene,[25] did not provide any promising result for this reaction, neither did simple Ph$_3$PAuNTf$_2$, as expected (entries 4 and 5).

While a basic dimethylamino group at the 4' position in the case of the ligand **L1** did not offer any improvement (entry 6) , its regioisomer **L4** with the substituent at the 3' position led to some notably improvement (entry 7), hinting that substitution at C3' might be better than at C4' for the reaction. Although **L2** and **L5** with relatively neutral ethyl ester group at 3' or 4' positions only gave trace products (entries 8 and 9), with piperidin-1-ylcarbonyl as the functional group at either the 4' or the 3' position in the case of ligand **L3** or **L6**, respectively, a much more efficient reaction with an observed catalyst TON of 80 was realized, suggesting that an amide is a suitable functional directing group for promoting the acid addition to the alkyne (entries 10 and 11). By lowering down the gold catalyst loading to 0.11%, the TONs reached 609 for **L3** (entry 12) and 827 for **L6** (entry 13), which are much better than the Ru case. [24] Again, ligand with directing group at C3' seemed to be better than at C4' position, which was consistent with the phenomena observed from **L1** and **L4**. TON was further increased to 1681 (entry 14) by further decreasing the loading of the better gold complex **L6AuCl** to 200 ppm with slightly more concentrated reaction condition (1 M).

Table 1. Screening Various Ligands and Optimizing Reaction Conditions.



entry	[Au]	solvent, temperature, conc.	time	NMR yield[a]		
				2-1a	TON	**2-2a**
1	$IPrAuNTf_2$ (1%)	DCE, 40 °C, 0.5 M	8 h	0.5%	0.5	0
2	$JohnPhosAuNTf_2$ (1%)	DCE, 40 °C, 0.5 M	8 h	trace	-	0
3	$BrettPhosAuNTf_2$ (1%)	DCE, 40 °C, 0.5 M	8 h	trace	-	0
4	$Ph_3PAuNTf_2$ (1%)	DCE, 40 °C, 0.5 M	8 h	trace	-	0
5	$Mor\text{-}DalPhosAuNTf_2$ (1%)	DCE, 40 °C, 0.5 M	8 h	trace	-	0
6	**L1**AuCl/$AgNTf_2$ (1.1%/1%)	DCE, 40 °C, 0.5 M	8 h	trace	-	0
7	**L4**AuCl/$AgNTf_2$ (1.1%/1%)	DCE, 40 °C, 0.5 M	8 h	6%	5	0
8	**L2**AuCl/$AgNTf_2$ (1.1%/1%)	DCE, 40 °C, 0.5 M	8 h	trace	-	0
9	**L5**AuCl/$AgNTf_2$ (1.1%/1%)	DCE, 40 °C, 0.5 M	8 h	trace	-	0
10	**L3**AuCl/$AgNTf_2$ (1.1%/1%)	DCE, 40 °C, 0.5 M	8 h	89%	80	7%
11	**L6**AuCl/$AgNTf_2$ (1.1%/1%)	DCE, 40 °C, 0.5 M	8 h	89%	80	7%
12	**L3**AuCl/$AgNTf_2$ (0.11%/0.1%)	DCE, 40 °C, 0.5 M	8 h	67%	609	0
13	**L6**AuCl/$AgNTf_2$ (0.11%/0.1%)	DCE, 40 °C, 0.5 M	8 h	91%	827	2%
14	**L6**AuCl/$AgNTf_2$ (220/200 ppm)	DCE, 40 °C, 1 M	12 h	37%	1681	0
15	**L7**AuCl/$AgNTf_2$ (220/200 ppm)	DCE, 40 °C, 1 M	12 h	27%	1227	0
16	**L8**AuCl/$AgNTf_2$ (220/200 ppm)	DCE, 40 °C, 1 M	12 h	35%	1590	0
17	**L9**AuCl/$AgNTf_2$ (220/200 ppm)	DCE, 40 °C, 1 M	12 h	36%	1636	0
18	**L10**AuCl/$AgNTf_2$ (220/200 ppm)	DCE, 40 °C, 1 M	12 h	43%	1954	0
19	**L10**$AuNTf_2$ (200 ppm)	DCE, 40 °C, 1 M	12 h	47%	2350	0
20	**L10**$AuNTf_2$ (50 ppm)/NaBARF (0.12%)	DCE, 80 °C, 2 M	12 h	85%	17000	0
21	**L10**$AuNTf_2$ (50 ppm)/NaBARF (0.12%)	PhCl, 80 °C, 2 M	12 h	93%	18600	0
22	**L10**$AuNTf_2$ (40 ppm)/NaBARF (0.12%)	PhF, 80 °C, 2 M	12 h	97%	24250	0
23	**L10**$AuNTf_2$ (25 ppm)/NaBARF (0.12%)	PhF, 80 °C, 2 M	12 h	86%	34400	0
24	**L10**AuCl (50 ppm)/NaBARF (0.12%)	PhF, 80 °C, 2 M	12 h	68%	13600	0
25	$JohnPhosAuNTf_2$(500 ppm)/ NaBARF (0.12%)	PhF, 80 °C, 2 M	12 h	2%	40	0

[a] The NMR yield is calculated by assuming that the triplet at around 0.9 ppm corresponds to the terminal methyl groups of all compounds derived from 2-dodecyne. NaBARF, sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate; DCE, 1,2-dichloroethane.

With little success in terms of other functional groups at the 3' position, the reaction optimization was then focused on modifying the amide *N*-substituents of **L6**. A family of ligands with different amide *N*-substituent, morpholine (**L7**), *N,N*-diethylamine (**L8**), *N,N*-diisopropyl amine (**L9**) and pyrrolidine (**L10**) were prepared to compare the efficiency; the results are shown in entries 15-19. **L10** turned out to be the most efficacious ligand, and **L10**AuNTf$_2$ afforded a TON of 2350 for 200 ppm loading, which was slightly higher than the combination of **L10**AuCl/AgNTf$_2$.

Table 2. C=O Stretching Wavelengths of Carbonyls in Ligands and Catalysts.

	L	$\nu_{C=O}$ (**L**)	$\nu_{C=O}$ (**L**AuCl)	TON
L7	$N(CH_2)_2O$	1639	1634	1350
L8	NEt_2	1635	1629	1750
L9	N^iPr_2	1634	1628	1800
L6	$N(CH_2)_5$	1630	1625	1850
L10	$N(CH_2)_4$	1628	1620	2150

A qualitative inverse correlation between the reaction yields and the wavenumbers of the amide carbonyl stretch band ($\nu_{C=O}$) of both the ligands and the corresponding gold complexes (Table 2) is revealed. The lower $\nu_{C=O}$ is, the more basic the carbonyl

oxygen of the amide group is and hence the stronger H-bond acceptor it is. Therefore, the tendency of the reaction yields positively correlate to the H-bond acceptor capacity of the amide carbonyl oxygens. This qualitative trend is consistent with the ligand design that demands the remote functional group to recruit the nucleophile via H-bonding.

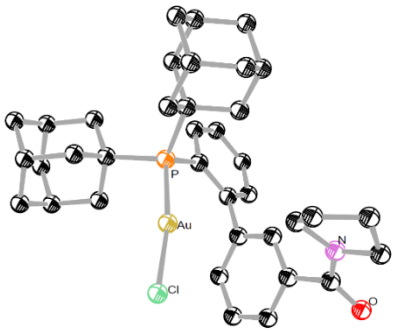
However, the reaction couldn't go to completion with 200 ppm **L10**$AuNTf_2$ even longer reaction time and higher temperature was provided. We suspected that the gold catalyst was deactivated or trapped by some coordinating anionic impurities possibly from the solvent. The crude product was analyzed and the results supported our speculation: no **L10**$AuNTf_2$ was detected after the reaction but a major peak of **L10**AuCl was observed in both ^{31}PNMR and ESI^+. The chloride could come from the leak of the solvent, 1,2-dichloroethane, under thermal condition after long reaction time.

Neat condition was then tried, however the result was even worse; it seemed that the solvent was necessary and possibly helped the hydrogen-bonding formation. Then different additives were tried to scavenge the Au catalyst, including $AgNTf_2$, AgOTf, $AgSbF_6$, NaOTf, KPF_6 and NaBARF (sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate. While silver salts tended to produce more benzoic anhydride **2-2a** which might indicate silver activates enol motif of the product toward the attack from benzoic acid, NaOTf and KPF_6 didn't help the reaction potentially due to their low solubility in relatively non-polar organic solvent. Much to our delight, NaBARF reactivated the catalyst without producing any side-products: 50 ppm

L10 AuNTf$_2$ plus 0.12 mol % NaBARF gave the desired product 2-dodecenyl benzoate **2-1a** in 85% yield and the TON was increased to 17000 (entry 20) at 80 °C under a little bit more concentrated condition (2 M).

Different solvents were also screened; none of the polar solvents (THF, 1,4-dioxane, ethyl acetate or acetone) gave promising result. Chlorobenzene (TON of 18600) performed a little bit better than 1,2-dichloroethane, but not as well as fluorobenzene, which achieved a TON of 24250 with almost full conversion (entries 21 and 22). Further decreasing the catalytic loading to 25 ppm allowed the TON to increase to 34400 (entry 23), but unfortunately the reaction couldn't go any further after 12 more hours. Interestingly, when **L10**AuCl was used instead of **L10**AuNTf$_2$, the TON was only 13600 (entry 24); presumably that's because the BARF ion is extremely weakly coordinating counterion so that the lifetime of the corresponding Au catalyst was significantly shorter than **L10**AuNTf$_2$. As a result, the overall efficiency of **L10**AuCl/NaBARF was less than **L10**AuNTf$_2$/NaBARF in spite of a higher reactivity. In comparison, under the same conditions a catalyst TON of 40 was reached for JohnPhosAuNTf$_2$ (entry 25). By considering that *t*-butyl and 1-adamantyl have similar steric bulk, the rate acceleration of 860 fold by **L10**AuNTf$_2$ over JohnPhosAuNTf$_2$ can be attributed to the mere incorporation of the remote 3'-amide group. The structure of the ligand **L10** is confirmed by the X-ray diffraction study of its gold complex **L10**AuCl. Thanks to Zhixun Wang for growing this single crystal.

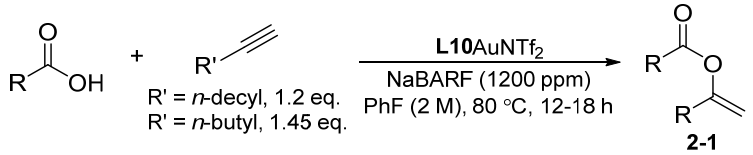
Figure 5. The ORTEP Drawing of L10AuCl at 50% Ellipsoid Probability

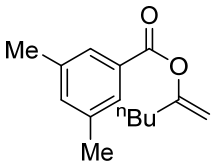
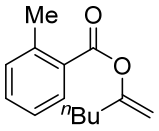
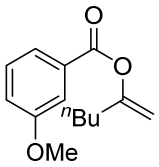
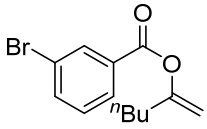
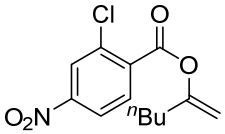
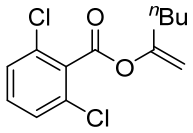
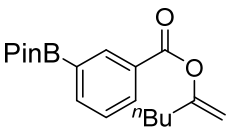
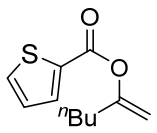
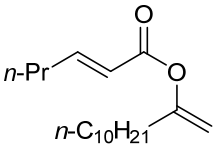
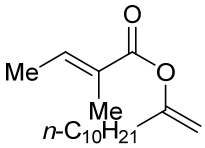
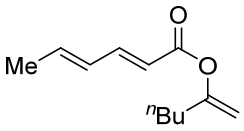
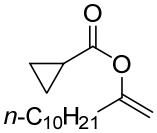
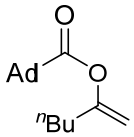
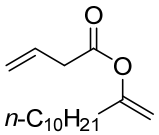
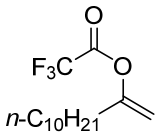
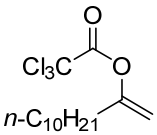
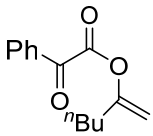
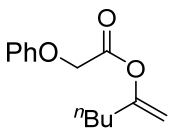
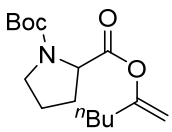
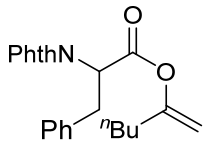


2.2.2. The Reaction Scope with Ultra-Low Catalyst Loadings

With the low sub-micromolar catalysis realized, its applicability to other carboxylic acids was first examined using 1-hexyne or 1-dodecyne as the alkyne partner. As shown in Table 3, various acids possessing a diverse range of functional groups were allowed, mostly resulting in nearly quantitative yields while with a catalyst loading of 100 ppm or less. For benzoic acids, substituents could be electron-withdrawing groups (3,5-dimehtyl/**2-1b**, 2-methyl/**2-1c**, 3-methoxyl/**2-1d**) and electron-donating groups (3-Bromo/**2-1e**, 2-Chloro-4-Nitro/**2-1f**, 2,6-dichloro/**2-1g**, 3-B(Pin)/**2-1h**) without affecting the reaction efficiency. Thiophene-2-carboxylic acid, enoic acids and dienoic acid (i.e., **2-1j**, **2-1k**, **2-1i**, **2-1l**) all proceeded very smoothly to give corresponding enol esters.

Table 3. Reactions of Various Acids with 1-Hexyne or 1-Dodecyne [a]



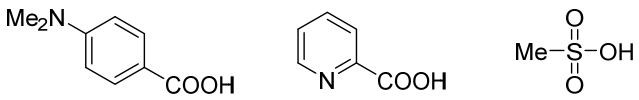
			
2-1b, 99%	**2-1c**, 99%	**2-1d**, 99%	**2-1e**, 99%
(65 ppm Au)	(60 ppm Au)	(100 ppm Au)	(75 ppm Au)
			
2-1f, 99%	**2-1g**, 99%	**2-1h**, 99%	**2-1i**, 99%
(75 ppm Au)	(50 ppm Au)	(150 ppm Au)	(50 ppm Au)
			
2-1j, 97%	**2-1k**, 96%	**2-1l**, 99%	**2-1m**, 99%
(100 ppm Au)	(100 ppm Au)	(65 ppm Au)	(75 ppm Au)
			
2-1n, 99%	**2-1o**, 98%	**2-1p**, 99%	**2-1q**, 99%
(100 ppm Au)	(80 ppm Au)	(10 ppm Au, 60 °C)	(20 ppm Au)
			
2-1r, 99%	**2-1s**, 99%	**2-1t**, 80%	**2-1u**, 99%
(75 ppm Au)	(100 ppm Au)	(600 ppm Au)	(150 ppm Au)

[a] Reactions run under N_2 in oven dried vial; isolated yield; NaBARF, sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

For alkyl carboxylic acids, cyclopropanecarboxylic acid, sterics-demanding 1-adamentanecarboxylic acid, acidity-sensitive vinyl acetic acid and 2-phenoxyacetic acid (i.e., **2-1m**, **2-1n**, **2-1o**, **2-1s**) reacted very well. While trichloroacetic acid (**2-1q**) only required 20 ppm catalyst to finish the reaction, more acidic trifluoroacetic acid only necessitated 10 ppm catalyst for full conversion (**2-1p**), giving a catalyst TON of at least 99,000. The reaction of phenylglyoxylic acid gave satisfying result too (**2-1r**). Whereas the reaction of *N*-Boc proline leading to **2-1t** require higher catalyst loading, the reaction of *N*-phthalimide phenylalanine afforded **2-1u** in 99% yield with only 150 ppm Au catalyst.

Relatively basic *N,N*-dimethyl aniline motif could be also tolerated with slightly more gold catalyst loading, but picolinic acid did not work at all. This is a common limitation in Au catalysis: substrates containing basic pyridine motif are often not suitable for most reactions. At the same, methanesulfonic acid gave very complicated results.

Figure 6. Other Acid Substrates

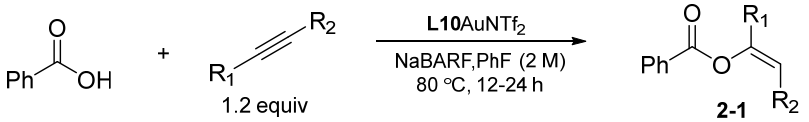


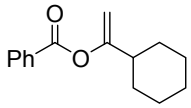
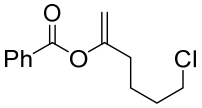
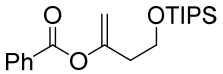
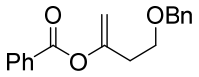
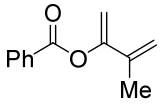
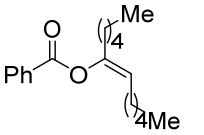
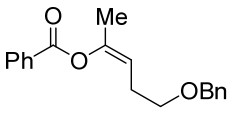
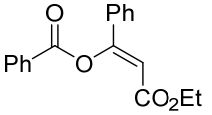
89%
900 ppm Au
(No NaBARF)

N.R.

very messy

Table 4. Reactions of Various Alkynes with Benzoic Acid [a]



		
2-1v, 99% (100 ppm Au)	**2-1w**, 95%, (300 ppm Au) no NaBARF, 40 °C	**2-1x**, 98%, (120 ppm Au)
		
2-1y, 89%, (150 ppm Au)	**2-1z**, 97%, (1500 ppm Au) 2 equiv. alkyne, 60 °C	**2-1aa**, 99%, (1500 ppm Au)
		
2-1ab, 85%, (500 ppm Au) 2.8:1	**2-1ac**, 98%, (150 ppm Au)	

[a] Reactions run under N_2 in oven dried vial; isolated yield; NaBARF, sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

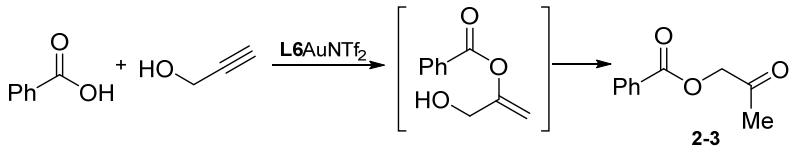
The scope of different alkynes was then probed using simple benzoic acid. As shown in

Table 4, terminal alkynes with different functionalities and protecting groups (Cl, OTIPS, OBn) were all suitable substrates and the reaction yields were mostly near to quantitative (i.e., **2-1v**, **2-1w**, **2-1x**, **2-1y**). Notably in the case of 6-chloro-1-hexyne, NaBARF does not help the reaction, possibly due to the potential interaction between

the chloro group and sodium ion of NaBARF. In the cases of an enyne (i.e., **1z**) and non-activated internal alkynes (i.e., **1aa** and **1ab**), the catalyst loadings were relatively high, likely due to lower reactivities of these substrates in comparison to aliphatic terminal alkynes; on the other hand, the activated internal alkyne ethyl 3-phenylpropiolate reacted pretty well to give **2-1ac** in 98% yield.

In the early stage of this research, I found out an interesting outcome: when propargyl alcohol was subjected to the reaction condition, the reaction did not stopped at the point of initial formation of enol ester, and went to further giving α-benzoyloxy ketone **2-3** as the final product.

Scheme 45. Propargyl Alcohol as the Substrate



2.2.3. Discussion

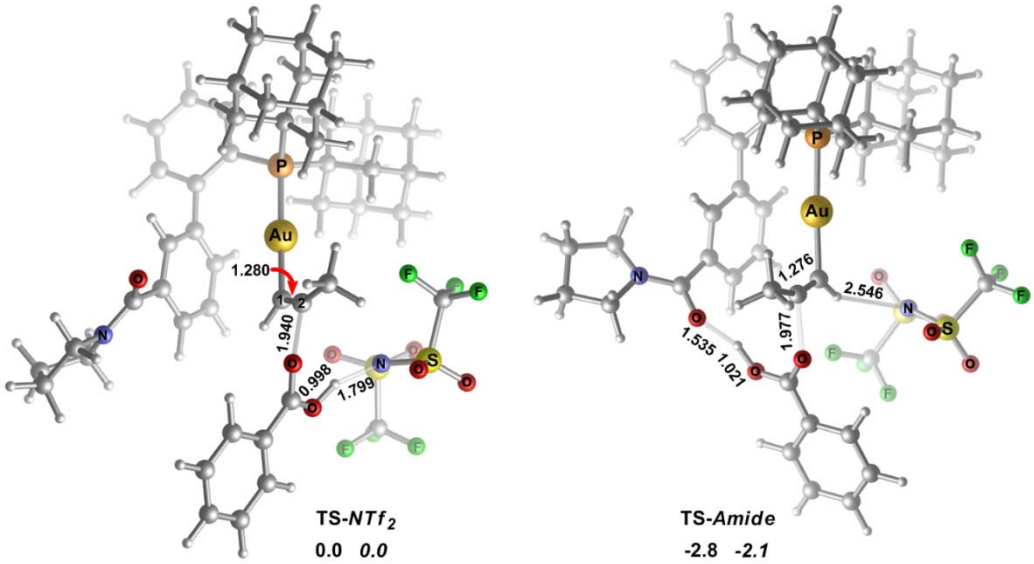
This dramatic increase of catalyst TON in this gold catalyzed reaction using the remotely amide-functionalized **L10** as ligand can be attributed to the H-bonding between the basic amide group on the ligand and the approaching carboxylic acid. This interaction not only allows the reaction to happen in a *quasi*-intramolecular fashion and hence decrease the entropy loss in the transition state, but also materializes a general base catalysis by basic amide moiety, via which the nucleophilicity of the acid is

enhanced. Moreover, the protonated amide motif after the initial attack should serve as an intramolecular proton source for the subsequent rapid protodeauration and therefore accelerate turnover frequency of the catalyst.

To authenticate this rationale and, hence, to offer theoretical support to our original design, density functional theory (DFT) [26,27] studies were performed with GAUSSIAN09 program and PBE1PBE[28,29] method by Dr. Yuxue Li. In the calculation, the ligand **L10**, one molecule of benzoic acid and one molecule of propyne were used; moreover, 6-31+G** basis set was used for the reactants, the NTf_2^- anion and the 3'-(pyrrolidin-l-ylcarbonyl) group, 6-311+G** basis set was used for P, 6-31G* basis set was used for other atoms in the ligand, and the SDD basis set with an Effective Core Potential (ECP)[30] was used for Au. Geometry optimization was performed in dichloroethane using the SMD[31] method. Harmonic vibration frequency calculations were carried out and each of the optimized transition states has one imaginary frequency.

We proposed that, in the catalytic reaction with JohnPhos as the ligand, the NTf_2^- counter anion will activate the benzoic acid and assist the proton transfer process. [32-34] However, in the catalytic reaction with **L10** the amide group is a better alternative to the NTf_2^- anion. To facilitate the comparison of these two scenarios, a reaction pathway using **L10** as the ligand but without involving its 3'-amide group was used to mimic the case of JohnPhos.

Figure 7. The Optimized NTf_2^- Anion Activated Transition State TS-*NTf_2* and Amide Group Activated Transition State TS-*Amide*. (The selected bond lengths are in angstroms, the relative energies ΔE_{sol} and free energies ΔG_{sol} (in italic, 298K) in dichloroethane are in kcal/mol.)



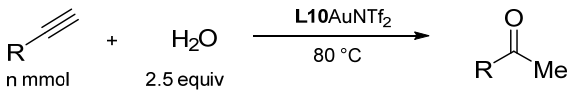
As shown in Figure 7, in the transition state **TS-*NTf_2***, the NTf_2^- anion stabilize the proton of the benzoic acid while its carbonyl oxygen attacks the C2 of propyne; notably, the amide group is a bystander. In **TS-*Amide***, the amide group stabilizes the proton, and the NTf_2^- anion is far away from the reaction center, binding to the system via weak hydrogen bonds. The **TS-*Amide*** is 2.1 kcal/mol more favorable in free energy than **TS-*NTf_2***, consistent with the experimental observation that **L10** is a better ligand than JohnPhos. In addition, in **TS-*Amide*** NTf_2^- does not participate in the reaction and hence needs not to be bound. [34] Such a binding in **TS-*Amide*** causes rigid body translational and rotational entropy loss, which was estimated to be 3.6~4.8

kcal/mol for the binding of small molecules to protein.[35] Based on this estimation, **TS-*Amide*** should be more than 5 kcal/mol more favorable than **TS-*NTf_2***, which is in line with the observed 860 fold increase of the TONs as the estimated energy barrier difference is around 4.7 kcal/mol if the TON difference is treated as the rate difference. These theoretical studies corroborate that the basic amide group and the intramolecular nature of the reaction are critical for the much improved TONs.

2.2.4. Scope of Nucleophiles and Synthetic Applications

Besides carboxylic acids, the remote amide group in **L10** can also facilitate nucleophilic attack by H_2O, resulting in substantially accelerated hydration of alkynes. As shown in Table 5, when the reaction was performed in toluene, a non-polar solvent which probably helps the formation of the H-bonding between the reacting partners, with only 2.5 equivalents of H_2O existing in the reaction, **L10** turned out to be a much more effective ligand than the non-functionalized 2-biphenyphosphine ligand JohnPhos and the NHC ligand IPr; the same trend was observed with methanol serving as the solvent, and notably without optimization the hydration was easily accomplished with 100 ppm of **L10**$AuNTf_2$ and a catalyst TON of at least 10,000. Remarkably IPrAu(I), which was utilized in hydration of alkynes with ppm catalyst loading at very high temperature (120 °C), presented much lower activity at lower temperature (80 °C).

Table 5. Gold-Catalyzed Hydration of Alkyne

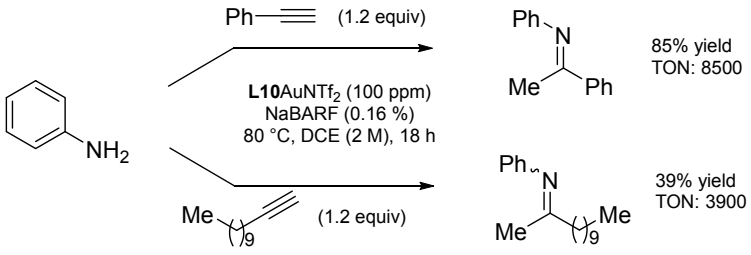


catalyst	yield[a]/**TON**	
	R = *n*-decyl, [Au] (500 ppm), toluene (0.25 x **n** mL), 5 h	R = *n*-butyl, [Au] (100 ppm), MeOH (0.3 x **n** mL), 6 h
JohnPhosAuNTf$_2$	8%/**160**	44%/**4400**
IPrAuNTf$_2$	9%/**180**	69%/**6900**
L10 AuNTf$_2$	38%/**760**	100%/**10000**

[a] NMR yields using diethyl phthalate as the internal reference

To further validate the generality of this ligand with remote amide group, hydroamination of alkynes with aniline was performed. As shown in Scheme 46, using **L10**AuNTf$_2$ as the catalyst, its turnover number with phenylacetylene as the substrate reached 8500, a nevertheless pleasing number even though lower than that (i.e., 22000) achieved by the best catalyst developed by LaVallo;[3] however, with 1-dodecyne as the substrate, **L10**AuNTf$_2$ was a much better catalyst than the one by LaVallo as its TON reached 3900 while a TON of 435 is reported in the latter case with a similar 1-hexyne as the substrate. These results achieved from both hydration and hydroamination of alkynes again highlight the essential role of the remote amide group, and more importantly suggest that the design principle is general and flexible enough to be applicable to other transformations.

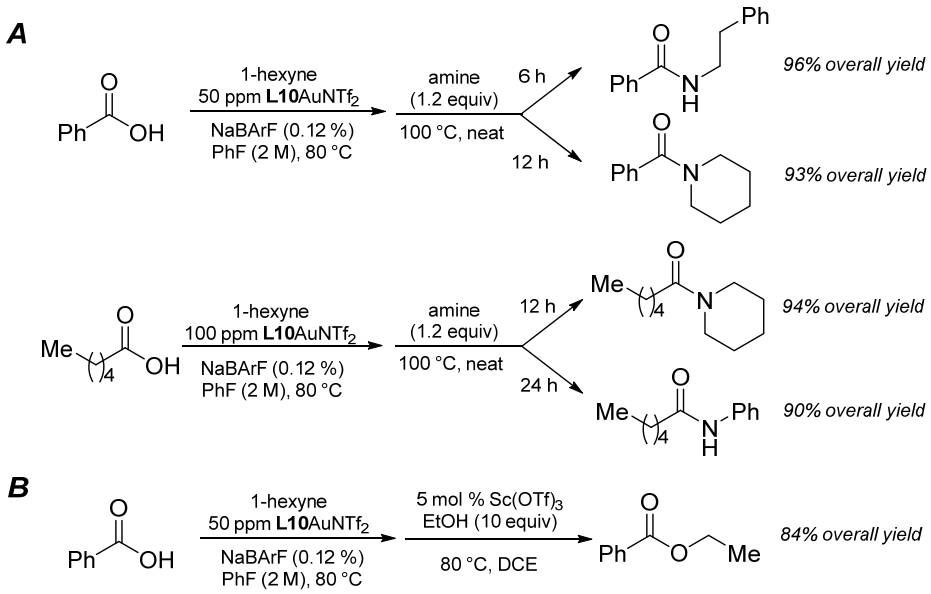
Scheme 46. Gold-Catalyzed Hydroamination of Alkynes



The synthetic utility of this chemistry is firstly exemplified by a two-step, high yielding synthesis of amides (Scheme 47-A), where the gold catalysis offered mild activation of carboxylic acids in a highly efficient manner. For the most part, amide-forming reactions involve "activating" the carboxylic acid and the best known method is the Schotten-Baumann reaction, which need convert the acids to acid chlorides first; toxic and corrosive thionyl chloride or oxalyl chloride is required. In the second step, more than one equivalent base has to be used to quench the hydrochloric acid generated during the reaction. None of above is following the principles of green chemistry, which is becoming more and more important in the future development of society. The other well-known way, DCC coupling, however, often suffered from the one equivalent waste produced during the process, which also increase the difficulty of isolation at the same time. Now I could start from carboxylic acids, generating enol esters very efficiently with ultra-low catalyst loading without purification in many cases, and then react with amines to afford corresponding amides with non-toxic, volatile and easily removed ketone as the only by-product. Moreover, the fact that the above two-step, one-pot reaction can be run in high concentration (2M for the first step

and no solvent for the second step), which significantly decreases the usage of organic solvents, also makes this synthetic sequence more interesting and attractive.

Scheme 47. Application in Amide and Ester Synthesis [a]



[a] Isolated yields. NaBARF, sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate; DCE, 1,2-dichloroethane.

In addition to amide synthesis, I wondered whether esters could be synthesized in the same way. Much to my delight, the above two-step/one-pot synthetic route also applied well to the synthesis of ester: with little optimization, the corresponding ethyl ester was formed in 84% overall yield. 5 mol % Lewis acid $Sc(OTf)_3$ was necessitated for the second step and ten equivalents of ethanol needed to be used to obtain decent yield (Scheme 47-B). Again, this synthetic sequence stands a green and mild way to couple carboxylic acid and alcohol.

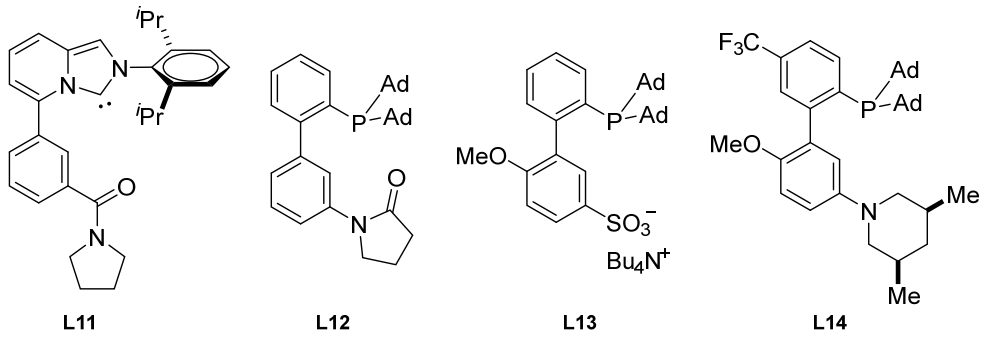
2.2.5. Conclusion

In summary, a novel ligand design that could dramatically improve the turnover frequency of gold catalysis has been successfully realized based on the privileged biphenylphosphine platform. It engages functional groups at the remote 3' position to direct and promote the *anti* attack of natural nucleophiles to the gold-activated alkynes, which is unprecedented in homogeneous gold catalysis, especially considering the spatial challenge of using ligand to reach *anti*-approaching nucleophile in a linear L-Au-alkyne centroid structure. With a basic, H-bond accepting (pyrrolidin-1-yl)carbonyl group at the 3' position, the gold(I) complex derived from the biphenylphosphine ligand becomes highly efficient in catalyzing acid addition to alkynes, with its TON up to 99,000. DFT calculations support the role of the amide moiety in directing the attack of carboxylic acid via H-bonding. Further applications of this catalyst to hydration and hydroamination of alkynes likewise realized high catalyst TONs, therefore confirming the general applicability of this ligand design. We anticipated that this design and the general principle of engaging bonding interactions between ligand and reactants could be employed to substantially improve an array of other gold catalyses, thereby promoting the application of gold chemistry in industrial scale processes, and might also be useful for improving catalysis by other transition metals.

2.3. Other Ligand-Promoted Interesting Transformations

During the process of ligand design, I also prepared the following ligands (Figure 8) and some of them do provide very exciting activities.

Figure 8. Other New Interesting Ligands



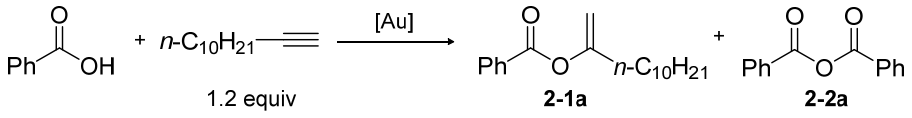
2.3.1. Acid Addition: Results of L11/L12Au(I)

It's known that bulky NHC ligand IPr provides incredible thermal stability for gold catalyst, so **L11**, a new type of carbene ligand with remote 3'-amide as the directing group, was prepared to achieve both stability and reactivity. Although a TON of 700 (Table 6, entry 1)was obtained for **L11**Au(I) for catalyzing acid addition to the alkyne, which was much better compared with IPr (TON of 0.5 at 40 °C), the catalyst is still not as good as **L10**Au(I) presumably due to the following two reactions: 1) carbene ligand is more electron-rich, which makes the corresponding gold catalyst less cationic and reactive; 2) the liner carbene-Au-alkyne axis is aligning far away from instead of paralleling to the pendant phenyl ring of **L11**Au(I), as a

result of which, the Au-activated alkyne might be more difficult to reach when the amide directs the acid to attack.

Compared with JohnPhosAu(I), which gave trace product under same condition, **L12**Au(I) afforded 23% yield with a TON of 23 (Table 6, entry 2), further confirming the directing effect of the functional group on the ortho phenyl ring, although the position of the carbonyl group on **L12** was probably not ideal.

Table 6. Other Ligand Effect for Acid Addition



entry	[Au]	solvent, temperature, conc.	time	NMR yield [a]		
				1a	TON	**2a**
1	**L11**AuCl/AgNTf$_2$ (0.11%/0.1%)	DCE, 80 ˚C, 1 M	19 h	70%	700	3%
2	**L12**AuCl/AgNTf$_2$ (1.1%/1%)	DCE, 40 ˚C, 0.5 M	6 h	23%	23	38%

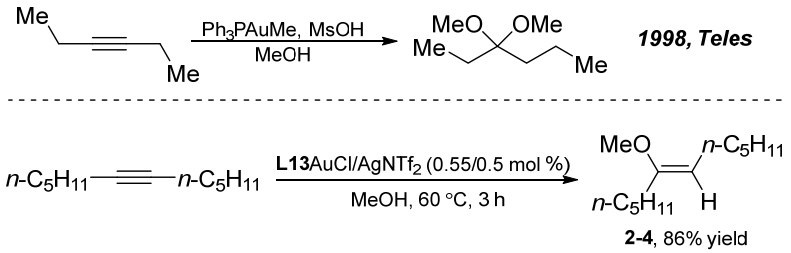
[a] The NMR yield is calculated by assuming that the triplet at around 0.9 ppm corresponds to the terminal methyl groups of all compounds derived from 2-dodecyne.

2.3.2. Alcohol Addition

Alkenyl ethers are versatile building blocks in organic synthesis and they are supposed be easy to obtain by the alcohol addition to alkyne under gold catalysis. However, as Teles et al.[36] reported in 1998, after the first alcohol addition, it was rather difficult to stop the reaction at the alkenyl ether stage and hence the second alcohol came to attack, gives the ketal as the final product. Again, by ligand design, a

breakthrough has been made in this area (Scheme 48). **L13** features a sulfonate functional group at 5' position, and the methoxy group at 2' position is for the easy installation and basicity enhancement of the sulfonate group. Its corresponding gold catalyst afforded the desired alkenyl methyl ether **2-4** in 86% NMR yield with 0.55 mol % loading after 3 h when 6-dodecyne was the substrate. Once the alkyne switched to terminal alkyne, unfortunately, ketal was the only product ever observed and quantitative yield was obtained at room temperature after 1 h even excess alkyne was used. It means more engineering work needs to be done about **L13**.

Scheme 48. Ligand Controlled Alcohol Addition to Alkyne



2.3.3. Alkyne Isomerization

Zhixun Wang recently found out that terminal alkyne **2-5** could isomerize to give 55% allene **2-6**, 12% internal alkyne **2-6'** with 19% staring material left when 3'-amino **L4**Au(I) was used in the reaction (Scheme 49-A). To increase the acidity of Au and basicity of amino group, I prepared **L14**, the enhanced version of **L4**. The structure of the ligand **L14** is confirmed by the X-ray diffraction study of its gold

complex **L14**AuCl (Figure 9), whose single crystal was grown in a mixture solvents of methylene chloride and acetonitrile.

Scheme 49. Ligand Promoted Gold Catalyzed Alkyne Isomerization

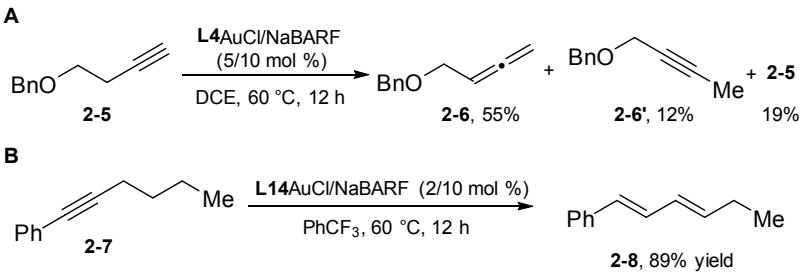
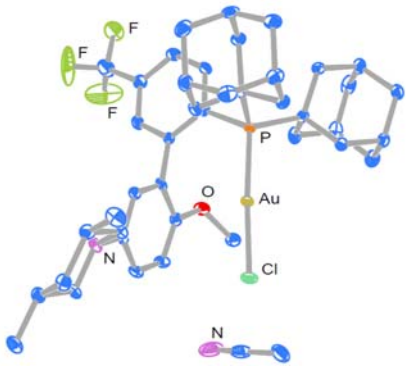


Figure 9. The ORTEP Drawing of L14AuCl at 50% Ellipsoid Probability

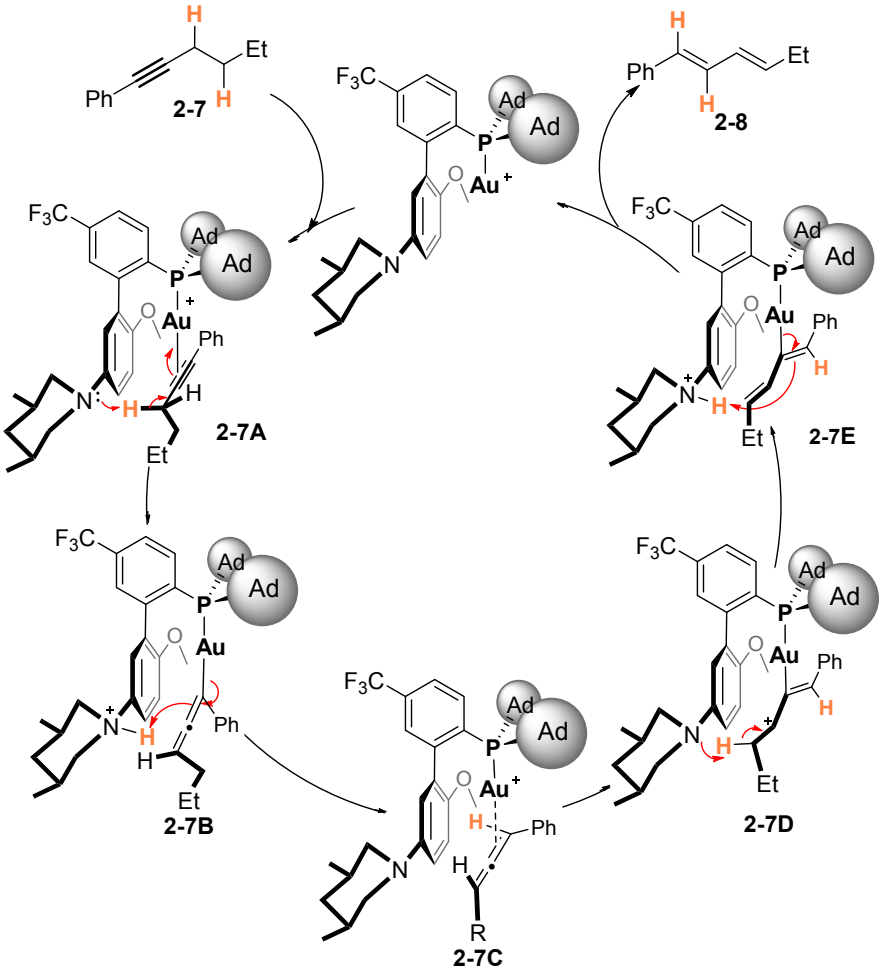


By using **L14**AuCl and NaBARF, we found out aryl internal alkynes **2-7** easily isomerized to afford 1,3-diene **2-8** in 89% isolated yield, which is very impressive. To explain this unusual reactivity, we proposed a mechanism in Figure 10 using **2-7** as the substrate: the coordination of alkyne **2-7** to **L14**Au^{+}, as shown in the structure **2-7A**, would force one of the propargylic hydrogen (shown in bold and colored) close to the basic aniline nitrogen and moreover, the C–H bond more or less parallel to $\pi_{\perp}$* and

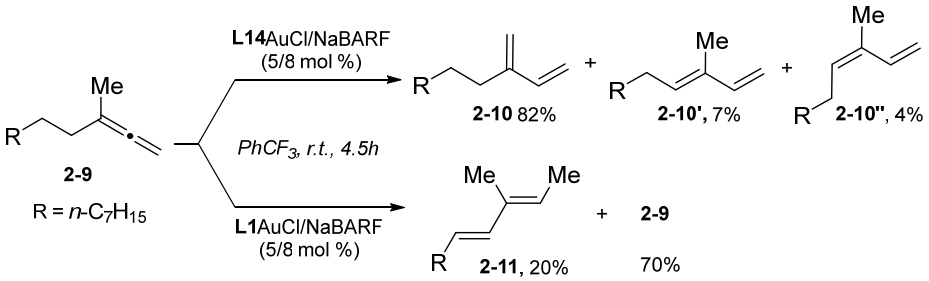
hence perpendicular to the Au-alkyne centroid; With the concerted 'pull' by cationic gold and 'push' by the ideally aligned nitrogen, propargylic deprotonation would occur even with such a weak base (pK_a in DMSO ~ 4). The resulting allenylgold intermediate **2-7B** could undergo *ipso*-protodeauration to deliver the gold allene complex **2-7C**. It is notable that the aniline nitrogen serves as an intramolecular proton shuttle in these two steps. If the allene substituents could stabilize a developing carbocation, it is conceivable that an equilibrium between **2-7C** and a gold-substituted allylic cation (i.e., **2-7D**) would be established. The latter structure would place a C–H bond, which is α to the allyl cation moiety (shown in bold and colored), near the aniline nitrogen once again. A consequential intramolecular deprotonation would then afford the dienylgold complex **2-7E**, which could undergo internal *ipso*-protodeauration to afford the diene product **2-8** and regenerate the catalyst **L14**Au$^+$.

During the mechanistic study, I found out an interesting phenomenon: when the substrate is allene, by using different catalysts, it could isomerize to different dienes (Scheme 50). When 3'-amino **L14**Au(I) was used, allene 2-9 was converted to terminal diene **2-10** in very high yield even at room temperature after 4.5 h, while 4'-amino **L1**Au(I) provided a different product, internal diene **2-11** in 20% yield with 70% starting material left after the same reaction time. More mechanistic study is on the way in our lab.

Figure 10. Proposed Mechanism for Alkyne Isomerization



Scheme 50. Ligand Effect on Allene Isomerization



2.4. Experimental Section

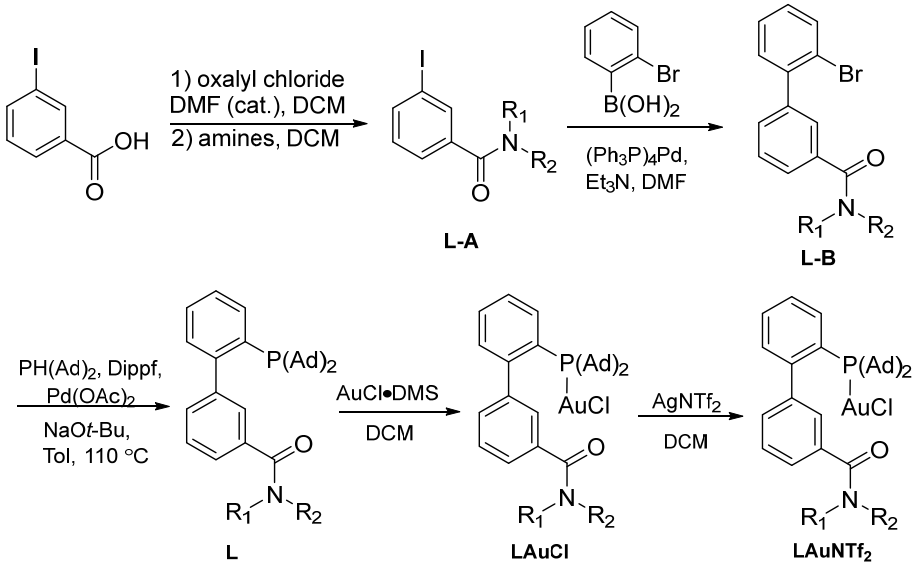
General. Ethyl acetate (ACS grade), hexanes (ACS grade), diethyl ether (ACS grade), were purchased from Fisher Scientific and used without further purification. Anhydrous 1,2-dichloroethane were bought from Acros and used directly. Fluorobenzene was purchased from Synquest Labs, Inc and distilled over P_2O_5 before use. Most commercially available carboxylic acids below 99.5% purify were recrystallized from distilled Fluorobenzene, and all commercially available alkynes were distilled over $NaBH_4$ before use. NaBARF was purchased from Synquest Labs and dried by heating to 100 °C under high vacuum for overnight. Reactions were monitored by thin layer chromatography (TLC) using Silicycle precoated silica gel plates. Flash column chromatography was performed over Silicycle silica gel (230-400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 500/600 MHz Unity plus spectrometer and a Varian 400 MHz spectrometer using residue solvent peaks as internal standards ($CDCl_3$, ^{1}H: 7.26 ppm; ^{13}C: 77.00 ppm). Infrared spectra were recorded with a Perkin Elmer FT-IR spectrum 2000 spectrometer and are reported in reciprocal centimeter (cm-1). Mass spectra were recorded Micromass QTOF2 Quadrupole/Time-of-Flight Tandem mass spectrometer by electrospray method.

General Procedure A: Synthesis of Ligands and Catalysts

As shown in Scheme 51, to a dispersion of 10 mmol 3-iodobenzoic acid (1 equiv) in 50 mL dry CH_2Cl_2 was added 25 mmol oxalyl chloride (2.5 equiv) and three drops

of DMF, and the mixture was stirred for 2 - 4 h at room temperature. The reaction mixture was evaporated under reduced pressure and dried under vacuum to yield 3-iodobenzoyl chloride, which was dissolved in 50 mL dry CH_2Cl_2 again and cooled in an ice bath. A 10 mL CH_2Cl_2 solution containing 15 mmol amine (1.5 equiv) and 20 mmol Et_3N (2 equiv) was then added and the reaction mixture was stirred at room temperature under a nitrogen atmosphere. After 1 h, the solution was treated with 50 mL water and 100 mL DCM, and the organic phase was separated, dried, evaporated, and then purified by column chromatography to yield compound **L-A** in 90 - 95% yield.

Scheme 51. General Procedure for Synthesis of Ligands and Catalysts [a]



[a] DMF, *N*, *N*-dimethylformamide; DCM, dichloromethane; Dippf, bis(diisopropylphosphinyl)ferrocene; Tol, toluene; DMS, dimethylsulfide.

A mixture of 8 mmol **L-A** (1 equiv), 8.8 mmol 2-bromophenylboronic acid (1.1 equiv) and 24 mmol Et_3N (3 equiv) in 40 mL DMF was stirred and bubbled with N_2

gas for 15 minutes, and then 0.4 mmol $Pd(PPh_3)_4$ (5 mol %) was added; the reaction mixture was heated at 90 °C for 4 - 8 h under nitrogen atmosphere. Once TLC indicated **A** was completely consumed, the reaction was diluted with 500 mL Et_2O and washed with water to remove DMF. Then the organic layer was dried over MgSO4, filtrated, evaporated, and then purified by column chromatography to yield product **L-B** in 85 - 92% yield.

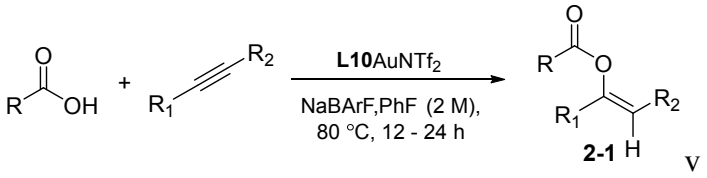
Under nitrogen atmosphere 2 mmol **L-B** (1 equiv), 0.1 mmol $Pd(OAc)_2$ (5 mol%), 0.12 mmol DiPPF (1,1'-bis(diisopropylphosphino)ferrocene, 6 mol%), 2.4 mmol NaOt-Bu (1.2 equiv) and 5 mL dry Toluene were added to a flamed dried Schlenk flask and the resulting suspension was stirred until apparently homogeneous (around 15 min). Added 2.2 mmol di(1-adamantyl)phosphine (1.1 equiv), the flask was heated at 110 °C in oil bath for 12 h, which then was cooled to room temperature, and purified by column chromatography without work-up to yield the final ligand **L** in 60 – 80% yield.

To a suspension of 1 mmol ligand **L** in 5 mL anhydrous DCM was added chloro(dimethylsulfide)gold(I) (294.5 mg, 1 mmol). The mixture was stirred for 30 min at room temperature and the solvent was evaporated off under reduced pressure to give the desired gold complex **L**AuCl in quantitative yield.

To a solution of 0.8 mmol ligand **L** in 4 mL anhydrous DCM was added Silver bis(trifluoromethanesulfonyl)imide (309 mg, 0.8 mmol). The mixture was stirred for 20 min at room temperature and the precipitating silver chloride was filtered. The solvent was evaporated off under reduced pressure to give the desired gold complex

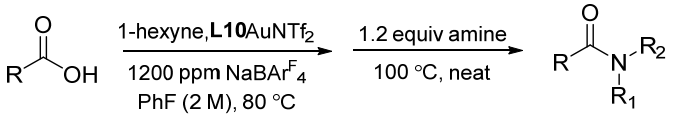
LAuNTf$_2$ in quantitative yield.

General Procedure B: Preparation of Enol Esters



In a sealed 1 dr reaction vial equipped with a magnetic stirring bar, 3 mmol carboxylic acids (1 equiv), 4.4 mmol 1-hexyne (1.45 equiv) or 3.6 mmol other alkynes (1.2 equiv) and 3.1 mg NaBARF (1200 ppm) were added to 0.6 mL fluorobenzene**. L10**AuNTf$_2$ (50 μL of a 3.09 mg/mL solution in PhF, 0.150 μmol, 50 ppm) was added to the above vial and then the reaction mixture was heated at 80 ºC for 12 - 24 h. Once the reaction finished by TLC, it was concentrated and left on the high vacuum pump for overnight to give the NMR pure product. If crude NMR was not pure, the residue was further purified through silica gel flash chromatography to give the desired product.

General Procedure C: One-pot Sequence Preparation of Amides

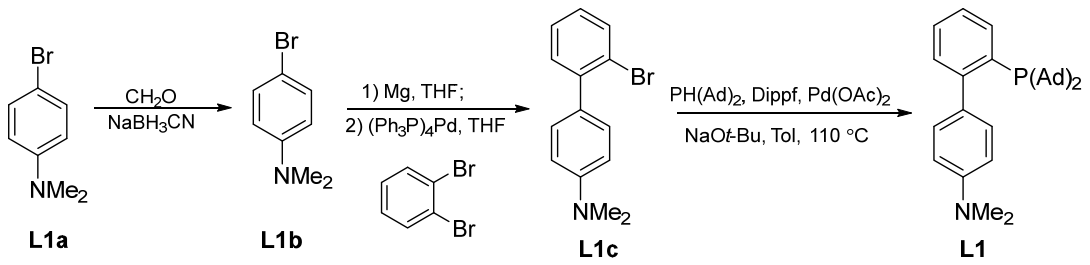


In a sealed 1 dr reaction vial equipped with a magnetic stirring bar, 3 mmol carboxylic acids (1 equiv), 4.4 mmol 1-hexyne (1.45 equiv) and 3.1 mg NaBARF (1200 ppm) were added to 0.6 mL fluorobenzene**. L10**AuNTf$_2$ (50 μL of a 3.09 mg/mL solution in PhF, 0.150 μmol, 50 ppm or 100 μL, 100 ppm) was added to the

above vial and then the reaction mixture was heated at 80 ºC for 12 - 18 h. Once the reaction finished by TLC, it was concentrated and left on the high vacuum pump for overnight to give the crude product, followed by adding 3.6 mmol amine (1.2 equiv) and stirring at 100 ºC for 6 - 24 h. Once the reaction completed by TLC, the mixture was purified through silica gel flash chromatography (eluents: ethyl acetate: hexanes = 1: 3) to give the desired product.

L1

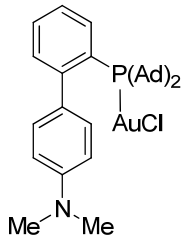
Scheme 52 Synthesis of Aniline Ligand L1



4-Bromo-*N,N*-dimethylaniline **L1b** was prepared according to the literature procedure[37] and biaryl compound **L1c** was obtained by using same literature procedure.[38] Ligand **L1** was then synthesized in 67% yield through general procedure A, step 3. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, J = 7.6 Hz, 1H), 7.35 (t, J = 7.3 Hz, 1H), 7.31 – 7.23 (m, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.75 – 6.70 (m, 2H), 3.00 (s, 6H), 1.90 (q, J = 12.2 Hz, 18H), 1.66 (s, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.00 (d, J = 32.1 Hz), 148.83, 136.62 (d, J = 2.9 Hz), 133.19 (d, J = 26.3 Hz), 132.23 (d, J = 7.1 Hz), 131.29 (d, J = 3.9 Hz), 131.06 (d, J = 6.0 Hz), 128.08, 124.62, 111.21, 41.88 (d, J = 13.1 Hz), 40.52, 37.28 (d, J = 25.9 Hz), 36.97, 28.86 (d, J = 8.5 Hz). ^{31}P NMR (162 MHz,

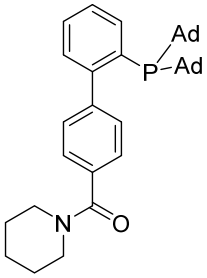
$CDCl_3$) δ 22.35 IR (neat): 3047, 2902, 2847, 1612, 1522, 1450, 1343, 1301, 1224, 1194, 1166, 1047, 970, 947, 814, 768, 743; HRMS ESI (*m/z*): $[MH]^+$ calcd. for $C_{34}H_{45}NP$, 498.3290; found, 498.3280.

L1AuCl



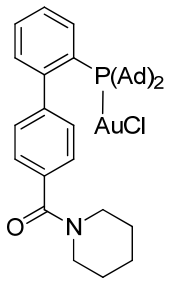
Au complex **L1AuCl** was obtained in quantitative yield according to general procedure A, step 4. ^1H NMR (600 MHz, $CDCl_3$) 7.83 (t, *J* = 7.5 Hz, 1H), 7.46 (dt, *J* = 23.5, 7.6 Hz, 2H), 7.36 – 7.29 (m, 1H), 6.97 (d, *J* = 8.1 Hz, 2H), 6.87 (s, 2H), 3.05 (s, 6H), 2.24 – 2.05 (m, 12H), 1.98 (s, 6H), 1.67 (s, 12H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 151.06, 134.35, 133.85 (d, *J* = 7.7 Hz), 130.27, 129.90, 129.66 (d, *J* = 7.8 Hz), 125.94 (d, *J* = 6.5 Hz), 124.12 (d, *J* = 45.1 Hz), 113.37 (d, *J* = 61.3 Hz), 42.45 (d, *J* = 23.5 Hz), 42.09 (d, *J* = 2.5 Hz), 36.25, 28.57 (d, *J* = 9.8 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 62.87. IR (neat): 2904, 2849, 2798, 1611, 1523, 1448, 1347, 1301, 1223, 1166, 1126, 1045, 972, 913, 815, 773, 744; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{34}H_{45}AuClNPNa$, 752.2463; found, 752.2448.

L3



Ligand **L3** was synthesized through general procedure A. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.5 Hz, 1H), 7.40 – 7.31 (m, 4H), 7.26 (t, *J* = 3.9 Hz, 3H), 7.22 (ddd, *J* = 7.3, 4.0, 1.7 Hz, 1H), 3.72 (bs, 2H), 3.47 (bs, 2H), 1.85 (q, *J* = 12.7 Hz, 18H), 1.67 (m, 18 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.57, 150.98 (d, *J* = 32.7 Hz), 145.27 (d, *J* = 6.9 Hz), 136.62 (d, *J* = 2.6 Hz), 133.78, 133.11 (d, *J* = 29.0 Hz), 130.68 (d, *J* = 4.1 Hz), 130.50 (d, *J* = 6.2 Hz), 128.19, 125.94, 125.53, 48.84, 43.26, 41.80 (d, *J* = 13.0 Hz), 37.34 (d, *J* = 26.2 Hz), 36.89, 28.78 (d, *J* = 8.6 Hz), 26.53, 25.72, 24.67. ^{31}P NMR (162 MHz, $CDCl_3$) δ 20.64. IR (neat): 2911, 2861, 1627, 1443, 1347, 1274, 1157, 1023, 751; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{38}H_{48}NOPNa$, 588.3371; found, 588.3395.

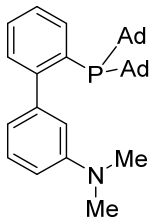
L3AuCl



Au complex **L3AuCl** was obtained in quantitative yield according to general procedure A, step 4. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 – 7.84 (m, 1H), 7.50 (d, *J* = 7.7 Hz, 4H), 7.16 (t, *J* = 7.5 Hz, 3H), 4.05 – 3.60 (m, 4H), 2.26 – 2.09 (m, 12H), 2.01 (s, 6H), 1.69 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.85, 150.07 (d, *J* = 13.0 Hz), 143.89 (d, *J* = 6.3 Hz), 136.25, 134.36 (d, *J* = 2.3 Hz), 133.94 (d, *J* = 7.5 Hz), 130.48 (d, *J* = 2.3 Hz), 129.68, 127.68, 126.44 (d, *J* = 6.4 Hz), 123.03 (d, *J* = 43.5 Hz), 49.77, 43.41, 42.66 (d, *J* = 23.9 Hz), 42.13 (d, *J* = 2.5 Hz) , 36.23, 28.57 (d, *J* = 9.8 Hz), 36.97, 25.78, 24.74. ^{31}P NMR (162 MHz, $CDCl_3$) δ 62.19. IR (neat): 2911, 2851,

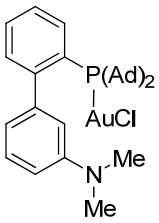
1627, 1443, 1347, 1274, 1157, 1023, 751; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $_{38}H_{48}AuClNNaOP$, 820.2725; found, 820.2709.

L4



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.5 Hz, 1H), 7.40 – 7.27 (m, 3H), 7.24 – 7.18 (m, 1H), 6.74 – 6.67 (m, 1H), 6.62 – 6.55 (m, 2H), 2.95 (s, 6H), 1.90 (q, *J* = 12.2 Hz, 18H), 1.65 (s, 12H).). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.63 (d, *J* = 32.5 Hz), 149.27, 144.77 (d, *J* = 7.5 Hz), 136.45 (*J* = 3.8 Hz), 133.10 (d, *J* = 26.3 Hz), 130.41 (d, *J* = 6.2 Hz), 127.96, 127.70, 125.08, 119.16 (d, *J* = 3.0 Hz), 115.72 (d, *J* = 3.6 Hz), 110.65, 42.00, 41.95 (d, *J* = 13.1 Hz), 37.18 (d, *J* = 26.0 Hz), 36.98, 28.87 (d, *J* = 8.5 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.26. IR (neat): 2901, 2847, 1602, 1584, 1498, 1449, 1343, 1301, 1047, 991, 955, 762, 743; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{34}H_{44}NPNa$, 520.3109; found, 520.3088.

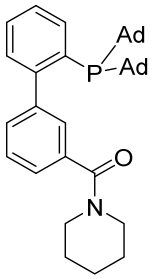
L4AuCl



Au complex **L4AuCl** was obtained in quantitative yield according to general procedure A, step 4. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (t, *J* = 7.6 Hz, 1H), 7.48 (dt, *J* = 21.5, 7.4 Hz, 2H), 7.37 – 7.33 (m, 1H), 7.28 (bs, 1H), 6.93 (bs, 1H), 6.60 – 6.30

(m, 2H), 3.01 (s, 6H), 2.27 – 2.05 (m, 12H), 1.98 (d, J = 21.1 Hz, 6H), 1.67 (d, J = 20.9 Hz, 12H).^{13}C NMR (125 MHz, $CDCl_3$) δ 151.42, 142.81, 134.24 (d, J = 2.3 Hz), 133.12 (d, J = 7.3 Hz), 130.17, 129.14, 125.95 (d, J = 6.2 Hz), 123.90, 123.55, 117.48, 113.95, 112.69, 42.31 (d, J = 45.5, 45 Hz), 42.14 (dd, J = 45.5, 2.7 Hz), 40.84, 36.28 (d, J = 8.2 Hz), 28.58 (dd, $J_1 = J_2$ = 9.9 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 62.61. IR (neat): 2904, 2849, 2803, 1600, 1585, 1500, 1450, 1431, 1355, 1344, 1301, 1260, 1178, 1163, 1124, 1045, 990, 972, 842, 770, 733; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{34}H_{44}AuClNPNa$, 754.2463; found, 754.2451.

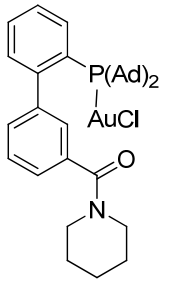
L6



Ligand **L6** was synthesized through general procedure A. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 – 7.84 (m, 1H), 7.41 – 7.31 (m, 4H), 7.29 (ddd, J = 7.3, 2.6, 1.6 Hz, 1H), 7.26 – 7.23 (m, 1H), 7.20 (d, J = 1.6 Hz, 1H), 3.71 (s, 2H), 3.47 (s, 2H), 1.85 (q, J = 11.9 Hz, 18H), 1.69 – 1.39 (m, 18H).^{13}C NMR (125 MHz, $CDCl_3$) δ 170.52, 150.92 (d, J = 32.3 Hz), 143.70 (d, J = 7.1 Hz), 136.53 (d, J = 2.6 Hz), 135.31, 132.92 (d, J = 27.9 Hz), 132.10 (d, J = 4.7 Hz), 130.58 (d, J = 6.1 Hz), 128.41 (d, J = 3.1 Hz), 128.37 (d, J = 1.1 Hz), 127.29, 125.65, 125.02, 48.95, 43.12, 41.89 (d, J = 12.9 Hz), 37.41 (d, J = 25.5 Hz), 36.91, 28.79 (d, J = 8.6 Hz), 26.68, 25.62, 24.63. ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.12. IR (neat): 2901, 2847, 1630, 1443, 1343, 1300, 1265, 1228, 1110, 1026, 1002,

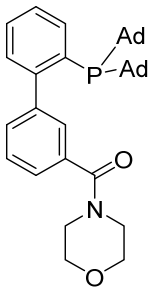
970, 907, 826, 809, 765, 731; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{38}H_{48}NOPNa$, 588.3371; found, 588.3361.

L6AuCl



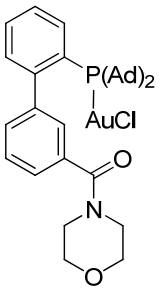
Au complex **L6AuCl** was obtained in quantitative yield according to general procedure A, step 4. ^1H NMR (600 MHz, $CDCl_3$) δ 7.88 – 7.82 (m, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.52 – 7.45 (m, 3H), 7.31 – 7.27 (m, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.11 (s, 1H), 3.86 – 3.53 (m, 4H), 2.28 – 1.91 (m, 18H), 1.84 – 1.42 (m, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.05, 149.81 (d, *J* = 12.9 Hz), 142.54 (d, *J* = 6.6 Hz), 136.66, 134.29, 134.27, 133.57 (d, *J* = 7.3 Hz), 130.50 (d, *J* = 2.2 Hz), 130.35, 129.05, 127.38, 126.70, 126.53 (d, *J* = 6.6 Hz), 123.49 (d, *J* = 43.9 Hz), 49.33, 43.16, 42.61 (*J* = 37.5 Hz, 23.8 Hz), 42.16 (dd, *J* = 55.0, 2.6 Hz) 36.25, 36.23, 36.22, 28.54 (dd, *J* = 15.1, 9.8 Hz),26.78, 25.75, 24.66. ^{31}P NMR (162 MHz, $CDCl_3$) δ 62.26. IR (neat): 2906, 2851, 2231, 1625, 1444, 1344, 1301, 1253, 1228, 1109, 1042, 1002, 972, 915, 852, 804, 772, 729; HRMS ESI (*m/z*): $[MNa]^+$ calcd. $C_{38}H_{48}AuClNNaOP$, 820.2725; found, 820.2717.

L7



Ligand **L7** was synthesized through general procedure A. ^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 5.2, 3.7 Hz, 1H), 7.45 – 7.33 (m, 4H), 7.31 – 7.27 (m, 1H), 7.25 – 7.19 (m, 2H), 3.86 – 3.39 (m, 8H), 1.84 (dd, *J* = 29.2, 9.6 Hz, 18H), 1.64 (q, *J* = 12.6 Hz, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.64, 150.66 (d, *J* = 32.2 Hz), 143.89 (d, *J* = 7.1 Hz), 136.54 (d, *J* = 2.7 Hz), 134.04, 132.87 (d, *J* = 27.6 Hz), 132.44 (d, *J* = 4.1 Hz), 130.54 (d, *J* = 6.1 Hz), 128.71 (d, *J* = 3.8 Hz), 128.44 (d, *J* = 1.1 Hz), 127.62, 125.81, 125.33, 67.02, 48.51, 42.48, 41.92 (d, *J* = 12.8 Hz), 37.43 (d, *J* = 25.2 Hz), 36.89, 28.76 (d, *J* = 8.6 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.17. IR (neat): 2902, 2848, 1639, 1450, 1301, 1273, 1166, 1115, 1018, 807, 743; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{37}H_{46}NO_2PNa$, 590.3164; found, 590.3174.

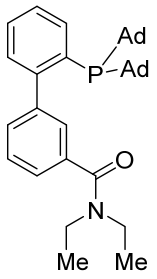
L7AuCl



Au complex **L7AuCl** was obtained in quantitative yield according to general procedure A, step 4. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 – 7.84 (m, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.54 – 7.46 (m, 3H), 7.30 – 7.26 (m, 1H), 7.18 – 7.10 (m, 2H), 4.03 –

3.48 (m, 8H), 2.27 – 2.13 (m, 6H), 2.04 (dd, *J* = 44.5, 13.8 Hz, 12H), 1.75 – 1.59 (m, 12H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.11, 149.56 (d, *J* = 12.9 Hz), 142.81 (d, *J* = 6.4 Hz), 135.49, 134.32, 133.53 (d, *J* = 7.3 Hz), 130.82, 130.57 (d, *J* = 2.1 Hz), 129.11, 127.69, 127.07, 126.66 (d, *J* = 6.6 Hz), 123.48 (d, *J* = 43.8 Hz), 67.55, 66.88, 48.80, 48.67, 42.65 (dd, *J* = 30.6, 23.7 Hz), 42.19 (d, *J* = 45.5 Hz), 36.23 (d, *J* = 8.0 Hz), 28.52 (dd, *J* = 16.5, 9.8 Hz). ^{31}P NMR (162 MHz, $CDCl_3$) δ 62.31. IR (neat): 2908, 2851, 1738, 1634, 1460, 1347, 1302, 1264, 1157, 1114, 1045, 799, 748; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{37}H_{46}AuClNNaO_2P$, 822.2518; found, 822.2507.

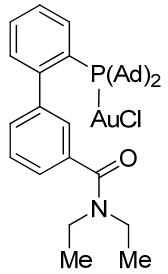
L8



Ligand **L8** was synthesized through general procedure A. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.5 Hz, 1H), 7.41 – 7.33 (m, 3H), 7.33 – 7.25 (m, 3H), 7.22 (s, 1H), 3.49 (m, 4H), 1.96 – 1.78 (m, 18H), 1.70 – 1.52 (m, 12H), 1.36 – 0.98 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.46, 150.89 (d, *J* = 32.1 Hz), 143.63 (d, *J* = 7.0 Hz), 136.54 (d, *J* = 2.6 Hz), 135.91, 132.90 (d, *J* = 28.0 Hz), 131.67 (d, *J* = 4.4 Hz), 130.56 (d, *J* = 6.1 Hz), 128.50 (d, *J* = 3.9 Hz), 128.40 (d, *J* = 1.0 Hz), 127.23, 125.63, 124.31, 43.36, 41.88 (d, *J* = 12.9 Hz), 39.12, 37.39 (d, *J* = 25.7 Hz), 36.89, 28.76 (d, *J* = 8.6 Hz), 14.28, 12.97. ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.01. IR (neat): 2902, 2847, 1635, 1449, 1345,

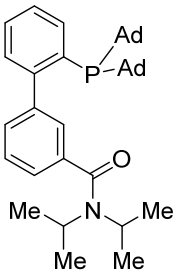
1303, 1218, 1100, 970, 767, 731; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{37}H_{48}NOPNa$, 576.3371; found, 576.3395.

L8AuCl



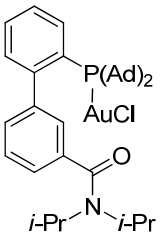
Au complex **L8AuCl** was obtained in quantitative yield according to general procedure A, step 4. ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 – 7.79 (m, 1H), 7.54 – 7.44 (m, 4H), 7.32 (dd, *J* = 9.1, 4.3 Hz, 1H), 7.16 (d, *J* = 7.4 Hz, 1H), 7.11 (s, 1H), 3.84 – 3.29 (m, 4H), 2.34 – 2.16 (m, 6H), 2.16 – 1.93 (m, 12H), 1.78 – 1.52 (m, 12H), 1.18 (dt, *J* = 45.6, 7.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.17, 149.86 (d, *J* = 12.6 Hz), 142.68 (d, *J* = 6.3 Hz), 137.60, 134.29 (d, *J* = 2.3 Hz), 133.71 (d, *J* = 7.4 Hz), 130.53 (d, *J* = 2.3 Hz), 130.23, 129.01, 127.00, 126.51 (d, *J* = 6.6 Hz), 126.00, 123.46 (d, *J* = 43.8 Hz), 43.62, 42.61 (dd, *J* = 46.3, 23.6 Hz), 42.18 (dd, *J* = 60.1, 2.6 Hz) 39.13, 36.24, 28.54 (dd, *J* = 17.8, 9.8 Hz) 14.54, 12.86. ^{31}P NMR (162 MHz, $CDCl_3$) δ 62.36. IR (neat): 2908, 2851, 1629, 1451, 1346, 1302, 1159, 1071, 1046, 771, 747; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{37}H_{48}AuClNNaOP$, 808.2725; found, 808.2700.

L9



Ligand **L9** was synthesized through general procedure A. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.5 Hz, 1H), 7.41 – 7.31 (m, 3H), 7.31 – 7.26 (m, 2H), 7.22 (dt, *J* = 7.4, 1.4 Hz, 1H), 7.17 (t, *J* = 1.5 Hz, 1H), 4.2 – 3.2 (m, 2H), 1.94 – 1.78 (m, 18H), 1.70 – 1.59 (m, 12H), 1.59 – 0.9 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.24, 151.01 (d, *J* = 32.1 Hz), 143.90 (d, *J* = 6.9 Hz), 137.85, 136.58 (d, *J* = 2.7 Hz), 132.76 (d, *J* = 27.9 Hz), 131.57 (d, *J* = 5.3 Hz), 130.78 (d, *J* = 6.2 Hz), 128.38 (d, *J* = 1.1 Hz), 127.43 (d, *J* = 2.6 Hz), 126.95, 125.54, 123.40, 50.72, 45.91, 41.89 (d, *J* = 12.9 Hz), 37.41 (d, *J* = 25.6 Hz), 36.90, 28.80 (d, *J* = 8.6 Hz), 20.79. ^{31}P NMR (162 MHz, $CDCl_3$) δ 21.17. IR (neat): 2905, 2849, 1738, 1634, 1445, 1373, 1340, 1212, 1158, 1041, 768; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{39}H_{52}NOPNa$, 604.3684; found, 604.3694.

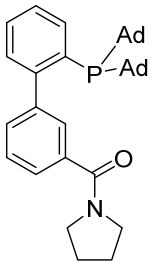
L9AuCl



Au complex **L9AuCl** was obtained in quantitative yield according to general procedure A, step 4. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (t, *J* = 7.9 Hz, 1H), 7.50 (q, *J* = 6.0, 4.2 Hz, 2H), 7.47 – 7.41 (m, 2H), 7.31 (t, *J* = 5.1 Hz, 1H), 7.12 (d, *J* = 7.0 Hz, 1H), 7.02 (s, 1H), 4.53 (bs, 1H), 3.49 (bs, 1H), 2.29 – 2.18 (m, 6H), 2.14 – 2.00 (m, 12H), 1.96 (s, 3H), 1.77 – 1.45 (m, 15H), 1.30 – 1.19 (m, 3H), 1.08 – 0.96 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.95, 149.94 (d, *J* = 13.1 Hz), 142.76 (d, *J* = 6.5 Hz), 139.05, 134.25, 133.68 (d, *J* = 7.3 Hz), 130.45, 129.59, 129.10, 126.46 (d, *J* = 6.5 Hz), 126.31, 124.97, 123.46 (d, *J* = 43.9 Hz), 51.38, 45.92, 42.53 (d, *J* = 93.5 Hz,

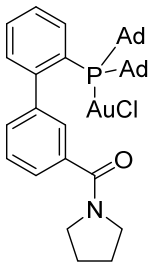
23.6 Hz), 42.17 (d, J = 82.5 Hz), 36.24, 28.54 (dd, J = 27.1, 9.8 Hz), 21.07, 20.67, 20.53. ^{31}P NMR (162 MHz, $CDCl_3$) δ 62.37. IR (neat): 2917, 2850, 1736, 1628, 1577, 1540, 1448, 1373, 1343, 1301, 1211, 1105, 1019, 973, 772, 747, 710; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{39}H_{52}AuClNNaOP$, 836.3038; found, 836.3021.

L10



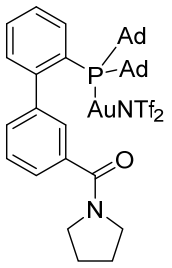
Ligand **L10** was synthesized through general procedure A. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 – 7.85 (m, 1H), 7.48 (dt, J = 7.6, 1.4 Hz, 1H), 7.42 – 7.31 (m, 4H), 7.29 (d, J = 7.6 Hz, 1H), 7.25 – 7.21 (m, 1H), 3.65 (t, J = 7.0 Hz, 2H), 3.53 (t, J = 6.6 Hz, 2H), 2.00 – 1.78 (m, 22H), 1.72 – 1.55 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.91, 150.94 (d, J = 32.3 Hz), 143.51 (d, J = 7.0 Hz), 136.52 (d, J = 2.7 Hz), 136.01, 132.93 (d, J = 27.7 Hz), 132.33 (d, J = 4.3 Hz), 130.60 (d, J = 6.1 Hz), 128.90 (d, J = 3.6 Hz), 128.35 (d, J = 1.1 Hz), 127.25, 125.65, 125.31, 49.90, 46.04, 41.89 (d, J = 12.9 Hz), 37.35 (d, J = 25.5 Hz), 36.90, 28.78 (d, J = 8.6 Hz), 26.40, 24.54. ^{31}P NMR (162 MHz, $CDCl_3$) δ 22.10. IR (neat): 2901, 2847, 1628, 1424, 1342, 1301, 1253, 1162, 1047, 971, 921, 808, 767, 730; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{37}H_{46}NOPNa$, 574.3215; found, 574.3214.

L10AuCl



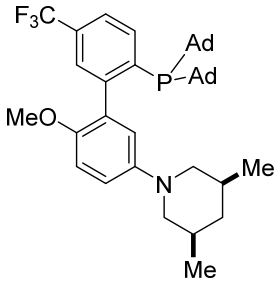
L10 AuCl was synthesized through general procedure A, step 4. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (t, *J* = 8.1 Hz, 1H), 7.69 (d, *J* = 7.8 Hz, 1H), 7.54 – 7.42 (m, 3H), 7.29 (d, *J* = 18.1 Hz, 2H), 7.16 (d, *J* = 7.6 Hz, 1H), 3.93 – 3.53 (m, 4H), 2.30 – 1.79 (m, 22H), 1.73 – 1.59 (m, 12H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.23, 149.83 (d, *J* = 13.0 Hz), 142.46 (d, *J* = 6.4 Hz), 136.92, 134.28 (d, *J* = 2.4 Hz), 133.66 (d, *J* = 7.4 Hz), 130.94, 130.51 (d, *J* = 2.4 Hz), 128.61, 128.14, 127.22, 126.54 (d, *J* = 6.5 Hz), 123.52 (d, *J* = 43.7 Hz), 50.16, 46.42, 42.58 (dd, *J* = 23.7, 11.7 Hz), 42.16 (dd, *J* = 28.6, 2.6 Hz), 36.23, 28.54 (dd, *J* = 9.9, 7.1 Hz), 26.57, 24.43. ^{31}P NMR (162 MHz, $CDCl_3$) δ 62.32. IR (neat): 2906, 2851, 2232, 1620, 1598, 1575, 1442, 1344, 1301, 1259, 1198, 1104, 1045, 972, 914, 806, 772, 730; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{37}H_{46}AuClNNaOP$, 806.2569; found, 806.2565.

L10AuNTf$_2$



L10$AuNTf_2$ was synthesized through general procedure A, step 5. ^1H NMR (600 MHz, $CDCl_3$) δ 7.91 – 7.85 (m, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.62 – 7.53 (m, 3H), 7.35 (bs, 1H), 7.30 (d, *J* = 7.3 Hz, 1H), 7.24 (bs, 1H), 3.72 – 3.40 (m, 4H), 2.24 – 1.82 (m, 22H), 1.76 – 1.53 (m, 12H).^{13}C NMR (150 MHz, $CDCl_3$) δ 169.75, 148.81 (d, *J* = 10.6 Hz), 142.12, 136.21, 134.06, 133.59 (d, *J* = 7.4 Hz), 131.69, 131.29, 128.88, 127.66 (d, *J* = 87.8 Hz), 127.11 (d, *J* = 7.4 Hz), 121.30 (d, *J* = 44.7 Hz), 119.62 (dd, *J* = 324 Hz), 50.24, 46.92, 43.08 (d, *J* = 24.6 Hz), 42.14 (d, *J* = 38.5 Hz), 36.03, 28.48 (dd, *J* = 12.3, 10.2 Hz), 26.20, 24.24. ^{31}P NMR (162 MHz, $CDCl_3$) δ 61.10. IR (neat): 2908, 2853, 1622, 1596, 1575, 1451, 1354, 1229, 1196, 1138, 1061; HRMS ESI^+ (*m/z*): $[M\text{-}NTf_2]^+$ calcd. for $C_{37}H_{46}NOAuP$, 748.2983; found, 748.2975; ESI^- (*m/z*) $[M\text{-}L8Au]^-$ calcd. For $C_2NO_4S_2F_6$, 279.9173; found, 279.9159.

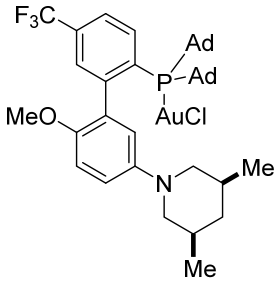
L14



^1H NMR ($CDCl_3$, 600 MHz, δ): δ 7.93 (d, *J* = 8.0 Hz, 1H), 7.54 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.50 (t, *J* = 2.5 Hz, 1H), 6.93 (dd, *J* = 8.6, 3.0 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 6.67 (d, *J* = 2.9 Hz, 1H), 3.67 (s, 3H), 3.10 – 2.91 (m, 4H). 2.00 – 1.87 (m, 9H), 1.87 -1.75 (m, 9H), 1.75 – 1.57 (m, 16H), 1.56 – 1.50 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 150 MHz, δ): 150.23, 149.08 (d, *J* = 35.1 Hz), 145.42, 139.49 (d, *J* = 30.6 Hz), 136.42 (d, *J* = 2.9 Hz), 131.52 (d, *J* =7.2 Hz), 130.00 (q, *J* = 32.2 Hz), 127.30 – 127.10 (m), 124.25

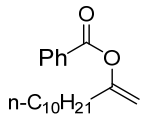
(q, J = 272.3 Hz), 123.00 (d, J = 2.1 Hz), 121.68 (d, J = 3.8 Hz), 117.26, 54.93, 52.30, 41.81 (dd, J = 66.9 Hz, 13.1 Hz), 37.12 (dd, J = 126 Hz, 26 Hz), 36.95 (d, J = 15.4 Hz), 28.85 (dd, J = 30 Hz, 8.6 Hz), 26.10, 24.23. ^{31}P NMR ($CDCl_3$, 162 MHz, δ): 19.89. ^{19}F NMR ($CDCl_3$, 376 MHz, δ): -66.69. MS ESI (*m/z*): $[MH]^+$ calcd. for $C_{39}H_{50}F_3NOP$, 636.36; found, 636.33.

L14AuCl



^{1}H NMR ($CDCl_3$, 600 MHz, δ): 7.96 (t, J = 7.4 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.53 (t, J = 2.6 Hz, 1H), 7.15 (bs, 1H), 6.88 (d, J = 9.0 Hz, 1H), 6.54 (bs, 1H), 3.65 (s, 3H), 3.10 (s, 2H), 2.21 – 2.08 (m, 12H), 2.00 (s, 6H), 1.71 – 1.61 (m, 18H), 1.53 (t, J = 6.3 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz, δ): 149.98, 148.66, 146.04, 134.59 (d, J = 2.6 Hz), 132.16 (q, J = 32.8 Hz), 130.30 - 130.00 (m), 129.61, 129.34, 123.47 (d, J = 273.1 Hz), 122.46, 120.85, 118.91, 112.50, 55.23, 51.94, 42.61 (dd, J = 28.1, 22.9 Hz), 42.15 (dd, J = 32.1, 2.8 Hz), 36.24 (dd, J = 5.5, 1.6 Hz), 28.59 (dd, J = 23.9, 9.9 Hz), 25.82, 24.16. ^{31}P NMR ($CDCl_3$, 162 MHz, δ): 57.59. ^{19}F NMR ($CDCl_3$, 376 MHz, δ): -67.23. MS ESI (*m/z*): $[MH]^+$ calcd. for $C_{39}H_{50}AuClF_3NOP$, 868.29; found, 868.30.

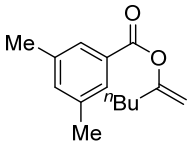
2-1a



99%
(50 ppm Au)

857 mg Compound **2-1a** was obtained in 99% yield according to general procedure B after chromatography (eluents: ethyl acetate: hexanes = 1: 30).^{1}H NMR ($CDCl_3$, 600 MHz, δ): 7.96 (t, *J* = 7.4 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.53 (t, *J* = 2.6 Hz, 1H), 7.15 (bs, 1H), 6.88 (d, *J* = 9.0 Hz, 1H), 6.54 (bs, 1H), 3.65 (s, 3H), 3.10 (s, 2H), 2.21 – 2.08 (m, 12H), 2.00 (s, 6H), 1.71 – 1.61 (m, 18H), 1.53 (t, *J* = 6.3 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 150 MHz, δ): 149.98, 148.66, 146.04, 134.59 (d, *J* = 2.6 Hz), 132.16 (q, *J* = 32.8 Hz), 130.30 - 130.00 (m), 129.61, 129.34, 123.47 (d, *J* = 273.1 Hz), 122.46, 120.85, 118.91, 112.50, 55.23, 51.94, 42.61 (dd, *J* = 28.1, 22.9 Hz), 42.15 (dd, *J* = 32.1, 2.8 Hz), 36.24 (dd, *J* = 5.5, 1.6 Hz), 28.59 (dd, *J* = 23.9, 9.9 Hz), 25.82, 24.16. ^{31}P NMR ($CDCl_3$, 162 MHz, δ): 57.59. ^{19}F NMR ($CDCl_3$, 376 MHz, δ): -67.23. MS ESI (*m/z*): $[MH]^+$ calcd. for $C_{39}H_{50}AuClF_3NOP$, 868.29; found, 868.30.

2-1b

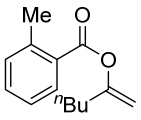


99%
(65 ppm Au)

693 mg Compound **2-1b** was obtained in 99% yield according to general procedure B without chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 2H), 7.23 (s, 1H), 4.83 (d, *J* = 0.5 Hz, 2H), 2.38 (d, *J* = 0.5 Hz, 6H), 2.35 (t, *J* = 7.5 Hz, 2H), 1.59 – 1.48 (m, 2H), 1.45 – 1.34 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ

165.07, 156.88, 138.09, 134.88, 129.73, 127.58, 101.16, 33.10, 28.64, 22.11, 21.11, 13.81. IR (neat): 3116, 2958, 2931, 2873, 2864, 1732, 1667, 1610, 1466, 1382, 1204, 867, 761; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{15}H_{20}O_2Na$, 255.1361; found, 255.1342.

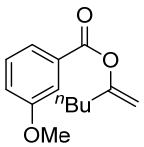
2-1c



99%
(60 ppm Au)

652 mg Compound **2-1c** was obtained in 99% yield according to general procedure B without chromatography. ^1H NMR (600 MHz, $CDCl_3$) δ 8.05 – 7.92 (m, 1H), 7.43 (td, *J* = 7.5, 1.3 Hz, 1H), 7.34 – 7.16 (m, 2H), 4.84 (dd, *J* = 6.1, 1.2 Hz, 2H), 2.64 (s, 3H), 2.35 (t, *J* = 7.5 Hz, 2H), 1.63 – 1.47 (m, 2H), 1.46 – 1.34 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.49, 156.79, 140.81, 132.31, 131.79, 130.86, 129.01, 125.75, 101.23, 33.15, 28.66, 22.10, 21.79, 13.82. IR (neat): 3072, 2957, 2932, 2873, 2864, 1735, 1666, 1603, 1458, 1383, 1294, 865, 737; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{14}H_{18}O_2Na$, 241.1204; found, 241.1199.

2-1d

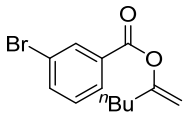


99%
(100 ppm Au)

698 mg Compound **2-1d** was obtained in 99% yield according to general procedure B without chromatography. ^1H NMR (600 MHz, $CDCl_3$) δ 7.71 – 7.64 (m, 1H), 7.59 (dd, *J* = 2.5, 1.5 Hz, 1H), 7.36 (dd, *J* = 10.3, 5.6 Hz, 1H), 7.12 (ddd, *J* = 8.2, 2.7, 0.8 Hz,

1H), 4.84 (dd, *J* = 15.3, 1.4 Hz, 2H), 3.85 (s, 3H), 2.34 (t, *J* = 7.8 Hz, 2H), 1.57 – 1.46 (m, 2H), 1.45 – 1.31 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.55, 159.55, 156.75, 131.14, 129.40, 122.24, 119.71, 114.25, 101.22, 55.36, 33.06, 28.61, 22.05, 13.78. IR (neat): 3078, 2957, 2932, 2873, 2864, 1735, 1666, 1586, 1488, 1466, 1432, 1278, 1213, 869, 750; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{14}H_{18}O_3Na$, 257.1154; found, 257.1151.

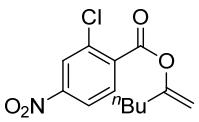
2-1e



99%
(75 ppm Au)

845 mg Compound **2-1e** was obtained in 99% yield according to general procedure B without chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (t, *J* = 1.8 Hz, 1H), 8.05 – 7.94 (m, 1H), 7.70 (ddd, *J* = 8.0, 2.0, 1.1 Hz, 1H), 7.34 (dd, *J* = 9.9, 5.9 Hz, 1H), 4.84 (dt, *J* = 3.7, 1.5 Hz, 2H), 2.33 (t, *J* = 7.5, 2H), 1.51 (tdd, *J* = 8.4, 7.3, 5.1 Hz, 2H), 1.38 (dq, *J* = 14.4, 7.3 Hz, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.36, 156.61, 136.15, 132.82, 131.81, 129.98, 128.43, 122.49, 101.47, 33.00, 28.59, 22.06, 13.78. IR (neat): 3070, 2959, 2932, 2873, 2864, 1737, 1668, 1571, 1468, 1423, 1291, 1251, 1233, 1173, 1116, 1067, 869, 806, 742; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{13}H_{15}BrO_2Na$, 305.0153; found, 305.0144.

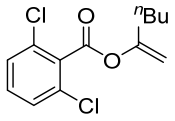
2-1f



99%
(75 ppm Au)

847 mg Compound **2-1f** was obtained in 99% yield according to general procedure B without chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (d, *J* = 2.2 Hz, 1H), 8.17 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.08 – 7.93 (m, 1H), 5.16 – 4.67 (m, 2H), 2.34 (t, *J* = 7.6 Hz, 2H), 1.57 – 1.47 (m, 2H), 1.38 (dq, *J* = 14.4, 7.3 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.18, 156.36, 149.49, 135.48, 134.90, 132.12, 126.00, 121.45, 101.90, 32.80, 32.80, 28.47, 28.47, 21.97, 21.97, 13.73, 13.73. IR (neat): 3041, 2959, 2931, 2873, 2864, 1745, 1668, 1590, 1528, 1467, 1388, 1348, 1280, 1220, 1127, 1042, 860, 764, 732; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{13}H_{14}ClNO_4Na$, 306.0509; found, 306.0508.

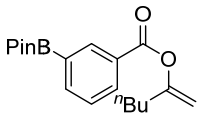
2-1g



99%
(50 ppm Au)

816 mg Compound **2-1g** was obtained in 99% yield according to general procedure B without chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 3H), 4.97 (d, *J* = 1.9 Hz, 1H), 4.88 (q, *J* = 1.3 Hz, 1H), 2.41 – 2.34 (m, 2H), 1.62 – 1.52 (m, 2H), 1.45 – 1.35 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) 162.82, 156.55, 133.28, 131.80, 130.98, 127.85, 101.94, 32.86, 28.42, 22.02, 13.79. IR (neat): 3087, 2959, 2933, 2874, 1756, 1670, 1586, 1565, 1434, 1381, 1272, 1225, 1196 1166, 1139, 1082, 1053, 931, 881, 802, 780, 746; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{13}H_{14}Cl_2O_2Na$, 295.0269; found, 295.0256.

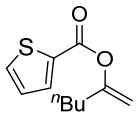
2-1h



99%
(150 ppm Au)

987 mg Compound **2-1h** was obtained in 99% yield according to general procedure B without chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (d, *J* = 18.9 Hz, 1H), 8.16 (dt, *J* = 7.8, 1.5 Hz, 1H), 8.01 (d, *J* = 7.4 Hz, 1H), 7.46 (dd, *J* = 9.3, 5.9 Hz, 1H), 4.93 – 4.71 (m, 2H), 2.35 (dd, *J* = 23.6, 16.1 Hz, 2H), 1.57 – 1.44 (m, 2H), 1.43 – 1.26 (m, 16H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.76, 156.84, 139.45, 136.05, 132.53, 129.26, 127.80, 101.17, 84.04, 43.36, 33.04, 28.58, 24.79, 22.07, 13.77. IR (neat): 3065, 2979, 2960, 2933, 2874, 1735, 1667, 1606, 1422, 1362, 1327, 1248, 1222, 1144, 965, 857, 753; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{18}H_{27}BO_4Na$, 353.1900; found, 353.1887.

2-1i

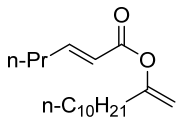


99%
(50 ppm Au)

627 mg Compound **2-1i** was obtained in 99% yield according to general procedure B without chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 – 7.80 (m, 1H), 7.68 – 7.51 (m, 1H), 7.19 – 7.05 (m, 1H), 4.87 (d, *J* = 1.3 Hz, 1H), 4.81 (s, 1H), 2.32 (t, *J* = 7.5 Hz, 2H), 1.70 – 1.48 (m, 2H), 1.45 – 1.25 (m, 2H), 0.91 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.16, 156.34, 134.03, 133.30, 132.92, 127.80, 101.38, 33.08, 28.55, 22.02, 13.77. IR (neat): 3116, 2956, 2932, 2873, 2864, 1725, 1667,

1524, 1417, 1254, 1071, 864,744; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{11}H_{14}O_4SNa$, 233.0612; found, 233.0605.

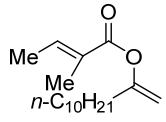
2-1j



97%
(100 ppm Au)

814 mg Compound **2-1j** was obtained in 97% yield according to general procedure B after chromatography (eluents: ethyl acetate: hexanes = 1: 30). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (dt, *J* = 15.6, 6.9 Hz, 1H), 5.85 (dt, *J* = 15.4, 1.5 Hz, 1H), 4.72 (d, *J* = 2.5 Hz, 2H), 2.25 – 2.15 (m, 4H), 1.55 – 1.42 (m, 4H), 1.33 – 1.21 (m, 14H), 0.94 (t, *J* = 7.3 Hz, 3H), 0.87 (t, *J* = 7.3 Hz, 3H) .^{13}C NMR (125 MHz, $CDCl_3$) δ 164.68, 156.58, 150.64, 120.88, 100.85, 100.84, 34.26, 33.37, 31.87, 29.55, 29.51, 29.34, 29.29, 28.97, 26.44, 22.65, 21.18, 14.06, 13.63. IR (neat): 3056, 2956, 2928, 2856, 1737, 1654, 1466, 1379, 1319, 1218, 1158, 1120, 983, 866; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{18}H_{32}O_2Na$, 303.2300; found, 303.2307.

2-1k

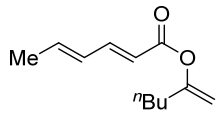


96%
(100 ppm Au)

766 mg Compound **2-1k** was obtained in 96% yield according to general procedure B after chromatography (eluents: ethyl acetate: hexanes = 1: 30). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (dddd, *J* = 8.4, 7.1, 5.8, 1.4 Hz, 1H), 4.78 – 4.58 (m, 2H), 2.23 (t, *J* = 7.5 Hz, 2H), 1.87 – 1.84 (m, 3H), 1.81 (dd, *J* = 7.1, 1.0 Hz, 3H), 1.49 – 1.41 (m, 2H),

1.34 (dq, J = 14.3, 7.1 Hz, 2H), 0.89 (t, J = 7.3 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.17, 156.88, 138.35, 128.39, 100.72, 33.07, 28.63, 22.06, 14.43, 13.79, 12.02. IR (neat): 3118, 2957, 2927, 2856, 1720, 1666, 1654, 1467, 1380, 1342, 1264, 1225, 1145, 1124, 1068, 868, 729; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{17}H_{30}NaO_2$, 289.2144; found, 289.2138.

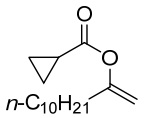
2-1l



99%
(65 ppm Au)

580 mg Compound **2-1l** was obtained in 99% yield according to general procedure B without chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.20 (m, 1H), 6.30 – 6.06 (m, 2H), 5.79 (dd, J = 19.5, 15.7 Hz, 1H), 4.78 – 4.67 (m, 2H), 2.23 (t, J = 7.5, 2H), 1.86 (d, J = 5.8 Hz, 3H), 1.50 – 1.40 (m, 2H), 1.34 (dq, J = 14.3, 7.1 Hz, 2H), 0.89 (t, J = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.33, 156.60, 146.12, 140.06, 129.68, 118.37, 100.85, 33.10, 28.57, 22.07, 18.65, 13.79. IR (neat): 3029, 2960, 2930, 2874, 2864, 1728, 1646, 1617, 1329, 1228, 1177, 1128, 1000, 867; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{12}H_{18}NaO_2$, 217.1204; found, 217.1205.

2-1m

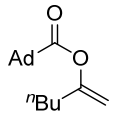


99%
(75 ppm Au)

748 mg Compound **2-1m** was obtained in 99% yield according to general procedure B after chromatography (eluents: ethyl acetate: hexanes = 1: 30). ^{1}H NMR (500 MHz,

$CDCl_3$) δ 4.69 (d, *J* = 2.8 Hz, 2H), 2.18 (t, *J* = 7.6 Hz, 2H), 1.65 (qd, *J* = 6.8, 5.6, 2.7 Hz, 1H), 1.45 (p, *J* = 7.4 Hz, 2H), 1.27 (d, *J* = 12.5 Hz, 15H), 1.08 – 1.02 (m, 2H), 0.93 – 0.89 (m, 2H), 0.87 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.00, 156.63, 100.78, 33.29, 31.87, 29.56, 29.51, 29.35, 29.30, 28.96, 28.96, 26.42, 22.65, 14.07, 12.93, 8.74. HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{11}H_{14}O_4SNa$, 275.1987; found, 275.1971.

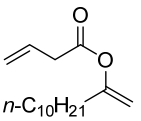
2-1n



99%
(100 ppm Au)

778 mg Compound **2-1n** was obtained in 99% yield according to general procedure B after chromatography (eluents: ethyl acetate: hexanes = 1: 30). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.68 (d, *J* = 1.0 Hz, 1H), 4.64 (s, 1H), 2.19 (t, *J* = 7.2 Hz, 2H), 2.03 (s, 3H), 1.93 (d, *J* = 2.9 Hz, 6H), 1.78 – 1.67 (m, 6H), 1.48 – 1.38 (m, 2H), 1.34 (dq, *J* = 14.3, 7.1 Hz, 2H), 0.90 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.59, 156.65, 100.46, 40.76, 38.64, 36.35, 32.82, 28.44, 27.82, 21.94, 13.71. IR (neat): 3115, 2957, 2933, 2908, 2864, 1743, 1666, 1454, 1212, 1181, 1065, 865, 736; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{17}H_{26}O_2Na$, 285.1830; found, 285.1821.

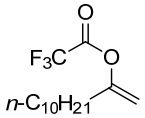
2-1o



98%
(80 ppm Au)

742 mg Compound **2-1o** was obtained in 98% yield according to general procedure B after chromatography (eluents: ethyl acetate: hexanes = 1: 30). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.94 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.25 – 5.08 (m, 2H), 4.71 (s, 3H), 3.16 (d, *J* = 7.0 Hz, 2H), 2.21 – 2.15 (m, 2H), 1.44 (p, *J* = 7.4 Hz, 2H), 1.35 – 1.20 (d, *J* = 11.8 Hz, 14H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.54, 156.52, 129.83, 118.81, 101.02, 39.12, 33.21, 33.21, 31.86, 29.54, 29.49, 29.33, 29.28, 28.92, 26.36, 22.64, 14.05. IR (neat): 3118, 3085, 2957, 2927, 2856, 1757, 1667, 1645, 1330, 1292, 1223, 1447, 1147, 992, 976, 921, 869; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{16}H_{28}O_2Na$, 275.1987; found, 275.1971.

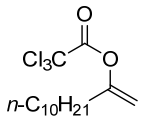
2-1p



99%
(10 ppm Au)

832 mg Compound **2-1p** was obtained in 99% yield according to general procedure B (60 °C) after chromatography (eluents: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.95 (d, *J* = 2.7 Hz, 1H), 4.91 – 4.85 (m, 1H), 2.27 (t, *J* = 7.6 Hz, 2H), 1.49 (p, *J* = 7.5 Hz, 2H), 1.38 – 1.20 (m, 14H), 0.88 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.71, 155.40 (q, *J* = 42.5 Hz), 114.50 (q, *J* = 283.75 Hz), 102.43, 32.63, 31.91, 29.56, 29.48, 29.32, 29.27, 29.27, 28.79, 26.11, 22.69, 14.05. ^{19}F NMR (376 MHz, $CDCl_3$) δ -75.09. IR (neat): 2929, 2886, 2858, 1798, 1675, 1468, 1360, 1228, 1172, 1142, 879, 771. HRMS FI (*m/z*): $[M]^+$ calcd. for $C_{14}H_{23}F_3O_2$, 280.1650; found, 280.1665.

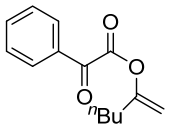
2-1q



99%
(20 ppm Au)

978 mg Compound **2-1q** was obtained in 99% yield according to general procedure B after chromatography (eluents: hexanes). ^{1}H NMR (500 MHz, $CDCl_3$ δ 4.93 (d, *J* = 0.8 Hz, 1H), 4.87 (d, *J* = 3.2 Hz, 1H), 2.30 (t, *J* = 7.6 Hz, 2H), 1.52 (p, *J* = 7.5 Hz, 2H), 1.36 – 1.20 (m, 14H), 0.87 (t, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.84, 156.69, 102.00, 89.78, 32.50, 32.50, 31.88, 29.54, 29.46, 29.30, 29.26, 28.79, 28.78, 26.16, 22.66, 14.08. IR (neat): 3121, 2957, 2928, 2856, 1779, 1673, 1467, 1379, 1201, 1107, 961, 878, 823; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{14}H_{23}Cl_3O_2Na$, 351.0661; found, 351.0650.

2-1r

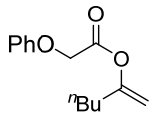


99%
(75 ppm Au)

693 mg Compound **2-1r** was obtained in 99% yield according to general procedure B without chromatography. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 – 7.95 (m, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.52 (t, *J* = 7.8 Hz, 2H), 5.00 – 4.84 (m, 2H), 2.34 (t, *J* = 7.6 Hz, 2H), 1.52 (dt, *J* = 15.3, 7.5 Hz, 2H), 1.45 – 1.31 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 185.48, 161.70, 156.04, 135.00, 132.25, 129.95, 128.92, 102.10, 32.82, 28.33, 21.94, 13.72. IR (neat): 3066, 2960, 2934, 2874, 2864, 1752,

1691, 1598, 1452, 1322, 1193, 1168, 987, 878, 746; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{14}H_{16}O_3Na$, 255.0997; found, 255.0988.

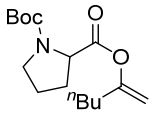
2-1s



99%
(100 ppm Au)

698 mg Compound **2-1s** was obtained in 99% yield according to general procedure B without chromatography. ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 2H), 7.01 (t, *J* = 7.4 Hz, 1H), 6.96 – 6.92 (m, 2H), 4.80 (d, *J* = 1.8 Hz, 1H), 4.77 (d, *J* = 1.6 Hz, 1H), 4.70 (s, 2H), 2.23 (t, *J* = 7.5 Hz, 2H), 1.42 (tt, *J* = 8.3, 6.9 Hz, 2H), 1.38 – 1.28 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.95, 157.56, 155.89, 129.42, 129.41, 121.66, 114.48, 114.46, 101.31, 65.08, 32.79, 28.30, 21.86, 13.62. IR (neat): 3067, 2959, 2933, 2873, 2864, 1777, 1652, 1668, 1601, 1590, 1497, 1459, 1458, 1438, 1379, 1162, 1108, 963, 876, 753; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{14}H_{18}O_3Na$, 257.1154; found, 257.1144.

2-1t

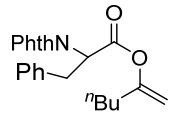


80%
(600 ppm Au)

712 mg Compound **2-1t** was obtained in 80% yield according to general procedure B (600 ppm **L10**AuNTf$_2$, 2500 ppm NaBARF) after chromatography (eluents: ethyl acetate: hexanes = 1: 2). ^1H NMR (500 MHz, $CDCl_3$) δ 4.79 – 4.59 (m, 2H), 4.33 (dd, *J* = 8.6, 3.6 Hz, 1H), 4.26 (dd, *J* = 8.7, 4.0 Hz, 1H), 3.59 – 3.31 (m, 2H), 2.34 – 2.13

(m, 3H), 2.07 – 1.78 (m, 3H), 1.46 – 1.42 (m, 4H), 1.40 (d, *J* = 6.5 Hz, 6H), 1.36 – 1.26 (m, 2H), 0.92 – 0.81 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.11 , 156.47 , 156.29 , 154.20 , 153.66 , 100.78 , 79.92 , 79.66 , 59.00 , 58.91 , 46.44 , 46.26 , 32.91 , 32.80 , 30.89 , 29.87 , 28.44 , 28.37 , 28.31 , 28.25 , 24.28 , 23.46 , 21.94 , 13.71. IR (neat): 3116, 2976, 2961, 2934, 2876, 1763, 1705, 1396, 1152, 1088, 957, 871, 773; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{16}H_{27}NO_4Na$, 320.1838; found, 320.1834.

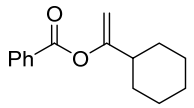
2-1u



99%
(150 ppm Au)

1128 mg Compound **2-1u** was obtained in 99% yield according to general procedure B without chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.68 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.22 – 7.10 (m, 5H), 5.23 (dd, *J* = 11.3, 5.2 Hz, 1H), 4.78 (d, *J* = 1.8 Hz, 1H), 4.75 (d, *J* = 1.7 Hz, 1H), 3.68 – 3.51 (m, 2H), 2.21 (td, *J* = 7.5, 4.5 Hz, 2H), 1.40 (qd, *J* = 8.1, 7.5, 5.6 Hz, 2H), 1.35 – 1.24 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.26, 167.08, 156.45, 136.51, 134.08, 131.50, 128.82, 128.51, 126.84, 123.42, 101.49, 53.24, 34.65, 32.73, 28.40, 21.94, 13.73. IR (neat): 3065, 2958, 2933, 2873, 2865, 1778, 1759, 1718, 1669, 1607, 1498, 1468, 1288, 1222, 1170, 1105, 1000, 961, 915, 876, 720; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{23}H_{23}NO_4Na$, 400.1525; found, 400.1515.

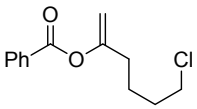
2-1v



99%
(100 ppm Au)

686 mg Compound **2-1v** was obtained in 99% yield according to general procedure B without chromatography. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 – 8.03 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 4.91 – 4.76 (m, 2H), 2.25 (td, *J* = 10.7, 3.0 Hz, 1H), 1.99 (t, *J* = 10.5 Hz, 2H), 1.87 – 1.73 (m, 2H), 1.72 – 1.64 (m, 2H), 1.34 – 1.13 (m, 6H).13C NMR (150 MHz, $CDCl_3$) δ 164.82, 160.66, 133.17, 129.94, 129.87, 128.40, 99.61, 41.80, 30.62, 26.05, 25.94. IR (neat): 3064, 2930, 2855, 1733, 1661, 1601, 1451, 1314, 1271, 1240, 1194, 1169, 1133, 1092, 1068, 1026, 872, 705; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{15}H_{18}NO_2Na$, 253.1208; found, 253.1204.

2-1w

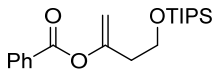


95%
(300 ppm Au)
no NaBARF

678 mg Compound **2-1w** was obtained in 95% yield when 1,2-dichloroethane was used as a solvent instead of PhF. (0.5 M, 300 ppm **L10**AuNTf, no NaBARF) after chromatography (eluents: ethyl acetate: hexanes = 1: 30). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (t, *J* = 8.4 Hz, 2H), 7.67 – 7.53 (m, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 4.88 (d, *J* = 21.0 Hz, 2H), 3.63 – 3.48 (m, 2H), 2.39 (t, *J* = 7.5 Hz, 2H), 1.88 (qd, *J* = 14.9, 6.9 Hz, 2H), 1.76 – 1.63 (m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 164.68, 155.79, 133.33, 129.88, 129.69, 128.45, 101.96, 44.64, 32.64, 31.70, 23.72. IR (neat): 3064, 2955,

2870, 2847, 1730, 1667, 1602, 1492, 1452, 1272, 1026, 875, 801, 746; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{13}H_{15}ClO_2Na$, 261.0658; found, 261.0654.

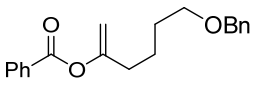
2-1x



98%
(120 ppm Au)

1023 mg Compound **2-1x** was obtained in 98% yield according to general procedure B (2500 ppm NaBARF) after chromatography (eluents: ethyl acetate: hexanes = 1: 50). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 – 8.01 (m, 2H), 7.69 – 7.52 (m, 1H), 7.50 – 7.37 (m, 2H), 5.00 – 4.84 (m, 2H), 3.89 (td, *J* = 6.6, 0.8 Hz, 2H), 2.69 – 2.51 (m, 2H), 1.17 – 0.97 (m, 21H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.74, 153.83, 133.27, 129.92, 128.41, 103.97 – 103.59 (m), 103.15, 99.07, 60.64, 37.38, 17.96, 11.95. IR (neat): 3064, 2944, 2893, 2867, 1736, 1670, 1602, 1464, 1384, 1268, 1233, 1175, 1092, 1069, 1026, 882, 706; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{20}H_{32}NaO_3Si$, 371.2018; found, 371.2020.

2-1y

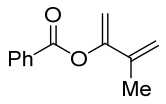


89%
(150 ppm Au)

828 mg Compound **2-1y** was obtained in 89% yield according to general procedure B (2500 ppm NaBARF) after chromatography (eluents: ethyl acetate: hexanes = 1: 20). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 – 7.97 (m, 2H), 7.63 – 7.54 (m, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.38 – 7.17 (m, 5H), 4.89 (d, *J* = 1.6 Hz, 1H), 4.87 – 4.85 (m, 1H), 4.51 (s, 2H), 3.51 (t, *J* = 6.1 Hz, 2H), 2.38 (t, *J* = 7.2 Hz, 2H), 1.77 – 1.51 (m, 4H). ^{13}C

NMR (125 MHz, $CDCl_3$) δ 164.69, 156.34, 138.51, 133.23, 129.88, 129.81, 128.41, 128.29, 127.54, 127.44, 101.59, 72.82, 69.88, 33.19, 29.02, 23.22. IR (neat): 3185, 2962, 2935, 2873, 2876, 1761, 1674, 1250, 1217, 847, 833; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{20}H_{22}O_3Na$, 333.1467; found, 333.1453.

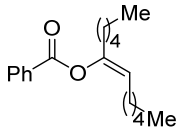
2-1z



97% (60 °C, 1500 ppm Au)

547 mg Compound **2-1z** was obtained in 97% yield according to general procedure B (2 equiv 2-methylbut-1-en-3-yne, 5000 ppm NaBARF, 60 °C) after chromatography (eluents: ethyl acetate: hexanes = 1: 20).^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (dtd, *J* = 8.1, 2.1, 1.3 Hz, 1H), 7.67 – 7.57 (m, 1H), 7.55 – 7.42 (m, 1H), 5.32 – 5.14 (m, 2H), 5.04 (ddd, *J* = 7.9, 2.9, 1.5 Hz, 2H), 2.01 (d, *J* = 0.7 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.13 – 164.49 (m), 154.09 – 153.24 (m), 136.63, 133.45, 130.04, 129.68 – 129.31 (m), 128.54, 113.92, 103.60, 19.46. IR (neat): 3063, 2976, 2954, 2928, 2902, 2855, 1738, 1603, 1452, 1263, 1152, 1090, 1068, 1026, 887, 707; HRMS EI (*m/z*): $[M]^+$ calcd. for $C_{12}H_{12}O_2$, 188.0837; found, 188.0835.

2-1aa

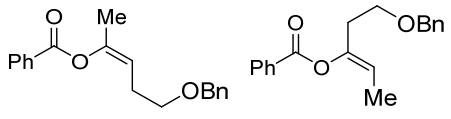


99% (1500 ppm Au)

855 mg Compound **2-1aa** was obtained in 99% yield according to general procedure B (5000 ppm NaBARF) after chromatography (eluents: ethyl acetate: hexanes = 1:

30). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (dt, *J* = 8.4, 1.6 Hz, 2H), 7.83 – 7.54 (m, 1H), 7.54 – 7.40 (m, 2H), 5.11 (t, *J* = 7.3 Hz, 1H), 2.41 – 2.19 (m, 2H), 1.97 (q, *J* = 7.3 Hz, 2H), 1.57 – 1.45 (m, 2H), 1.43 – 1.16 (m, 10H), 0.98 – 0.74 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.39, 148.58, 133.10, 129.91, 129.87, 128.40, 116.53, 33.43, 31.36, 31.23, 28.77, 26.37, 25.31, 22.41, 22.40, 13.98, 13.96. IR (neat): 3064, 2957, 2930, 2872, 2859, 1733, 1452, 1259, 1089, 1068, 1026, 708; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{19}H_{28}O_2Na$, 311.1987; found, 311.1977.

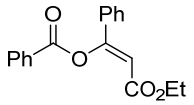
1ab + 1ab'



85% (2.8:1)
(500 ppm Au)

755 mg Compounds **2-1ab** and **2-1ab'** were obtained in 85% yield (2.8:1) according to general procedure B (2500 ppm $NaBAr^F{}_4$) after chromatography (eluents: ethyl acetate: hexanes = 1: 15). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 – 8.07 (m, 2H), 7.64 – 7.58 (m, 1H), 7.52 – 7.46 (m, 2H), 7.38 – 7.26 (m, 5H), 5.31 (qd, *J* = 6.8, 0.9 Hz, 0.25H), 5.25 – 5.19 (m, 0.73H), 4.54 (s, 0.52H), 4.51 (s, 1.55H), 3.65 (td, *J* = 6.6, 1.1 Hz, 0.53H), 3.50 (td, *J* = 6.8, 1.1 Hz, 1.56H), 2.70 – 2.61 (m, 0.52H), 2.41 – 2.30 (m, 1.57H), 2.07 – 1.99 (m, 2.35H), 1.59 (dd, *J* = 6.8, 1.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.32, 164.25, 146.42, 146.26, 138.34, 138.23, 133.24, 133.21, 129.91, 129.89, 129.65, 129.60, 128.41, 128.27, 127.60, 127.57, 127.47, 127.46, 113.45, 112.85, 72.86, 72.75, 69.24, 67.26, 34.22, 26.19, 19.63, 10.81. HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{19}H_{20}O_3Na$, 319.1310; found, 319.1313.

2-1ac



98%
(150 ppm Au)

870 mg Compound **2-1ac** was obtained in 98% yield according to general procedure B after chromatography (eluents: ethyl acetate: hexanes = 1: 4). This compound is known and the spectrum are consistent with literature data.[1] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (dd, *J* = 8.3, 1.2 Hz, 2H), 7.72 – 7.59 (m, 3H), 7.53 (dd, *J* = 10.8, 4.8 Hz, 2H), 7.47 – 7.34 (m, 3H), 6.38 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.08, 163.82, 157.83, 133.70, 133.45, 130.95, 130.37, 129.11, 128.84, 128.64, 125.95, 106.84, 60.38, 14.05. IR (neat): 2918, 2951, 1742, 1714, 1636, 1449, 1279, 1234, 1157, 1080, 1064, 1023, 765; HRMS ESI (*m/z*): $[MNa]^+$ calcd. for $C_{18}H_{16}O_4Na$, 319.0946; found, 319.0943.

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3. Rapid Access to Chroman-3-Ones via Gold-Catalyzed Oxidation of Propargyl Aryl Ethers

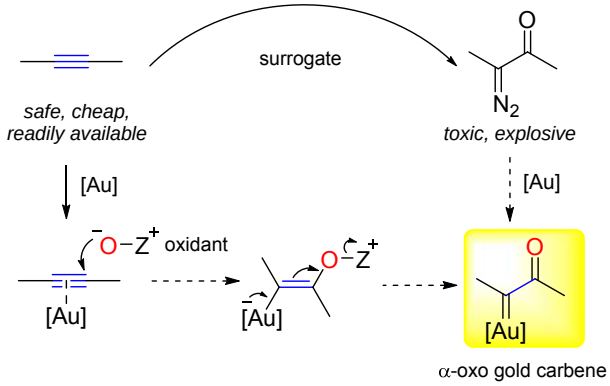
3.1. Introduction

Metal-promoted dediazotizations of diazo carbonyl compounds are the most reliable strategy to access α-oxo metal carbenes/carbenoids, which are versatile intermediates that can go through various synthetically challenging but also highly valuable transformations, such as C–H insertion, ylide formation, and cyclopropanation reactions.[1] Of particular synthetic importance are those methods based on Rh catalysis, which allow enantioselective transformations with chiral coordinating ligands utilized. Unfortunately, this strategy is largely limited by the hazardous nature of the diazo carbonyl substrates, due to the highly energetic diazo moiety and hence the toxicity and potential of explosion. Consequently, although large scale processes have been executed with engineering ingenuity,[2,3] these reactions are still recommended to perform in small scales to avoid possible safety related issues. Moreover, the preparations of these precursors typically require robust reagents, hence putting further strain on operational safety, and often entail multiple-step synthetic sequence unless the methylene group is fairly acidic.[1] As a result, the development of safe surrogates of diazo carbonyl compounds while maintaining the ease of accessing the corresponding metal carbenes would address this incapacitating issue and provide extensive benefit to synthetic practices.

Even though diazo carbonyl compounds have been used to access α-oxo gold

carbene/carbenoid,[4-8] we believe the same intermediate could be generated from a C–C triple bond instead of an energetic diazo moiety by a strategy involving an external oxidant (Scheme 53). Therefore, the hazardous α-diazo carbonyl compounds in principle could be replaced with readily available and most benign alkynes, at least in the jurisdiction of gold catalysis. Due to the largely unexplored reactivities of α-oxo gold carbenes and their ease of efficient access enabled by this oxidative strategy, many other research groups were drawn to the synthetic potential of the approach as well after our group explored some versatile reactivities of these carbene intermediates.

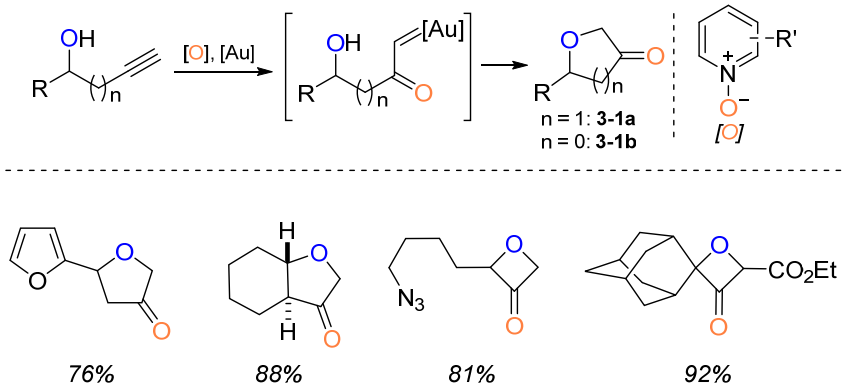
Scheme 53. Generation of α-Oxo Gold Carbenes via Alkynes Oxidation: Alkynes as Surrogates of α-Diazo Carbonyl Compounds



In 2010, our group reported the first example of accessing α-oxo gold carbenes via intermolecular oxidation of terminal alkynes under mild reaction conditions (Scheme 54).[9] By using pyridine *N*-oxide as the external oxidant, homopropargylic alcohols was facilely converted to α-oxo gold carbene intermediate under gold

catalysis, which was then trapped by intramolecular O-H group, yielding the products dihydrofuran-3-ones **3-1a** in good yields. Significantly, the intermolecular approach makes alkynes equivalent to hazardous α-diazo ketones and, moreover, offers much synthetic flexibility. Half year later, our group successfully utilized the same strategy to oxidize propargyl alcohols to oxetan-3-ones **3-1b**, a highly valuable substrate for drug discovery (Scheme 54).[10] The facile formation of the strained oxetane ring provides strong support for the intermediacy of α-oxo gold carbenes.

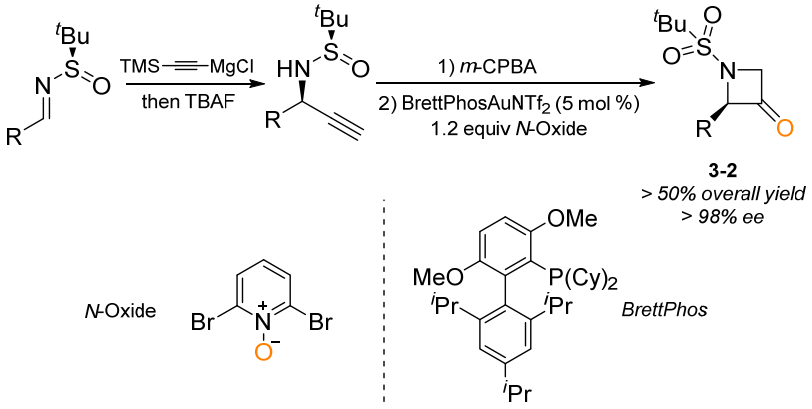
Scheme 54. Intramolecular O-H Insertion by α-Oxo Gold Carbene



In 2011, the same approach was applied to a one-step synthesis of azetidin-3-ones from propargylic amides (Scheme 55).[11] The chiral Bus (tert-Butylsulfonyl) was chosen to be the protecting group of amine because it's easy to access and allows highly stereoselective construction of the stereogenic propargylic position according to Ellman's chemistry.[12] Using bulky ligand BrettPhos and bulky 2,6-dibromopyridine *N*-oxide, azetidin-3-ones **3-2** were facilely obtained in overall >50% yield with >98% ee after a four-step sequence from Bus imines. This reaction permits

an expedient access to various chiral azetidin-3-ones and tolerates sensitive functional groups such as azido and NHBoc due to the exceedingly mild conditions

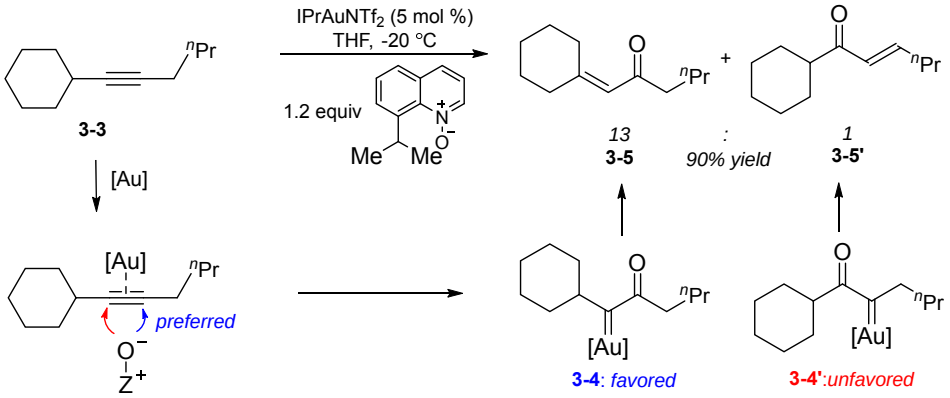
Scheme 55. Access to Azetidin-3-ones by Au-Catalyzed Oxidation Reactions



At the same time, a gold-catalyzed intermolecular oxidations of internal alkynes was also accomplished by our group with high regioselectivities using 8-alkylquinoline *N*-oxides as oxidants.[13] For the sterically biased internal alkyne substrate **3-3**, the combination of $IPrAuNTf_2$ and 8-isopropylquinoline *N*-oxide led to selective formation of enone **3-5** over its isomer **3-5'**, which are formed upon 1,2-C–H insertions by the isomeric α-oxo gold carbenes **3-4** and **3-4'**, respectively (Scheme 56). The regioselectivity is ascribed to the preferred approach of the oxidant to the less hindered end of the C–C triple bond. For the first time, synthetically versatile α,β-unsaturated ketones are obtained directly from alkyne moieties in good to excellent yields and with excellent *E*-selectivities. This reaction allows α,β-unsaturated carbonyl compounds to be masked as relatively stable and readily available alkynes, thus offering a practical solution to compatibility issues with these

functional groups likely encountered in the syntheses of complex structures.

Scheme 56. Formation of Enones by Au-Catalyzed Oxidation of Alkynes



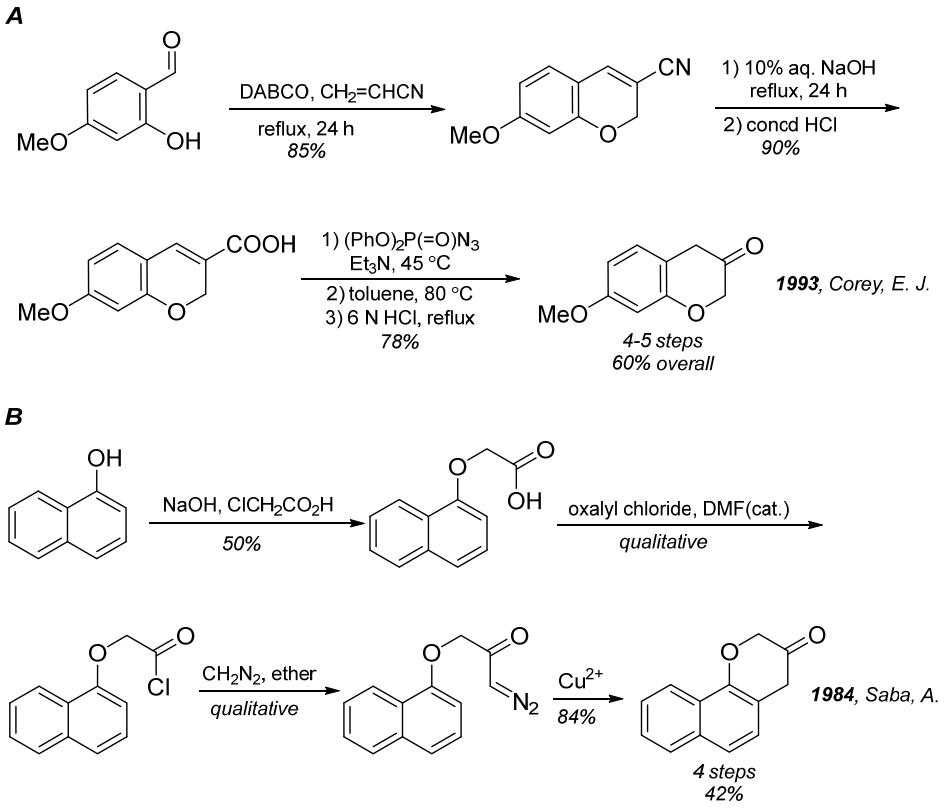
3.2. The Design of Accessing Chroman-3-ones by α-Oxo Gold Carbenes

After the α-oxo gold carbenes were successfully trapped by O-H and N-H bonds, we started to wonder if C–H bond insertion would occur in the same manner. By this strategy, we were hoping to access to chroman-3-ones rapidly because it's an important structural motif and its derivatives have served as key intermediates in the total synthesis of natural products such as miroestrol,[14] (+)-myristinin A,[15] and afzelechin,[16] as well as in accessing a range of bioactive chromans for managing various diseases including hypertension,[17] HIV,[16] sexual dysfunction,[18] and melanoma.[19]

In their 1991 review,[20] Danan and Kirkiacharian concluded that there was a lack of efficient synthetic methods for this structure. Little progress[21] has been made

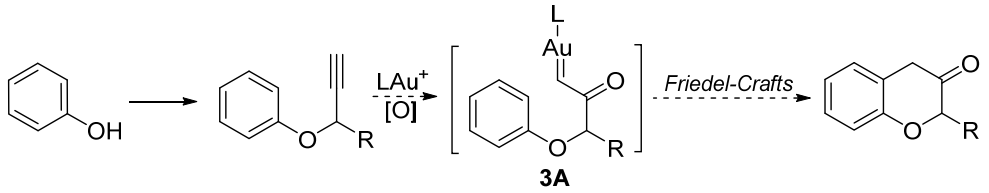
since then, which makes the twenty-years-old statement still remain essentially true to date. Perpetually, these compounds are prepared through multistep routes [20,22] from basic chemicals (i.e., phenol). For example, a typical route was reported by Corey et al. (Scheme 57-A): starting from a basic condensation of salicylaldehyde with acrylonitrile to form 2H-chromene-3-carbonitrile under refluxing conditions, followed by basic hydrolysis, acidification and formation of acyl azide, the subsequent Curtius rearrangement and acidic hydrolysis of the resulting vinyl isocyanate afforded the corresponding chroman-3-one.[14,22,23] While the overall yield could be as high as 60%, the step and atom economy is very low and strong acidic and basis conditions were unavoidable.

Scheme 57 Access to Chroman-3-ones: Previous Work



Alternatively, a similarly long approach took advantage of copper carbene intermediate (Scheme 57-B): starting from phenols or naphthanols,[24] a sequence of *O*-alkylation, chlorination of carboxylic acid and diazo-substitution gave the key precursor, α-diazo-α'-phenoxy acetones. Treated with $Cu(CF_3CO_2)_2$, the copper carbenoid was generated and the succeeding C–H insertion led to the final chroman-3-one products. However, no application of this method has been reported in the literature because of its limited substrate scope another clear drawback associated with using toxic and explosive diazomethane.[25]

Scheme 58. Access to Chroman-3-ones: New Design



To solve the above problem with a long history, we envisioned that our oxidative strategy to generate α-oxo gold carbene would allow replacement of α-diazo-α′-phenoxy acetones with readily available propargyl aryl ethers, which are only one-step away from phenols of easy access and often obtained in quantitative yields, thereby establishing a concise, safe, and potentially highly efficient itinerary to this class of heterocycles. Generally metal carbenes can be generated via dediazotization, but this Au-catalyzed alkyne oxidation strategy permits the replace of

toxic, potentially explosive and difficult-to-access α-diazo ketones since alkynes are benign and readily available.

3.3. Conditions Optimizations

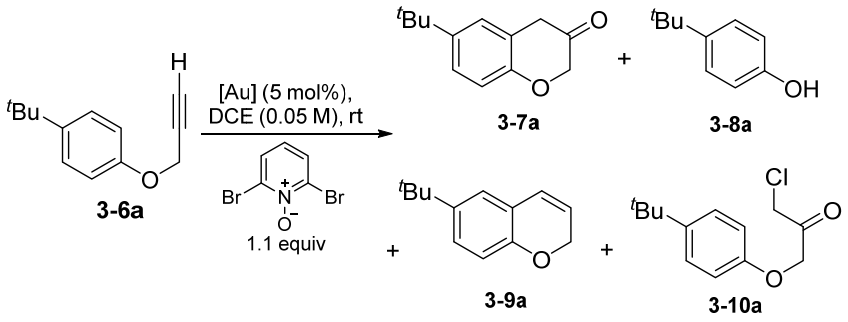
3.3.1. Ligand Investigation

On the onset, 4-*tert*-butylphenyl propargyl ether **3-6a** was chosen as the standard substrate for condition optimization. Bulky electron-deficient 2,6-dibromopyridine *N*-oxide was used as the external oxidant and DCE (1,2-dichloroethane) as the solvent (Table 7). When either $Ph_3PAuNTf_2$ (entry 1) or the more electrophilic phosphite-coordinated $(ArO)_3PAuNTf_2$ (Ar = 2,4-di-*tert*-butylphenyl, entry 2) was employed as the catalyst, both reactions were sluggish. The desired chroman-3-one **3-7a** was formed in <10% yield with almost half amount of starting material left;3-4% α-chloro ketone **3-10a** was also detected, which was probably from α-oxo gold carbene trapped by the halogenated solvent DCE. Notably, relatively bulky $IPrAuNf_2$ improve the reaction significantly, provide 45% **3-7a**, 7% phenol **3-8a**, 3% directly-cyclized 2*H*-chromene **3-9a** and 3% **3-10a** with 8% starting material **3-6a** left after 16 h (entry 3).

In the previous work of our group on azetidine-3-one synthesis, [11] we noticed that gold catalysts based on biphenylphosphine ligands were increasingly effective as the ligand became more and more bulky and $BrettPhosAuNTf_2$ was the optimal catalyst. As expected, the same trend was observed for this reaction as well comparing

sterics-increasing cy-JohnPhosAuNTf$_2$, ^{t}BuXPhosAuNTf$_2$ and BrettPhosAuNTf$_2$ (entries 4-6); chroman-3-one **3-7a** was formed in 65% NMR yield within only 30 min with BrettPhosAuNTf$_2$ as the catalyst (entry 6). Me$_4$^{t}BuXPhos[26-28] is a bulkier ligand than BrettPhos; seeking to further improve this reaction, I made Me$_4$^{t}BuXPhosAuNTf$_2$ and tested it out. To our delight, the yield did get improved to 78% (entry 7**)** with other reaction condition unchanged.

Table 7. Catalyst Optimization [a]



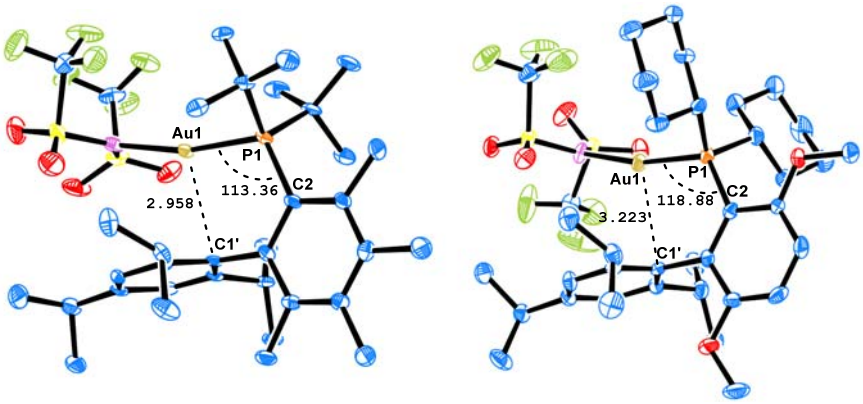
entry	catalyst	time	**3-6a** remained	yield			
				3-7a	**3-8a**	**3-9a**	**3-10a**
1	Ph$_3$PAuNTf$_2$	16 h	41%	6%	-	-	3%
2	(ArO)$_3$PAuNTf$_2$ [b]	16 h	58%	7%	-	-	4%
3	IPrAuNTf$_2$	16 h	8%	45%	7%	3%	3%
4	Cy-JohnPhosAuNTf$_2$	16 h	17%	9%	5%	2%	6%
5	^{t}BuXPhosAuNTf$_2$	16 h	-	27%	10%	4%	5%
6	BrettPhosAuNTf$_2$	0.5 h	-	65%	5%	4%	3%
7	**Me$_4$^{t}BuXPhosAuNTf$_2$**	**0.5 h**	**-**	**78%**	**5%**	**8%**	**-**

[a] Estimated by 1H NMR using diethyl phthalate as the internal reference. [b] Ar is 2,4-di-*tert*-butylphenyl

Single crystal X-ray diffraction studies established the structure of this effective catalyst (Figure 11-A). In comparison with BrettPhosAuNTf$_2$ (Figure 11-B), the

Au1-P1-C2 angle is smaller by 5.52˚, and the distance between Au1 and C1' is shorter by 0.265 Å, suggesting that Me$_4$^{t}BuXPhos forces Au center more toward the shielding pendant 2,4,6-triisopropylphenyl group and hence increase the steric crowding of the metal center. In a simplistic picture, the gold center in Me$_4$^{t}BuXPhosAuNTf$_2$ is positioned in a deeper pocket than in the case of other catalysts. This crowding could also be reflected by its %V_{Bur} value[29,30] (61.8 based on the X-ray structure of its AuNTf$_2$ complex and 60.6 on its AuCl complex[31]), which is significantly bigger than that of BrettPhos (53.7 %V_{Bur} based on the X-ray structure of its AuNTf$_2$ complex[11]).

Figure 11. Ortep Ellipsoid Drawing of Complexes Me$_4$^{t}BuXPhosAuNTf$_2$ and BrettPhosAuNTf$_2$ with 50% Probability. (The hydrogen atoms have been omitted for clarity. The distances shown are in Å, and the angles in degree.)



A: Me$_4$^{t}BuXPhosAuNTf$_2$ B: BrettPhosAuNTf$_2$

In fact, Me$_4$^{t}BuXPhosAuNTf$_2$ has a higher %V_{Bur} value than any of the LAu(I) complexes investigated by Clavier and Nolan. [30] As a result, side reactions with the corresponding gold carbene **3A** via intermolecular processes might become less detrimental due to the enhanced difficulty of access, and the more imposing

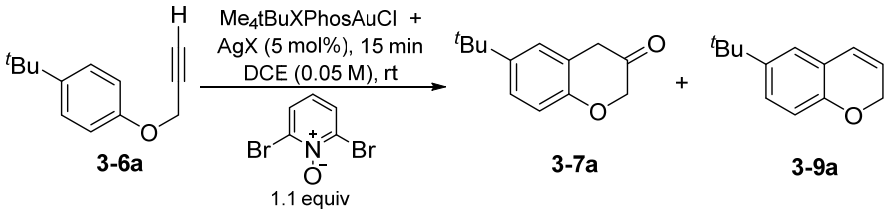
2,4,6-triisopropylphenyl group might also facilitate the carbene moiety to adopt conformations with bending backbones that are poised to undergo productive intramolecular cyclization, both of which could lead to increased efficiency. Conspicuously, Barriault et al. [31] recently reported that $[Me_4{}^tBuXPhosAuNCMe]^+SbF_6^-$ is the best catalyst for selectively promoting 6-*endo-dig* carbocyclizations of alkenyl silyl ether to alkynes over typically favored *5-exo-dig* ones.

3.3.2. Counter Ion Investigation

Counter ions play very important roles in organometallic catalysis, certainly including gold catalysis. After fixing the best ligand for the gold catalyst, we further looked into the counter ion effect for this reaction. As shown in Table 8, most counter ion afforded relatively satisfying results (entries 1-5), among which NTf_2^-, PF_6^-, and SbF_6^- performed similarly well. However, OTf^- only gave 42% desired product **3-7a** with 22% starting material **3-6a** left (entry 6). Because PF_6^- and SbF_6^- are weak-coordinating counter ion, their corresponding gold catalysts are not very stable to store and have to be generated in situ by mixing $Me_4{}^tBuXPhosAuCl$ and silver salt every time. Although both of them gave just as good results as NTf_2^-, to make the operations of running reactions easier, I chose to prepare the stable $Me_4{}^tBuXPhosAuNTf_2$ first due to its ease of handling. When the counter ion was

changed to strong coordinating tosylate, benzoate and trifluoroacetate, no reaction was observed possibly due their low activities.

Table 8. Counter Ion Effect [a]



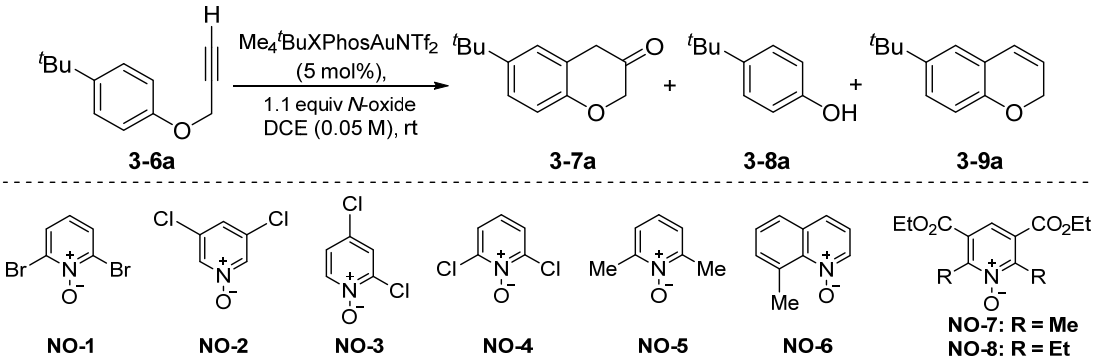
entry	counter ion	**3-6a** remained	yield **3-7a**	yield **3-9a**
1	**NTf_2**	**-**	**78%**	**8%**
2	PF_6	-	76%	8%
3	BARF	-	66%	10%
4	**SbF_6**	**-**	**78%**	**8%**
5	BF_4	-	72%	10%
6	OTf	22%	42%	4%

[a] Estimated by 1H NMR using diethyl phthalate as the internal reference.

3.3.3. Oxidant Investigation

Since no more improvement could be made by modifying gold catalysts, then I began to investigate the oxidants, *N*-oxides (Table 9). Other common oxidants (3,5-dichlropyridine *N*-oxide, 2,4-dichlropyridine *N*-oxide, 2,6-dichlropyridine *N*-oxide, lutidine *N*-oxide and 8-methylquinoline *N*-oxide) that we used previously [9,10,11] did not improve the reaction any better (entries 2-6). However, it was clear that hindered and electron-deficient *N*-oxides fared better.

Table 9. Oxidant Effect [a]

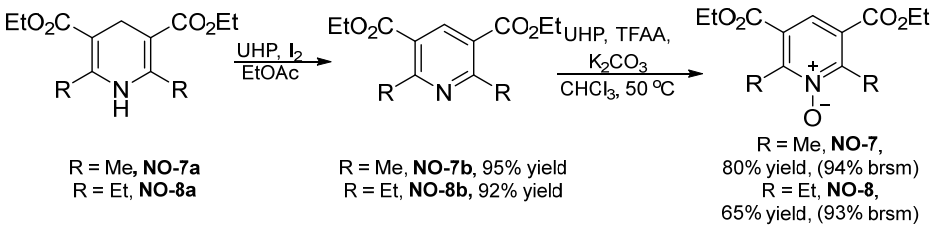


entry	*N*-Oxide	time	**3-6a** remained	yield		
				3-7a	**3-8a**	**3-9a**
1	NO-1	15 min	-	78%	5%	8%
2	NO-2	15 h	18%	38%	2%	1%
3	NO-3	15 h	7%	53%	-	2%
4	NO-4	15 min	-	67%	4%	6%
5	NO-5	15 h	39%	29%	-	-
6	NO-6	15 h	10	45%	-	5%
7	**NO-7** [b]	**1 h**	**-**	***84%*** [d]	**-**	**2%**
8	**NO-8** [c]	**1 h**	**-**	***87%***	**-**	**2%**

[a] Estimated by 1H NMR using diethyl phthalate as the internal reference. [b] 1.3 equivalent. [c] 1.2 equivalent. [d] 82% isolated yield.

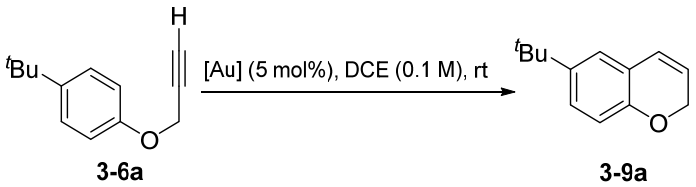
Consequently, I prepared pyridine *N*-oxides **NO-7** and **NO-8** by a quick sequence of double oxidations of the corresponding Hantzsch esters (Scheme 59). To the best of our knowledge, these hindered and electron-deficient *N*-oxides have never been used as oxidants before. Gratifyingly, with 1.3 equivalent of **NO-7**, the reaction yield was improved to 84% (entry 7); a slightly better yield 87% was obtained with 1.2 equivalent of even more hindered **NO-8** (entry 8).

Scheme 59. Synthesis of *N*-oxides NO-7 and NO-8 [a]



[a] TFAA=trifluoroacetic anhydride, UHP=urea hydrogen peroxide.

Table 10. Direct Cyclization without *N*-Oxide [a]



entry	catalyst	time	yield of **3-9a**
1	$Ph_3PAuNTf_2$	1 h	66%
2	$(ArO)_3PAuNTf_2$ [b]	1 h	73%
3	$IPrAuNTf_2$	1 h	80%
4	Cy-JohnPhosAuNTf$_2$	1 h	64%
5	^{t}BuXPhosAuNTf$_2$	1 h	76%
6	BrettPhosAuNTf$_2$	15 min	87%
7	Me$_4{}^t$BuXPhosAuNTf$_2$	25 min	79%

[a] Estimated by 1H NMR using diethyl phthalate as the internal reference

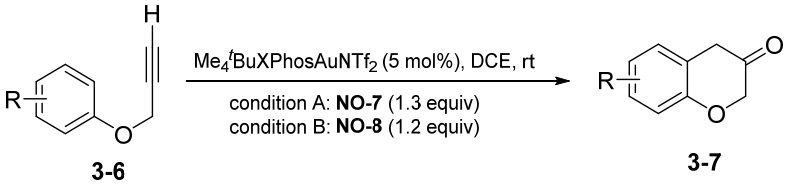
In these reactions, only small amounts of benzopyran **3-9a** were formed via competitive gold-catalyzed 6-*endo-dig* cyclizations. However, in the absence of oxidant **4a**, this cyclization was rather fast and generally efficient in the presence of a array of gold catalysts (Table 10). These results indicated that the *N*-oxide, besides

being the oxidant, might hinder the side reaction by changing the activity of the gold catalyst through, most likely, its coordination to the LAu(I).

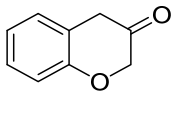
3.4. Substrates Scope

With the best gold catalyst $Me_4{}^tBuXPhosAuNTf_2$, and the new oxidants **NO-7** and **NO-8** as the optimal combination, I quickly explored the reaction scope with the help of Dr. Kegong Ji. As shown in Table 11, with the parent phenyl propargyl ether as substrate, unsubstituted chroman-3-one **3-7b** was obtained in a decent 75% yield. An *ortho*-Me substitution on the benzene ring were inconsequential (**3-7c**, 78%). The cyclization in the case of a *meta*-Me (**3-7d**, 67%) was highly regioselective, favoring the less hindered position *para* to the Me group (12:1); an even higher regioselectivity was achieved with a *ortho*-^{t}Bu substrate (**3-7e**, 16:1). A second methyl substitution on the benzene ring did not affect much the reaction yield (**3-7f**, 70%). Substrates with differently substituted methoxy groups reacted smoothly, affording corresponding products in good yields (**3-7g/h/i**; 70 – 83%). Importantly, the regioselectivity in the case of a *meta*-methoxy group could be improved to 11:1 when the reaction was run at 0 °C (**3-7i**) without affecting the reaction efficiency much. Markedly, these chroman-3-ones, **3-7g/h/i**, were previously prepared from more expensive methoxy-substituted salicylaldehydes following the aforementioned multistep sequence, and the overall yields were mostly less than 41 %. [22]

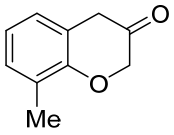
Table 11. Suberate Scope [a]



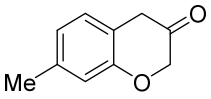
3-6 **3-7**



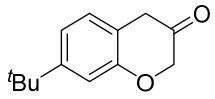
3-7b, (76%, B)



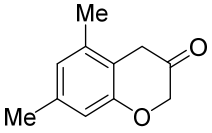
3-7c, (78%, B)



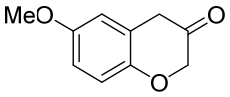
3-7d, (67%, *p:o*=12:1, A)



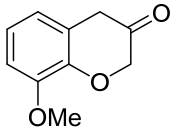
3-7e, (74%, *p:o*=16:1, A)



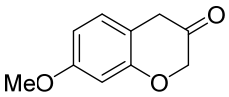
3-7f, (70%, A)



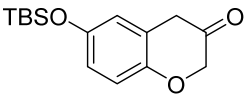
3-7g, (83%, B)



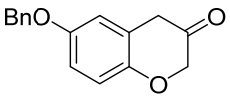
3-7h, (70%, B)



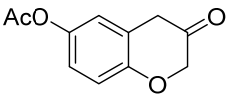
3-7i, (75%, *p:o*=11:1, B) [b]



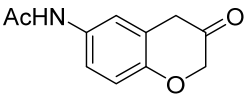
3-7j, (70%, A)



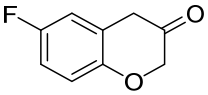
3-7k, (86%, B)



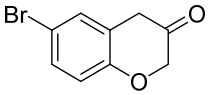
3-7l, (63%, B)



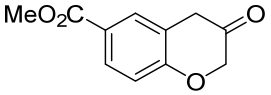
3-7m, (81%, A)



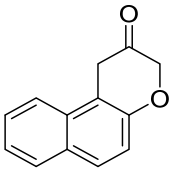
3-7n, (54%, B)



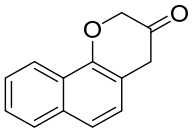
3-7o, (50%, B)



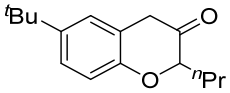
3-7p, (43%, A)



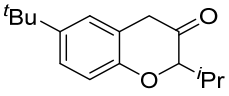
3-7q, (68%, A)



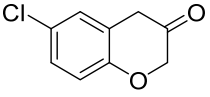
3-7r, (81%, A)



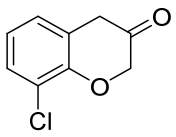
3-7s, (83%, A)



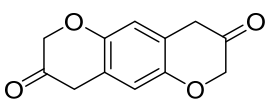
3-7t, (66%, A)



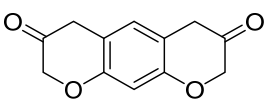
3-7v, (50%) [c]



3-7w, (35%) [c]



3-7x, (60%, *l:b*=8:1, B) [b]



3-7y, (61%, *l:b*=3.3:1, B) [b]

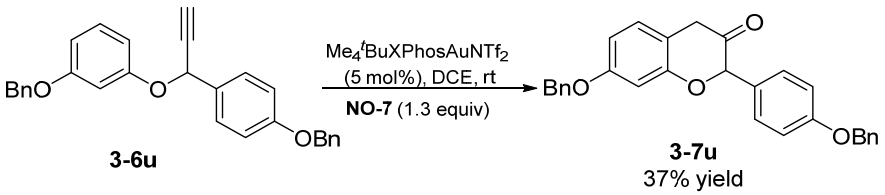
[a] The reactions were run in a vial without exclusion of air and moisture, and the substrate concentration was 0.05 M. Yields of isolated products are reported. [b] The reaction was run at 0 °C. [c] 1.1 equivalent 2,6-dibromopyridine N-oxide was used; NMR yield using diethyl phthalate as the internal reference. Bn=benzyl, TBS=*tert*-butyldimethylsilyl. *l*/*b*=linear/bent.

After the reaction, one equivalent (at least) of pyridine **NO-7b** or **NO-8b** would be generated and sometimes its polarity was very close to the desired product **3-9**. To make the purification easier, for most substrates we tried the both condition A and B at first and then chose whichever provided a less difficult purification since both conditions gave similarly good results.

The functional group tolerance of this chemistry is also well-demonstrated: substrates with a TBS ether (**3-7j**), a benzyl ether (**3-7k**), an acetate (**3-7l**), and a secondary amide (**3-7m**) all reacted smoothly to give 63 – 86% yield. However, electron-withdrawing groups including halides (**3-7n**, **3-7o**) and methoxycarbonyl (**3-7p**), the reactions were less efficient notwithstanding still useful considering the short sequences (43 – 54%). This chemistry also worked well with naphthalene substrates (**3-7q/r**, 68 – 81%), showing excellent regioselectivities.

Aliphatic substitutions at the propargyl position, including the sterically demanding isopropyl group, were readily endured with substantial yield afforded (**3-7s/t**, 66 – 83%). Notably, the diazo ketone approach could not afford this type of 2-alkyl-substituted product effectively because of a major side Buchner ring expansion reaction leading to norcaradiene side products. [25] However, in the case of a phenyl group at the propargylic position, the yield was very low (37 %, **3-7u**),

possibly due to the sensitivity of the substrate **3-6u** in the presence of the Lewis acidic gold complex.



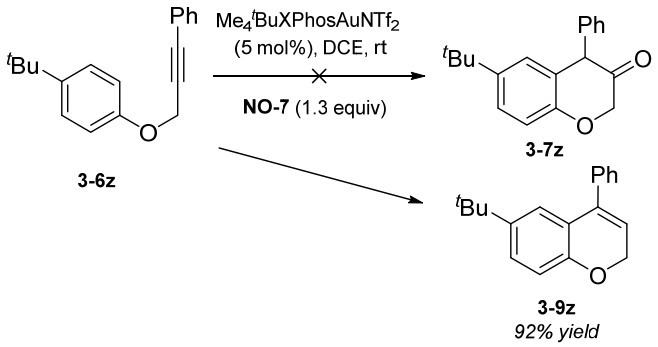
3-6u

3-7u
37% yield

The cases of **3-7v** and **3-7w** were generated in the early stage of this research. Even not under the optimal conditions, the substrates substituted by *para*-Cl and *ortho*-Cl groups could give the desired products in moderate yields. Notably as the inductive effect increased for the electron-withdrawing groups, the efficiency of the reaction diminished comparing **3-7v** (50%, *para*-Cl) and **3-7w** (35%, *ortho*-Cl). With the bis(ether) substrate derived from *p*-hydroquinone, double oxidative cyclization occurred smoothly to afford the linear tricycle **3-7x** in a respectable yield and selectivity (60%, 8:1). A similar reaction was achieved with the substrate derived from resorcinol although the regioselectivity was moderate (**3-7y**, 61%, 3.3:1).

One limitation of this methodology is that internal alkyne substrate did not work (Scheme 60). Under the optimum conditions **3-6z** proceeded to from benzopyran **3-9z** in high yield instead of chroman-3-one **3-7z**, which is disappointing but understandable. Both sterics and electronic property of the internal alkyne halted the intermolecular oxidation reaction, favoring the intramolecular 6-*endo-dig* cyclization.

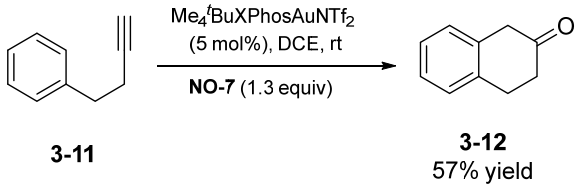
Scheme 60. Reactions of Internal Alkyne Substrate



3.5. Other Types of Substrates

Besides aryl propargyl ether, but-3-yn-1-ylbenzene **3-11** also reacted relatively efficiently to afford 3,4-dihydronaphthalen-2(*1H*)-one **3-12** in 57% yield under the previous optimal conditions for the formation of chroman-3-ones (Scheme 61). Considering the electronic difference between those two types of substrates, potential improvement remained possible and ligand tuning might help.

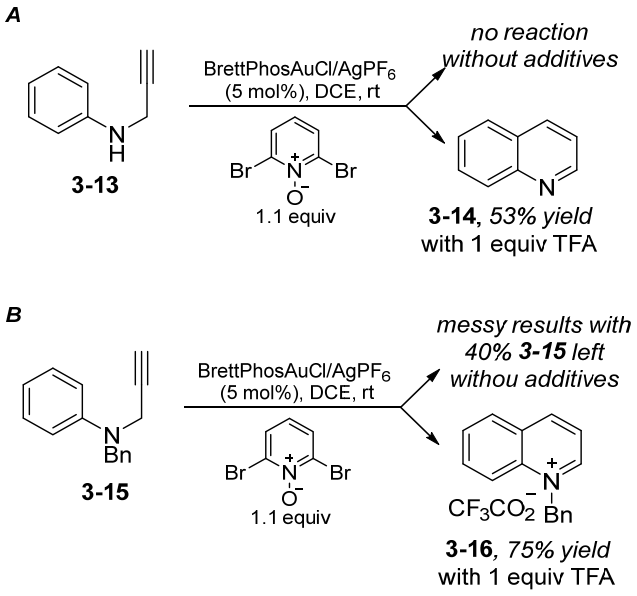
Scheme 61. Synthesis of 3,4-dihydronaphthalen-2(1H)-one



Aryl propargyl amine **3-13** did not provide any product under the condition shown in Scheme 62-A, presumably due to the basicity of the nitrogen, which shut down the catalysis. After one equivalent of TFA (trifluoroacetic acid) was added to

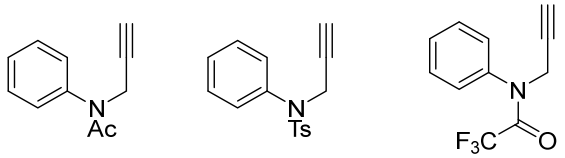
the reaction, no desired product but quinoline **3-14** was formed in 53% yield. With a benzyl protecting group on the nitrogen (Scheme 62-B), **3-15** did not give any desired product in spite of a 60% conversion without acidic additive. Similar to **3-13**, when one equivalent TFA was added quinoline salt **3-16** was formed in a yield 75%. The formation of quinolines most likely resulted from an initial gold-catalyzed 6-*endo-dig* cyclization and a subsequent oxidation by 2,6-dibromopyridine *N*-oxide.

Scheme 62. Reactions of Aryl Propargyl Amines



Then electron-withdrawing protecting groups were also examined, including acetyl, tosyl and trifluoroacetyl groups (Figure 12), but no positive results were obtained out of those substrates.

Figure 12. Other Aryl Propargyl Amines



3-17 **3-18** **3-19**

3.6. Summary

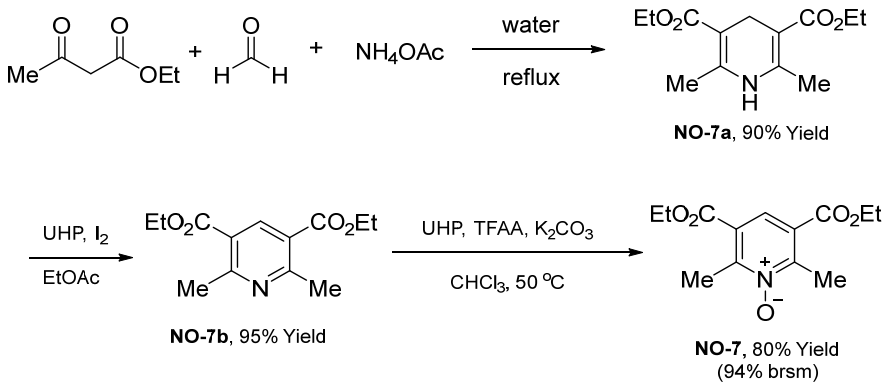
In summary, one-step efficient synthesis of chroman-3-ones from readily available propargyl aryl ethers was documented. This gold-catalyzed oxidation strategy is step- and atom-economic compared with literature protocols, and should be able to facilitate research involving this versatile type of heterocyclic compounds. No toxic or explosive reagents are involved and the reaction conditions are rather mild. A new gold catalyst, $Me_4{}^tBuXPhosAuNTf_2$, was prepared and fully characterized. Its hindered nature is revealed by X-ray diffraction studies. This study as well as the work of Barriault et al. suggests this cationic gold complex based on bulky $Me_4{}^tBuXPhos$ can be exclusively effective and should be included in the ligand selection of practitioners who are interested in gold catalysis. In addition, two easily accessible pyridine *N*-oxides derived from Hantzsch esters were demonstrated to be highly potent oxidants; they should help enable the development of gold-catalyzed alkyne oxidation reactions, which permit excellent synthetic efficiency and step economy.

3.7. Experimental Section

General Procedure A: Preparation of Propargyl Aryl Ethers 3-6

Propargyl aryl ethers **3-6** were prepared by alkylation of the corresponding phenols with propargyl bromide. In a general procedure, a mixture of phenol (10 mmol) and anhydrous potassium carbonate (30 mmol) in DMF (20 mL) was heated to 60 ℃ for half an hour under inert atmosphere with proper stirring. The reaction mixture was then cooled to room temperature and propargyl bromide (12 mmol) was added slowly. The reaction was monitored by TLC and after completion (1 - 4 h) the mixture was diluted with ether and washed at least 3 times with brine. The ethers were purified with flash silica gel column chromatography after solvent evaporation.

Preparation of *N*-oxides NO-7

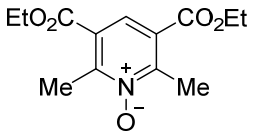


Hantzsch Ester **NO-7a** was prepared in 90% yield according known procedure.[32] A mixture of paraformaldehyde (100 mmol), ethyl acetoacetate (400 mmol), and ammonium acetate (200 mmol) in 200 mL of water was vigorously stirred at refluxing temperature for 2h. The reaction was monitored by TLC. After the reaction was completed, the reaction mixture was cooled to room temperature, then filtrated and

washed with 10mL of water twice. The obtained yellow solid product was nearly pure and used in the next step without further purification.

Pyridine **NO-7b** was achieved in 95% yield according to the literature procedure.[33] To a solution of **NO-7a** (10 mmol) in EtOAc (100 mL), molecular iodine (510 mg, 2 mmol, 20 mol %) and UHP (1.9 g, 20 mmol) were added. The reaction mixture was stirred at rt for 1h. After that to the reaction mixtures, water (10 mL) and solid $Na_2S_2O_5$ in small portions were added to complete decolouration. The phases were separated and the aqueous phase was additionally extracted with EtOAc (10 mL). The combined organic layers were dried over Na_2SO_4, filtered and evaporated to dryness. The solid product was nearly pure and could be used directly in the next step. The pure pyridine might also be obtained by recrystallization from diisopropyl ether.

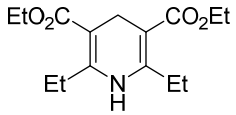
NO-7



K_2CO_3 (20 mmol) and UHP (10 mmol) were stirred in dry 1,4-dioxane or CHCl3 (100 ml) for 1 h, then TFAA (10 mmol) was added dropwise at 0 °C. The mixture was allowed to reach r.t., **NO-7** (1 mmol) added and the mixture stirred overnight at 50 °C (1, 4-dioxane, if used, was then removed by evaporation and replaced with DCM). The mixture was washed with water (50 ml), the organic layer dried over MgSO4 and the solvent removed by evaporation. The crude product was purified with flash silica gel column chromatography after solvent evaporation and *N*-oxide **NO-7** was

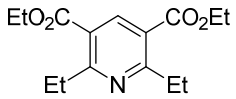
obtained in 80% yield (15% staring material recovered). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 4.42 (q, *J* = 7.1 Hz, 4H), 2.84 (s, 6H), 1.42 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.70, 153.64, 126.48, 126.28, 62.22, 15.97, 14.16; 296.15; IR (neat): 2993, 1725, 1366, 1299, 1232, 1065; MS (ES^+) Calculated for $[C_{13}H_{18}NO_5]^+$: 268.12; Found: 268.12.

NO-8a



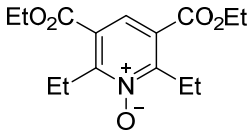
Hantzsch Ester **NO-8a** was prepared in 65% yield according to the literature procedure.[34] ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 4H), 3.27 (s, 2H), 2.61 (q, *J* = 7.5 Hz, 4H), 1.28 (dd, *J* = 9.1, 5.2 Hz, 6H), 1.15 (td, *J* = 7.6, 3.7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.53, 150.47, 98.56, 59.62, 25.78, 24.88, 14.43, 12.61.

NO-8b



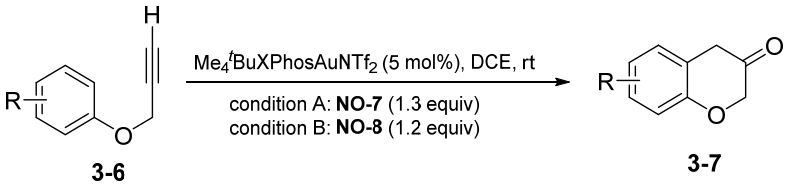
Pyridine **NO-8b** was prepared in 92% yield in the same way to **NO-7b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 4.39 (q, *J* = 7.1 Hz, 4H), 3.18 (q, *J* = 7.5 Hz, 4H), 1.41 (t, *J* = 7.1 Hz, 6H), 1.30 (t, *J* = 7.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.78, 166.13, 141.02, 122.55, 61.36, 30.43, 14.23, 13.82; IR (neat): 2979, 1725, 1594, 1292, 1236, 1106; MS (ES^+) Calculated for $[C_{15}H_{22}NO_6]^+$: 280.15; Found: 280.16.

NO-8



N-oxide **4e** was prepared in 65% yield (30% starting material recovered) in the same way to **NO-7**. ^{1}H NMR (400 MHz, cdcl$_3$) δ 8.02 (s, 1H), 4.41 (q, *J* = 7.1 Hz, 4H), 3.31 (q, *J* = 7.3 Hz, 4H), 1.41 (t, *J* = 7.1 Hz, 6H), 1.30 (t, *J* = 7.3 Hz, 6H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 164.73, 157.88, 126.41, 126.33, 62.15, 22.77, 14.14, 10.55; IR (neat): 2983, 1724, 1297, 1206, 1082; MS (ES$^+$) Calculated for [$C_{15}H_{22}NO_5$]$^+$: 296.15; Found: 296.15.

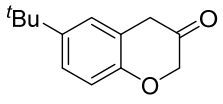
General Procedure B: Preparation of Chroman-3-Ones 3-7



3-6 **3-7**

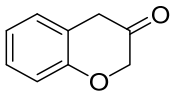
Pyridine *N*-oxide **NO-7** (0.65 mmol, 1.3 equiv.) or **NO-8** (0.6 mmol, 1.2 equiv.) was added to a solution of the propargyl aryl ether **3-6** (0.50 mmol) in DCE (10 mL. 0.05M) at room temperature, followed by Me$_4$^{t}BuXPhosAuNTf$_2$ (0.025 mmol, 5 mol %). The reaction mixture was stirred at r.t. and the progress of the reaction was monitored by TLC. The reaction typically took 1 – 3 h. Upon completion, the mixture was concentrated and the residue was purified by chromatography on silica gel (eluent: hexanes/ethyl acetate) to afford the desired products **3-7**.

3-7a



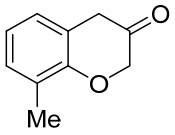
This compound was prepared in 82% yield using **NO-7** as oxidant according to the general procedure B. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 1H), 7.16 – 7.10 (m, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 4.40 (s, 2H), 3.63 (s, 2H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.99, 152.21, 146.32, 125.70, 125.37, 120.73, 117.04, 73.02, 41.21, 34.31, 31.46; IR (neat): 2961, 1736, 1615, 1502, 1262, 1042; GCMS *m*/*z* 204.00 (M^+).

3-7b



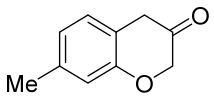
This compound was prepared in 76% yield using **NO-8** as oxidant according to the general procedure B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.20 (m, 1H), 7.12 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.05 (dd, *J* = 11.3, 4.4 Hz, 2H), 4.41 (s, 2H), 3.62 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.48, 154.50, 128.91, 128.40, 123.27, 121.46, 117.63, 77.25, 77.00, 76.74, 72.90, 40.83.

3-7c



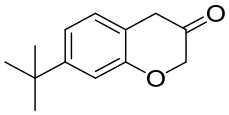
This compound was prepared in 78% yield using **NO-8** as oxidant according to the general procedure B. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.06 (m, 1H), 6.98 – 6.92 (m, 2H), 4.42 (s, 2H), 3.60 (s, 2H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.24, 152.77, 129.68, 127.20, 126.34, 122.88, 121.20, 77.32, 77.00, 76.68, 72.85, 41.09, 15.60; IR (neat): 2922, 1730, 1601, 1476, 1038, 763; GCMS *m*/*z* 162.00 (M^+).

3-7d



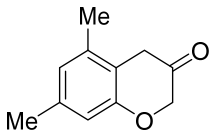
This compound was prepared in 67% yield (*p:o* = 12:1) using **NO-7** as oxidant according to the general procedure B.^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (d, *J* = 7.5 Hz, 1H), 6.87 (d, *J* = 8.9 Hz, 2H), 4.38 (s, 2H), 3.57 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.75, 154.33, 138.58, 128.57, 124.04, 118.20, 118.09, 72.91, 40.47, 21.09. IR (neat): 1621, 1582, 1506, 1431, 1267, 1238, 1148, 1120, 928, 813; GCMS *m/z* 162(M^+).

3-7e



This compound was prepared in 74% yield (*p:o* = 16:1, mixed with 3% **3-7a**) using **NO-7** as oxidant according to the general procedure B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (dt, *J* = 4.2, 1.8 Hz, 2H), 7.06 (dt, *J* = 8.4, 0.8 Hz, 1H), 4.41 (s, 2H), 3.59 (s, 2H), 1.32 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.75, 154.17, 152.30, 128.41, 120.36, 118.21, 114.65, 73.01, 40.39, 31.26; IR (neat): 2963, 1737, 1504, 1276, 1050; GCMS *m/z* 189(M^+).

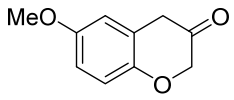
3-7f



This compound was prepared in 70% yield using **NO-7** as oxidant according to the general procedure B. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.74 (d, *J* = 11.0 Hz, 2H), 4.37 (s, 2H), 3.50 (s, 2H), 2.30 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.63,

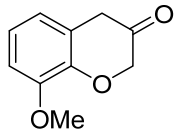
154.20, 137.73, 136.64, 125.41, 116.64, 115.72, 72.63, 37.55, 20.96, 18.68; IR (neat): 2919, 1735, 1583, 1298, 1083; GCMS *m*/*z* 175.95 (M^+).

3-7g



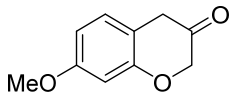
This compound was prepared in 83% yield using **NO-8** as oxidant according to the general procedure B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (d, *J* = 8.8 Hz, 1H), 6.76 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.64 (d, *J* = 2.6 Hz, 1H), 4.35 (s, 2H), 3.77 (s, 3H), 3.58 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.62, 155.51, 148.42, 122.54, 118.25, 113.72, 113.67, 73.14, 55.67, 41.18; IR (neat): 2961, 1732, 1499, 1248, 1198, 1058; GCMS *m*/*z* 177.95 (M^+).

3-7h



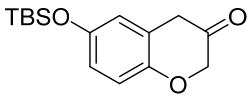
This compound was prepared in 70% yield using **NO-8** as oxidant according to the general procedure B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (t, *J* = 7.9 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 6.73 (dd, *J* = 7.6, 0.8 Hz, 1H), 4.46 (s, 2H), 3.90 (s, 3H), 3.61 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.39, 149.30, 143.56, 123.36, 122.61, 120.47, 110.79, 73.07, 56.00, 40.74; IR (neat): 2963, 1733, 1588, 1486, 1270, 1088; GCMS *m*/*z* 177.95 (M^+).

3-7i



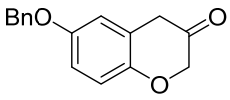
This compound was prepared in 75% yield (*p:o* = 11:1) at 0 °C using **NO-8** as oxidant according to the general procedure B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (d, *J* = 9.2 Hz, 1H), 6.62 (dd, *J* = 6.0, 2.5 Hz, 2H), 4.39 (s, 2H), 3.79 (s, 3H), 3.55 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.56, 159.94, 155.29, 129.32, 113.09, 109.59, 103.14, 72.92, 55.43, 40.07. IR (neat): 1733, 1620, 1587, 1506, 1447, 1290, 1274, 1201, 1158, 1108; GCMS *m/z* 178(M^+).

3-7j



This compound was prepared in 70% yield using **NO-7** as oxidant according to the general procedure B. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.91 (d, *J* = 8.7 Hz, 1H), 6.69 (dd, *J* = 8.7, 2.8 Hz, 1H), 6.59 (d, *J* = 2.8 Hz, 1H), 4.36 (s, 2H), 3.55 (s, 2H), 0.98 (s, 9H), 0.21 – 0.13 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 207.79, 151.31, 148.82, 122.44, 119.78, 119.64, 118.16, 73.14, 41.10, 25.63, 18.12, -4.50; IR (neat): 2930, 2858, 1737, 1493, 1252, 1199, 968, 839; GCMS *m*/*z* 277.95 (M^+).

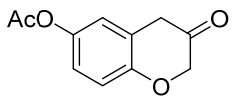
3-7k



This compound was prepared in 86% yield using **NO-8** as oxidant according to the general procedure B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.37 (m, 4H), 7.37 – 7.31 (m, 1H), 6.99 (d, *J* = 8.8 Hz, 1H), 6.85 (dd, *J* = 8.8, 3.0 Hz, 1H), 6.74 (d, *J* = 2.9 Hz, 1H), 5.03 (s, 2H), 4.37 (s, 2H), 3.58 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.61,

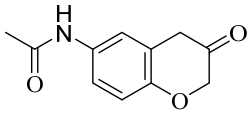
154.66, 148.60, 136.82, 128.55, 127.97, 127.36, 122.57, 118.29, 114.83, 114.74, 73.12, 70.54, 41.18; IR (neat): 1732, 1494, 1196, 1044; GCMS *m*/*z* 253.90 (M^+).

3-7l



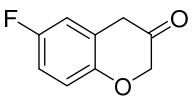
This compound was prepared in 63% yield using **NO-8** as oxidant according to the general procedure B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 – 7.03 (m, 1H), 6.97 – 6.91 (m, 1H), 6.87 (dt, *J* = 6.8, 2.9 Hz, 1H), 4.40 (d, *J* = 1.9 Hz, 2H), 3.60 (s, 2H), 2.31 – 2.26 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.66, 169.69, 152.11, 145.94, 122.53, 121.81, 121.47, 118.47, 77.25, 77.00, 76.75, 72.90, 40.79, 20.99; IR (neat): 1758, 1736, 1493, 1213, 1189, 1040; MS (ES^+) Calculated for $[C_{11}H_{10}KO_4]^+$: 245.02; Found: 245.09.

3-7m



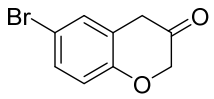
This compound was prepared in 81% yield using **NO-7** as oxidant according to the general procedure B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.39 (d, *J* = 2.1 Hz, 1H), 7.18 (dd, *J* = 8.6, 2.4 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 1H), 4.35 (s, 2H), 3.53 (s, 2H), 2.13 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.24, 168.65, 151.03, 133.26, 121.94, 121.00, 120.46, 117.83, 72.94, 40.85, 24.24; IR(neat):) 3288, 1732, 1663, 1552, 1498, 1423, 1256, 1205, 1043; ESI($M+Na^+$): 228.07

3-7n



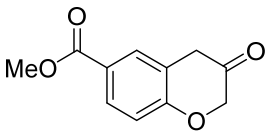
This compound was prepared in 54% yield using **NO-8** as oxidant according to the general procedure B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (dd, J = 8.9, 4.7 Hz, 1H), 6.95 – 6.90 (m, 1H), 6.87 – 6.83 (m, 1H), 4.39 (s, 2H), 3.60 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.64, 158.49 (d, J_{C-F} = 240 Hz), 150.57, 123.14 (d, J_{C-F} = 8.8 Hz), 118.80 (d, J_{C-F} = 8.8 Hz), 115.22 (d, J_{C-F} = 25 Hz), 115.01 (d, J_{C-F} = 23.8 Hz), 72.99, 40.89; IR (neat): 1736,1493, 1436, 1196, 1042, 820; GCMS *m/z* 166(M^+).

3-7o



This compound was prepared in 50% yield using **NO-8** as oxidant according to the general procedure B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (ddd, J = 8.6, 1.8, 0.6 Hz, 1H), 7.28 – 7.24 (m, 1H), 6.94 (d, J = 8.6 Hz, 1H), 4.40 (s, 2H), 3.59 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.13, 153.60, 131.55, 131.37, 123.61, 119.45, 115.48, 72.83, 40.41; IR (neat): 2892, 1727, 1485, 1262, 1179, 1044, 821; GCMS *m/z* 225.9 (M^+).

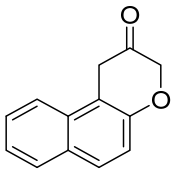
3-7p



This compound was prepared in 43% yield using **NO-7** as oxidant according to the general procedure B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 – 7.90 (m, 1H), 7.86 – 7.83 (m, 1H), 7.08 (d, J = 8.5 Hz, 1H), 4.47 (s, 2H), 3.90 (s, 3H), 3.66 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.75, 166.33, 158.10, 130.96, 130.33, 125.16, 121.07, 117.70,

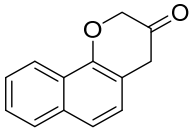
72.76, 52.11, 40.38; IR (neat): 1715, 1615, 1498, 1438, 1263, 770; GCMS *m/z* 206 (M^+).

3-7q



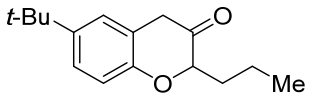
This compound was prepared in 68% yield using **NO-7** as oxidant according to the general procedure B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.1 Hz, 1H), 7.74 (dd, *J* = 8.4, 3.6 Hz, 2H), 7.55 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.44 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 7.24 (d, *J* = 8.9 Hz, 1H), 4.53 (s, 2H), 3.91 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.09, 151.67, 131.86, 129.97, 128.86, 128.74, 127.02, 124.41, 121.39, 118.51, 112.52, 72.49, 36.21, IR (neat): 1732, 1625, 1601, 1470, 1399, 1243, 1216, 1088, 1038, 814; GCMS *m/z* 198(M^+).

3-7r



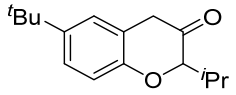
This compound was prepared in 81% yield using **NO-7** as oxidant according to the general procedure B. ^{1}H NMR (600 MHz, $cdcl_3$) δ 8.23 (d, *J* = 8.1 Hz, 1H), 7.86 – 7.81 (m, 1H), 7.59 – 7.48 (m, 3H), 7.19 (d, *J* = 8.3 Hz, 1H), 4.59 (s, 2H), 3.73 (s, 2H); ^{13}C NMR (150 MHz, $cdcl_3$) δ 207.53, 149.68, 133.63, 127.63, 126.39, 126.17, 126.10, 125.22, 122.79, 121.35, 115.08, 72.94, 40.41; IR (neat): 3053, 2924, 1734, 1580, 1384, 1266, 1100, 811; GCMS *m/z* 198.00 (M^+).

3-7s



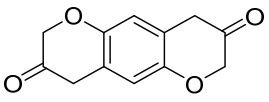
This compound was prepared in 83% yield using **NO-8** as oxidant according to the general procedure B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.22 (m, 1H), 7.11 – 7.07 (m, 1H), 6.96 (d, *J* = 8.5 Hz, 1H), 4.23 (dd, *J* = 8.5, 4.3 Hz, 1H), 3.58 (s, 2H), 1.85 – 1.72 (m, 2H), 1.61 – 1.49 (m, 2H), 1.31 (s, 9H), 0.96 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.42, 151.51, 145.94, 125.34, 125.22, 121.16, 117.23, 81.92, 40.96, 34.28, 32.88, 31.48, 18.36, 13.68; IR (neat): 2873, 1728, 1612, 1499, 1463, 1364, 1265, 1238, 1136, 825; GCMS *m/z* 246(M^+).

3-7t



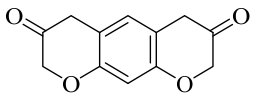
This compound was prepared in 66% yield using **NO-7** as oxidant according to the general procedure B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.23 (m, 1H), 7.10 – 7.06 (m, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 3.98 (d, *J* = 4.8 Hz, 1H), 3.55 (s, 2H), 2.32 (dtd, *J* = 13.7, 6.9, 4.8 Hz, 1H), 1.30 (s, 9H), 1.05 (dd, *J* = 58.4, 6.9 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.04, 151.86, 145.77, 125.33, 125.24, 120.95, 117.05, 86.44, 41.68, 34.26, 31.48, 30.24, 18.83, 17.02; IR (neat):1729, 1501, 1240, 1010; GCMS *m/z* 246 (M^+).

3-7u



This compound was prepared in 60% yield (*l:o* = 8:1) at 0 °C using **NO-8** as oxidant according to the general procedure B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.84 (s, 2H), 4.38 (s, 4H), 3.59 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.93, 150.26, 121.77, 117.62, 73.09, 40.80; IR (neat): 1733, 1496, 1442, 1406, 1261, 1188, 1169, 1048, 898, 726; GCMS *m/z* 218(M^+).

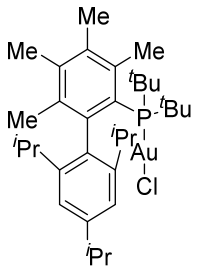
3-7v



This compound was prepared in 61% yield (*l:o* = 3.5:1) at 0 °C using **NO-8** as oxidant according to the general procedure B. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.91 – 6.83 (m, 1H), 6.78 (s, 1H), 4.39 (s, 4H), 3.56 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.83, 154.39, 128.62, 116.47, 107.23, 72.91, 40.24; IR (cm^{-1}) 1730, 1505, 1161, 1115; GCMS *m/z* 218 (M^+).

Synthesis of $Me_4{}^{t}$BuXPhosAuNTf$_2$

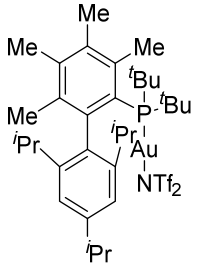
$Me_4{}^{t}$BuXPhosAuCl: Chloro(2-Di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl)gold(I)



To a suspension of 2-Di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl (480.8 mg, 1 mmol) in anhydrous DCM was added

chloro(dimethylsulfide)gold(I) (294.5 mg, 1 mmol). The mixture was stirred for 1 h at room temperature. The solvent was evaporated off under reduced pressure to give the desired gold complex (677 mg, 95%) as a white powder.

$Me_4{}^tBuXPhosAuNTf_2$



To a suspension of Chloro(2-Di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2',4',6'-triisopropyl-1,1'-biphenyl)gold(I) (677 mg, 0.95 mmol) in anhydrous DCM was added $AgNTf_2$ (386 mg, 0.95 mmol). The mixture was stirred for 1 h at room temperature. The AgCl was filtered and the solvent was evaporated off under reduced pressure to give the desired gold complex in quantitive yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15 (s, 2H), 2.97 (m, 1H), 2.63 (s, 3H), 2.39 – 2.28 (m, 5H), 2.24 (s, 3H), 1.54 (d, J = 18 Hz, 18H), 1.48 (s, 3H), 1.35 (d, J = 6 Hz, 6H), 1.29 (d, J = 6 Hz, 6H), 0.87 (d, J = 6 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ148.79, 146.25, 145.65 (d, J = 18 Hz), 140.79, 137.68 (d, J = 3 Hz), 137.51, (d, J = 7.5 Hz), 135.99 (d, J = 7.5 Hz), 123.26, 122. 80, 122.49, 120.65, 118.50, 42.59 (d, J = 21 Hz), 33.64, 33.22 (d, J = 7.5 Hz), 30.84, 28.15, 25.40, 24.68, 23.82, 22.55 (d, J = 2.7 Hz), 17.76, 17.27; ^{31}P NMR (162 MHz, $CDCl_3$) δ 76.61.

3.8. References

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4. Homogeneous Au-Catalyzed Indole Synthesis

4.1. Au-Catalyzed Synthesis of 2-Alkylindole from N-Arylhydroxylamines and Terminal Alkynes

4.1.1. Introduction and Design

Indole derivatives are probably the most ubiquitous heterocycles in nature. On account of the great structural diversity and biological activity of indoles, it is not surprising that the indole ring has become an extremely important structural component in pharmaceuticals,[1] agrochemicals[2] and even material science.[3] Substituted indoles have been always referred to as "privileged structures" since they are capable of binding to many receptors with high affinity.[4] For well over a century, the synthesis and functionalization of indoles has been a hot research area for synthetic organic chemists, and numerous methods for the preparation of indoles have been developed.[5] Starting material availability and functional group tolerance often serve as the key factors to decide that which particular indole synthesis will be suitable.

One of the oldest but most reliable methods for synthesizing substituted indoles is the Fischer indole synthesis, which has been subjected to extensive modifications/improvements and applied extensively including in the synthesis of various indole alkaloids since the original report by Fischer in 1893. This annulation between an arylhydrazine and a ketone relies on a crucial 3,3-sigmatropic rearrangement of an *N*-alkenyl-*N*'-arylhydrazine intermediate. While it has been

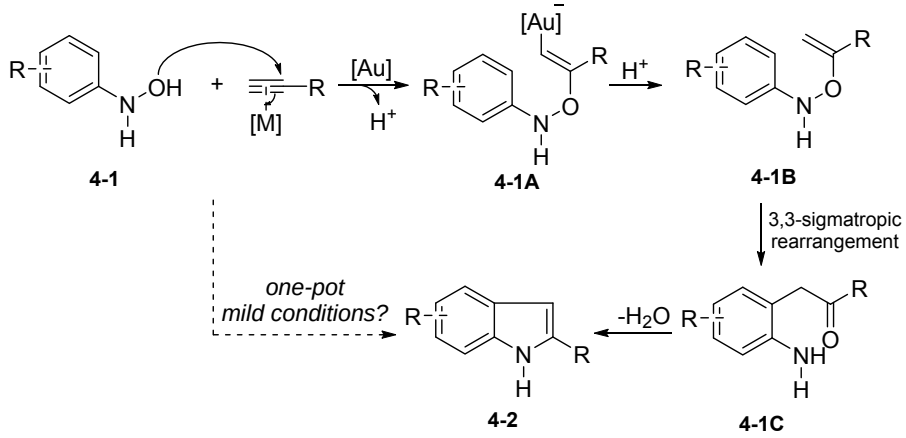
subjected to various modifications/improvements, there are still notable deficiencies including: 1) harsh reaction conditions, like strong acidic conditions and high temperature; 2) the difficulty in achieving excellent regioselectivities with unsymmetric ketones; 3) failure to indolize α,β-unsaturated ketones due to the preferred formation of pyrazolines; 4) and low efficiencies with substrates containing electron-withdrawing substituents on the aromatic ring. While catalytic hydroamination of alkynes has been developed as an alternative approach to *N*-alkenylhydrazines, the reported reaction scopes are mostly limited to arylalkynes and reaction conditions are still strong.[6,7]

Similarly to Fisher indole synthesis, 3,3-rearrangements of *O*-vinyl-*N*-arylhydroxylamines or its derivatives can lead to indole synthesis upon successive cyclodehydration. A prominent example is the Bartoli indole synthesis. While this indolization typically proceeds at much lower temperatures than in the case of the Fischer indole synthesis, three equivalents of vinyl Grignard reagent were obligatory if nitroarenes are the substrates; for nitrosoarene, two equivalents of Grignard reagent were indispensable. Considering being severely limited by the requirement of an *ortho* substitution in the nitroarene substrate, the functional group tolerance and the moderate efficiency of this reaction, it's safe to say that there is a lack of mild, general and straightforward methods for the generation of *O*-alkenyl-*N*-arylhydroxylamines.

We anticipated that these *O*-alkenyl-*N*-arylhydroxylamine intermediates **4-1B** could be formed via gold-promoted addition of the HO group of

N-arylhydroxylamines **4-1** onto C-C triple bonds. After the facile 3,3-sigmatropic rearrangement, intermediates **4-1C** were formed and gave the 2-substituted indoles **4-2** through dehydrated cyclization (Scheme 63). By using alkynes as substrates, this indole synthesis may offer solutions to some of the difficulties in the Fischer indole synthesis and Bartoli indolization. To our surprise, this strategy has not been realized although related reactions using propiolates and hydroxamic acids in the presence of bases have been reported.[8,9]

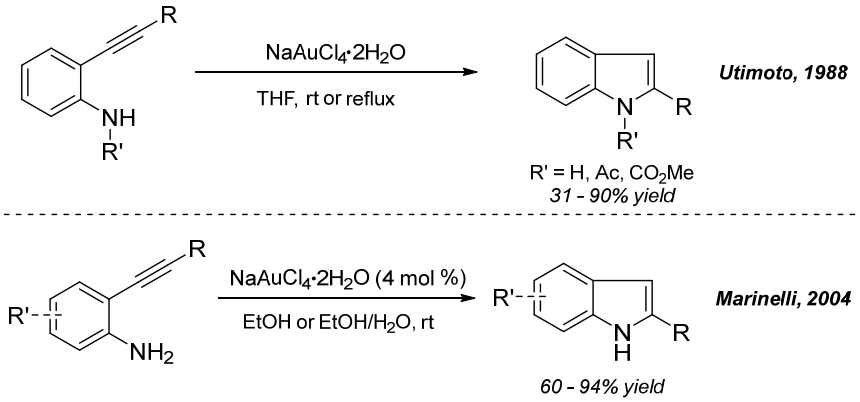
Scheme 63. Formation of *O*-Alkenyl-*N*-phenylhydroxylamines via HO Addition to Alkynes en Route to Indoles



Gold-catalyzed synthesis of indoles has been realized long time ago and the first example was reported by Utimoto et al.[10] in 1988. Catalyzed by $NaAuCl_4$, 2-substitued indoles were efficiently prepared starting from 2-alkylnylanilines in THF by an intramolecular *5-endo-dig* cyclization. *N*-protected anilines reacted analogously to give *N*-protected indoles in good yields. Sixteen years later, Marinelli et al.[11] came

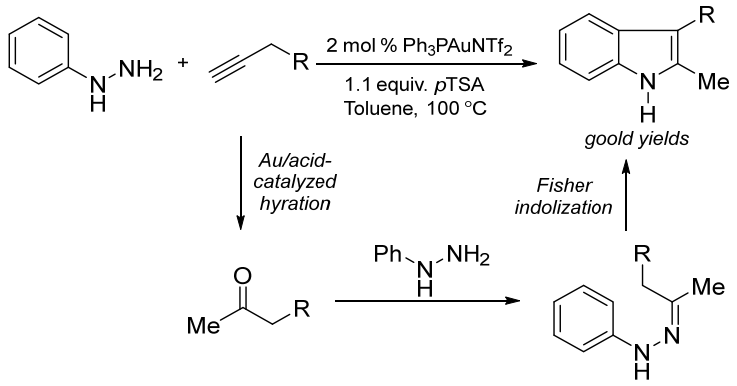
up with a broader substrates scope for this reaction with the same catalyst but different solvent (Scheme 64)

Scheme 64. Au(III)-Catalyzed Indole Synthesis from 2-Alkylnylalines



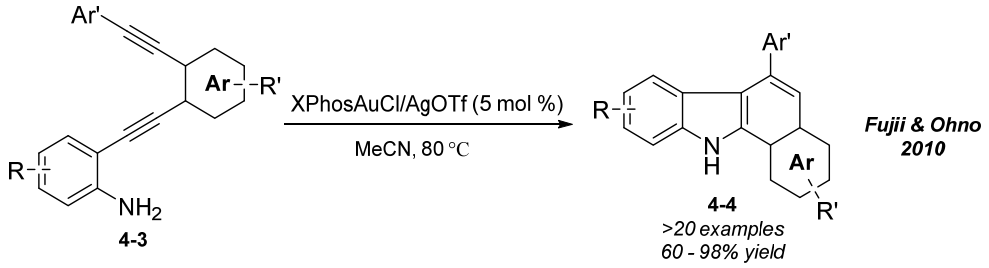
An efficient method involving a formal tandem hydrohydrazination/Fischer indolization reaction to synthesize 2-methyl-3-substituted indoles from alkynes and arylhydrazines was developed by Patil et al.[12] in 2010 using a $Ph_3PAuNTf_2$/*p*TSA·H_2O binary catalytic system (Scheme 65). One feather of this methodology is that the reaction is not sensitive to moisture since water is essential to get the reaction going. The mechanism of these reactions has been investigated and the authors proposed an interesting mechanistic dichotomy. When alkynes have OH/COOH groups in the tether, hydroalkoxylation/hydrocarboxylation occurred to generate exocyclic enol ethers/lactones that reacted with hydrazines to produce indoles. In cases where the alkynes lack OH/COOH groups, Au/acid promoted hydration occurs first to generate ketones, which then react with arylhydrazines to give the desired indoles.

Scheme 65. Formal Tandem Hydrohydrazination/Fischer Indolization Catalyzed by $Ph_3PAuNTf_2$/*p*TSA Binary System



In 2011, Fujii and Ohno reported that through a gold-catalyzed intramolecular cascade *5-endo-dig* hydroamination followed by a *6-endo-dig* cycloisomerization, diynes **4-3** were smoothly converted to various fused indoles **4-4**, such as aryl-annulated carbazoles, dihydrobenzo indoles, and azepino- or oxepinoindole derivatives, in good to excellent yields (Scheme 66).[13]

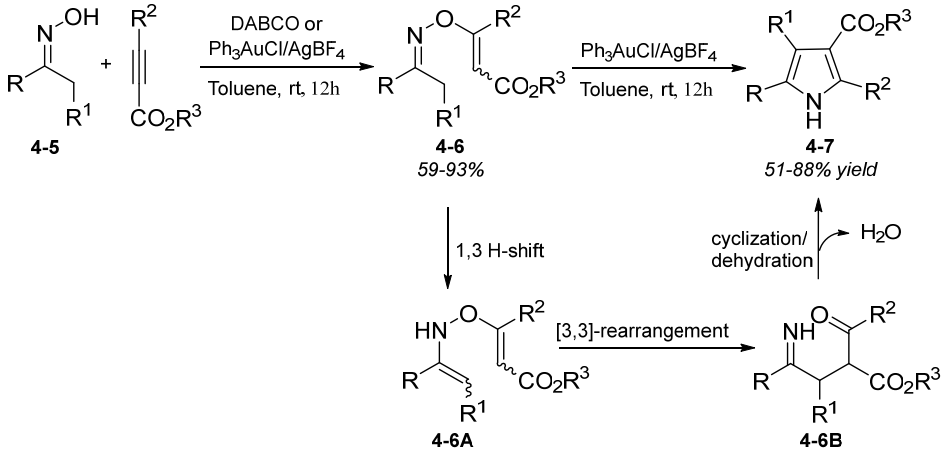
Scheme 66. Gold(I)-Catalyzed Fused-indole Synthesis



Early in 2011, through the reaction of oximes **4-5** with activated alkynes promoted by base or $Ph_3PAu(I)$, Camp et al.[14] synthesized *O*-vinyl oximes **4-6**,

which undergo a 1,3-hydrogen shift to afford 1,5-diene **4-6A**. Subsequent gold catalysis introduced 3,3-rearrangement to give intermediates **4-6B**, followed by cyclodehydration to yield the highly substituted pyrroles **4-7** in an efficient and region-controlled process (Scheme 67).

Scheme 67. Gold-Catalyzed Pyrrole Synthesis from Oxime and Activated Alkynes

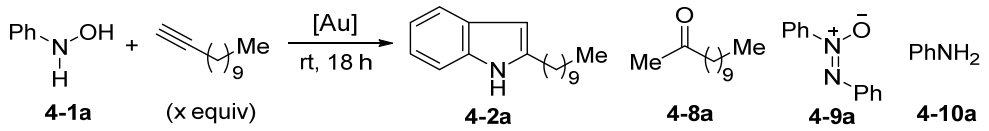


Efficient additions of various nucleophiles (NuH) to C–C triple bonds have been successfully realized in gold catalysis; however, hydroxylamines have not been used as nucleophiles so far. We envisioned that *O*-alkenyl-*N*-arylhydroxylamine **4-1B** (Scheme 63) should be easily formed via the nucleophilic attacks of *N*-arylhydroxylamines **4-1** toward the gold-activated alkynes under mild reaction conditions.

4.1.2. Conditions Study

Having this design shown in Scheme 63 in mind, I quickly put the idea to the test. The results of condition optimization were summarized in Table 12. *N*-phenylhydroxylamine **4-1a** was selected to be the standard nucleophile as it's easy to access from the reduction of nitrobenzene, and two equivalents of 1-dodecyne was used as the reaction partner. When the first time I run the reaction with $Ph_3PAuNTf_2$ as the catalyst, delightfully 2-*n*-decylindole **4-2a** was indeed formed in 57% yield at room temperature after 18 h (entry 1). Methyl ketone **4-8a** was the major side product (62% yield, based on 1 equivalent of **4-1a**), plus small amount of diazene *N*-oxide **4-9a** and aniline **4-10a** (10%). We ascribed the formation of **4-8a** partly to the competitive N-H addition of **4-1a** to the alkyne and subsequent hydrolysis of nitrone **4-1a'** (Scheme 68-A), and partly to direction gold-catalyzed hydration of alkynes. H_2O consumed in these hydration processes should mostly come from the cyclodehydrative indole formation. To minimize the costume of alkynes, 4Å molecular sieve was added to the reaction, but unfortunately it slowed down the reaction rate significantly, giving less than 20% product after 18 h. *N*-arylhydroxylamine **4-1a** is known to disproportionate easily to produce aniline **4-10a** and nitrosobenzene **4-11a**, which was probably *in-situ* trapped by **4-1a**, followed by dehydration to give diazene *N*-oxide **4-9a**.

Table 12. Condition Optimization



4-1a (x equiv) **4-2a** **4-8a** **4-9a** **4-10a**

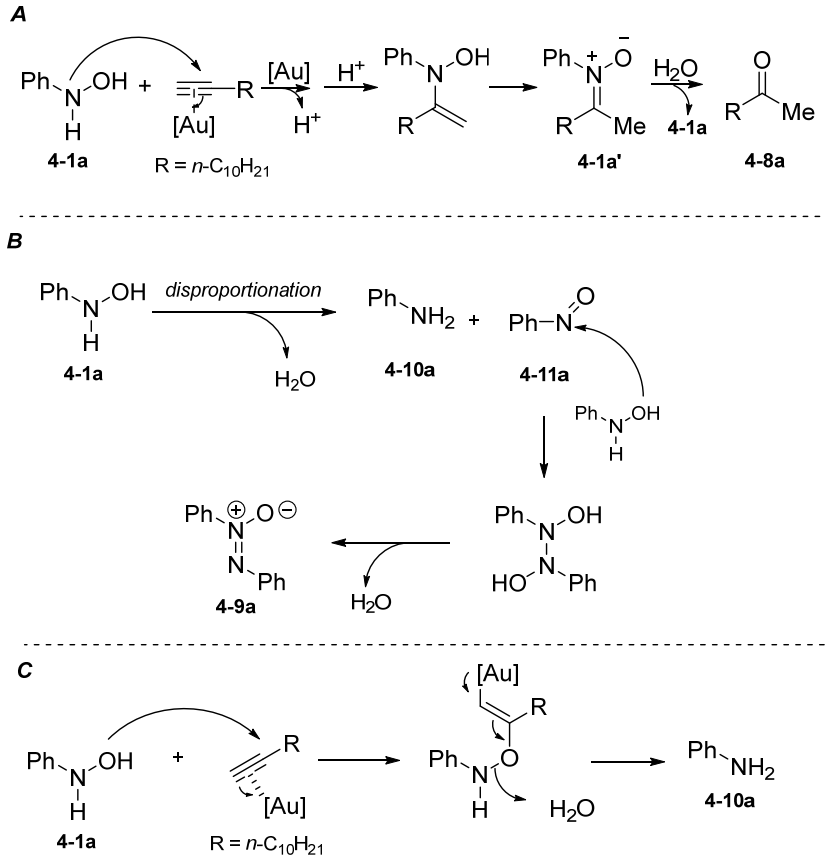
entry	catalyst	x	Solvent [a]	Yield [b]			
				4-2a	**4-8a**	**4-9a**	**4-10a**
1	$Ph_3PAuNTf_2$	2	DCM	57%	62%	trace	9%
2	$(4\text{-}CF_3Ph)_3PAuNTf_2$	2	DCM	74%	72%	trace	6%
3	$IPrAuNTf_2$	2	DCM	63%	55%	trace	8%
4	$(ArO)_3PAuNTf_2$	2	DCM	83%	74%	1%	3%
5	$Et_3PAuNTf_2$	2	DCM	46%	61%	trace	10%
6	$BrettphosAuNTf_2$	2	DCM	21%	67%	0%	10%
7	$(F_5Ph)_3PAuNTf_2$	2	DCM	4%	8%	9%	7%
8	$QPhosAuNTf_2$	2	DCM	30%	70%	3%	20%
9	$(ArO)_3PAuNTf_2$	2	DCE	94%	71%	2%	4%
10	$(ArO)_3PAuNTf_2$	2	Et_2O	93%	80%	3%	1%
11	$(ArO)_3PAuNTf_2$	2	THF	40%	78%	6%	2%
12	$(ArO)_3PAuNTf_2$	2	acetone	52%	66%	4%	5%
13	$(ArO)_3PAuNTf_2$	2	CH_3CN	38%	24%	4%	5%
14	$(ArO)_3PAuNTf_2$	2	toluene	93%	65%	1%	2%
15	$(ArO)_3PAuNTf_2$	2	hexanes	28%	60%	trace	4%
16	$(ArO)_3PAuOTf$	2	DCE	55%	57%	3%	4%
17	$Ph_3PAuClO_4$	2	DCE	57%	45%	2%	6%
18	$Hg(OTf)_2$	2	DCE	2%	35%	15%	13%
19	$(ArO)_3PAuNTf_2$	1.8	DCE	86%[c]	75%	1%	2%
20	$(ArO)_3PAuNTf_2$	1.6	DCE	76%	63%	2%	4%

[a] Anhydrous solvents were used; [**1a**] = 0.1 M; under nitrogen. [b] Estimated by ^1H NMR using diethyl phthalate as internal reference. [c] 84% isolated yield. Ar = 2,4-di-*tert*-butylphenyl.

Different gold catalysts were immediately screened (entries 2-7). When the ligand changed from Ph_3P to more electron-deficient $(4\text{-}CF_3Ph)_3P$, the reaction was improved from 57% (entry 1) to 74% (entry 2). Gold catalyst based on electron-rich ligands (i.e., IPr, Et_3P, BrettPhos and QPhos) gave no promising results (entries 3, 5,

6, 8), and $(F_5Ph)_3PAuNTf_2$ turned out to be useless for unknown reasons (entry 7). More electron-deficient phosphite-based cationic gold(I) complex, $(ArO)_3PAuNTf_2$ (Ar = 2,4-di-*tert*-butylphenyl), gave the best 83% yield (entry 4). Dichloro(2-picolinato)Au(III) only provided significant amount of diazene *N*-oxide **4-9a**, but no desired product was detected.

Scheme 68. Possible Pathways of By-products Formation



During the catalyst screening, I found out that more electron-rich gold(I) catalysts yielded more aniline **4-10a**, 10% for $Et_3PAuNTf_2$, 10% for BrettphosAuNTf$_2$ and 20% for even more electron-rich QPhosAuNTf$_2$. These results might indicate that another pathway could also possibly contributed to the formation of **4-10a** (Scheme

68-C). Just like the pyridine *N*-oxide, it's possible that **4-1a** oxidizes the alkyne to α-oxo gold carbene and generate aniline as the side-product. Higher temperature was also tried, but hydroxylamine **4-1a** decomposed even at 40 °C, giving around 40% yield.

After the catalyst investigation, solvents were then examined. To my surprise, DCE somehow was a better solvent than DCM, and the yield was increased to 94% (entry 9). While diethyl ether provided as good yield as DCE (entry 10, 93%), more polar THF, acetone and acetonitrile gave worse results (entries 11-13). Relatively non-polar toluene worked very well (entry 14, 93%), but extremely non-polar hexanes gave very poor result (entry 15). With DCE as the ideal solvent, $(ArO)_3PAuOTf$, which is only different from the contour ion of the best catalyst, was then tested but gave very lousy outcome (entry 16); so do did $Ph_3PAuClO_4$ (entries 17). Nonsterically demanding π-acid $Hg(OTf)_2$ was also investigated; **4-8a** (35%), **4-9a** (15%) and **4-10a** (13%) were the major products observed and the desired indole **4-2a** was only formed in 2% yield (entry 18). The reaction yield decreases as the amount of the alkyne decreases (entries 19 and 20). With 1.8 equivalent of 1-dodecyne, the reaction yield was still pretty good, and the isolated yield was 84%.

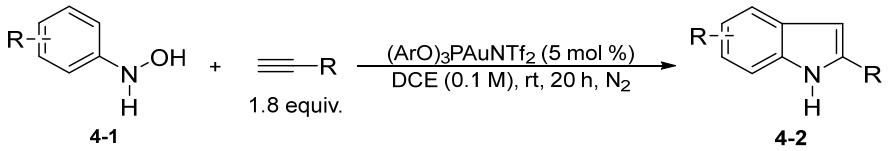
4.1.3. Substrates Scope

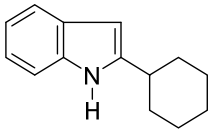
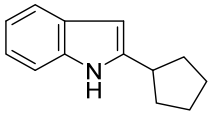
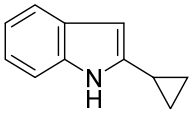
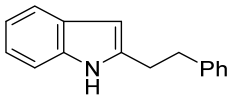
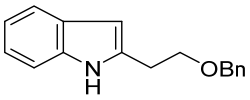
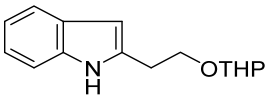
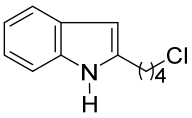
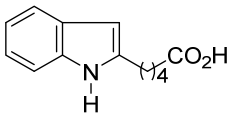
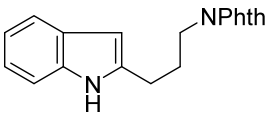
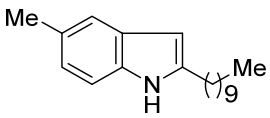
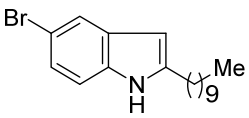
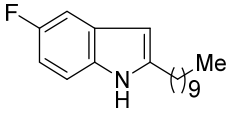
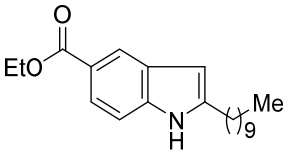
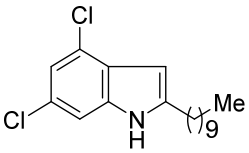
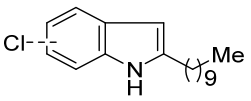
After the optimal conditions got figured out, the scope of alkynes was first studied. As shown in Table 13, this gold-catalyzed indole synthesis worked well with

various cycloalkylacetylenes (**4-2b/c/d**), including cyclopropylacetylene (**4-2d**). Linear aliphatic terminal alkynes containing various functional groups also reacted well. These functional groups include phenyl (**4-2e**), benzyl protected hydroxyl group (**4-2f**), chloro (**4-2h**), free carboxylic acid (**4-2i**) and a protected amino group (**4-2j**). Of particular note is the tolerance of the acid labile THP group (**4-2g**), confirming the exceptionally mild nature of this indolization; again, in contrast, the Fischer indole synthesis is typically performed under highly acidic environment. This mild reaction conditions also permit the preparation of chloroindole **4-2h** without affecting with the chloro moiety. However, terminal enynes and internal alkynes (Figure 13) were not suitable substrates and the reactions gave either complicated results or low reactivities.

The scope of *N*-arylhydroxylamines **4-1** were then inspected. A weakly electron-donating methyl group (**4-2k**) or electron-withdrawing halides (**4-2l/m/o/p**) and ester group (**4-2n**) at the benzene ring *para* or *meta* to the hydroxylamine moiety permitted good to efficient reaction outcomes although there was almost no regioselectivity for *N*-(3-chlorophenyl)hydroxylamine (**4-2p**). A few limitations still exist: an *ortho*-Me group led to poor yield (<10%), and *N*-(4-methoxyphenyl)hydroxylamine was too labile for this chemistry. The general allowance of electron-withdrawing groups in this chemistry nicely complement the Fischer indole synthesis, where low yields are normally obtained. For the above examination of substrate scope, Dr. Longwu Ye offered tremendous help.

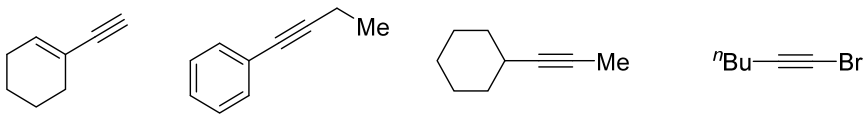
Table 13. Reaction Scope Studies



		
4-2b, 77%,	**4-2c**, 62% [a]	**4-2d**, 70%
		
4-2e, 89%	**4-2f**, 84%	**4-2g**, 67%
		
4-2h, 74%	**4-2i**, 73%	**4-2j**, 72%
		
4-2k, 64%	**4-2l**, 86%	**4-2m**, 82%
		
4-2n, 76%,	**4-2o**, 63%,	**4-2p**, 85% (4-Cl/6-Cl = 1/1.3.)

[a] Toluene as the solvent. Ar = 2,4-di-*tert*-butylphenyl.

Figure 13. Problematic Alkynes



An important feature of this methodology is the exclusive selectivity toward 2-alkylindoles, and no 3-alkylindoles were observed. This excellent regioselectivity benefits from the Markovnikov additions of *N*-arylhydroxylamines to the gold-activated terminal alkynes. In contrast, with corresponding methyl ketones as substrates coupled with *N*-arylhydrazines in the Fischer indole synthesis, strongly acidic mediums (e.g., 5 % P_2O_5/neat MsOH[15] or neat polyphosphoric acid[16]) are compulsory to yield 2-alkylindoles, and the regioselectivities were typically low to moderate.

4.1.4. Conclusions

A novel access to *O*-alkenyl-*N*-arylhydroxylamines via the first gold-catalyzed addition of *N*-arylhydroxylamines to aliphatic terminal alkynes has been developed. This mild gold catalysis took advantage of a facile *in situ* 3,3-rearrangement and subsequent cyclodehydration, affording 2-alkylindoles regiospecifically in typically good yields under exceptionally mild reaction conditions. An additional feature of this strategy is the allowance of electron-withdrawing substituents on the benzene ring, offering corresponding indole products with much higher yields than in the case of the Fischer indole synthesis. To overcome the limitation of this chemistry, which is limited substrate scope of alkynes, we came up with following methodology, a strategic push-pull dual catalysis.

4.2. Combining Zn ion Catalysis with Homogeneous Gold Catalysis: an Efficient Annulation Approach to N-Protected Indoles

4.2.1. Introduction

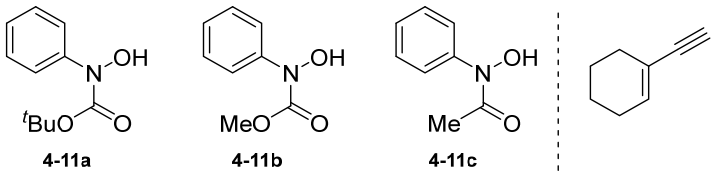
Although the above chemistry represents a significant improvement in the synthesis of 2-alkylindoles over the Fischer indole synthesis and Bartoli indolization, our attempts to extend this methodology to the synthesis of other types of indoles were thwarted by intrinsic slow rate of the reactions and terrible thermo stabilities of *N*-arylhydroxylamines. The aliphatic terminal alkynes used in the previous studies seem to be the only effective substrates for this chemistry, and the reactions still required 18 h or so to reach completion at room temperature under the protection of inert atmosphere. Increasing reaction temperature was injurious as *N*-arylhydroxylamines easily underwent disproportionation and/or decomposition. When less reactive internal alkynes, terminal arylalkynes and enynes were employed, the reaction yields were generally less than 15%. As a result, an improved synthetic approach to access the key intermediates *O*-alkenyl-*N*-arylhydroxylamines or their derivatives is crucial in order to establish a broadly applicable alternative to the Fischer and Bartoli indole synthesis. Additional drawbacks with the previous work are the necessity to use large excess of alkynes (typically 1.8 equivalent) in order to compensate the competing hydration reaction of alkynes resulting from *in situ* formed H_2O, and often

difficulties in separating the indole products from the generated methyl ketones.

4.2.2. Conditions Study and New Design

Reasoning that the thermostability of *N*-arylhydroxylamines can be considerably improved by mounting the nitrogen with electron-withdrawing groups, I converted the *N*-phenylhydroxylamine **4-1a** into *N*-hydroxycarbamates (**4-11a**, **4-11b**) and hydroxamic acid (**4-11c**) (Figure 14); however, this modification is at the expense of the nucleophilicity of the HO group and hence the reaction rate would decrease for sure.

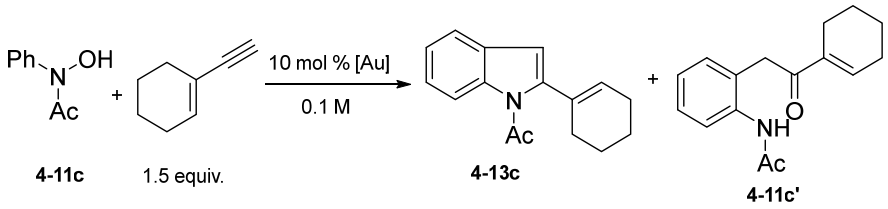
Figure 14. *N*-Protected Arylhydroxylamines



Terminal enyne 1-Ethynylcyclohex-1-ene was used to test the reactivity of *N*-protected hydroxylamines **4-11a/b/c** since it's one of the challenging substrates and it would afford synthetically valuable 2-alkenylindole. We thought that increasing the reaction temperature might compensate the loss of reaction rate, but little improvement was realized for *N*-hydroxycarbamates **4-11a** and **4-11b**. Surprisingly, when hydroxamic acid **4-11c** was then tested in toluene with 10 mol % gold(I) complex at 100 °C, both desired indole product **4-13c** and the

intermediate **4-11c'** before the cyclodehydration step were observed. Simple $Ph_3PAuNTf_2$ gave a 31% yield and its electron-deficient version $(4\text{-}CF_3Ph)_3PAuNTf_2$ improved the yield to 50% (entries 1, 2). Again, similarly to the cases of *N*-arylhydroxylamines (Table 12): electron-rich $Et_3PAuNTf_2$ led to a disappointing result (entry 3), and more electron-deficient phosphite-based cationic gold(I) complex, $(ArO)_3PAuNTf_2$ (Ar = 2,4-di-*tert*-butylphenyl) provided an optimal 59% yield (entry 5). Although only 14% **4-13c** was afforded for $IPrAuNTf_2$, 35% intermediate **4-11c'** also formed, which gave a decent combined yield of 49%. Considering the good thermal stability of this catalyst, longer reaction time could potentially lead to a high yield, but no further experiment was run to demonstrate this possibility because the high catalyst loading and harsh thermal condition would not be ideal. Nano gold supported on ZrO_2 or CeO_2 did not deliver any product **4-12c** or intermediate **4-11c'** (entries 6, 7). Notably, most gold(I) catalysts were not stable at such high temperature except $IPrAuNTf_2$, and gold(0) metal were often observed after 1-2 hours at a such high temperature. A few more polar solvents were also examined, but none of them gave any promising results (entries 8-10), which is also consistent with Table 12. Slightly high temperature gave a slightly better yield, 66% **4-12c** and 4% **4-11c'** (entry 11). Again, the gold catalyst $(ArO)_3PAuNTf_2$ crashed out in less than 2 hours.

Table 14. Catalysts Screening [a]



entry	catalyst	solvent	temp	time	**4-13c**	**4-11c'**
1	$Ph_3PAuNTf_2$	toluene	100 °C	2 h	31%	trace
2	$(4\text{-}CF_3Ph)_3PAuNTf_2$	toluene	100 °C	2 h	50%	trace
3	$Et_3PAuNTf_2$	toluene	100 °C	2 h	6%	trace
4	$IPrAuNTf_2$	toluene	100 °C	2 h	14%	35%
5	$(ArO)_3PAuNTf_2$ [b]	toluene	100 °C	2 h	59%	-
6	Au/ZrO_2	toluene	100 °C	12 h	-	-
7	Au/CeO_2	toluene	100 °C	12 h	-	-
8	$(ArO)_3PAuNTf_2$	CH_3CN	100 °C	2 h	trace	26%
9	$(ArO)_3PAuNTf_2$	anisole	100 °C	2 h	27%	-
10	$(ArO)_3PAuNTf_2$	1,4-dioxane	100 °C	2 h	4%	-
11	$(ArO)_3PAuNTf_2$	toluene	110 °C	2 h	66%	4%

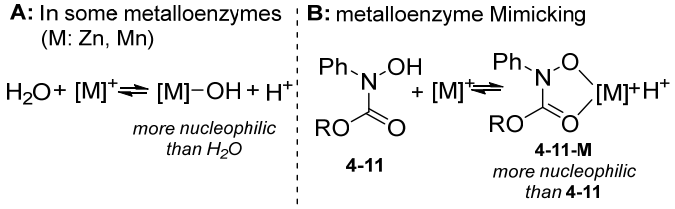
[a] Yield was estimated by ^1H NMR using diethyl phthalate as internal reference. Ar = 2,4-di-*tert*-butylphenyl.

Variation of other reaction conditions did not offer any further improvement, we concluded that a new scheme had to be developed to dramatically improve this chemistry. A push-pull strategy came to our mind: with the gold catalyst coordinating to the alkyne and enhancing its electrophilicity, the most promising breakthrough relies on the enhancement of the nucleophilicity of the *N*-protected hydroxylamines in some special way.

Inspired by the fact that metal ions are able to enhance the nucleophilicity of H_2O by forming metal hydroxides in metalloenzyme catalysis (Scheme 69-A),[17] we believed that the nucleophilicity of **4-11** could be boosted in a similar

enzyme-mimicking style as well. In fact, compared with H_2O, **4-11** possesses a stronger capability to coordinate metal ions which could be bound by the two oxygen atoms of **4-11**. In the area of coordination chemistry, it's well-known that hydroxamic acids are excellent ligands for their chelating competence.

Scheme 69. Enhancing the Nucleophilicity of 4-11 by a Metal Ion.

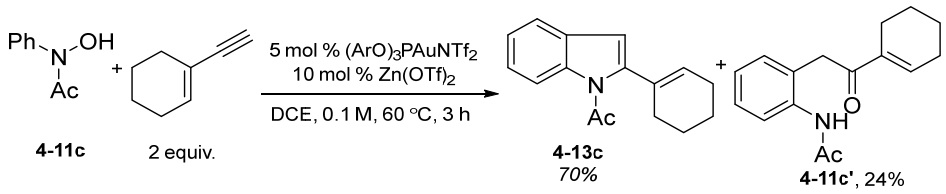


As shown in Scheme 69-B, **4-11** could react with a metal ion to form metal chelate **4-11-M** and proton reversibly. Because of the bidentate nature of the deprotonated **4-11**, **4-11-M** should be generated in a significant amount.[18] As in metalloenzyme catalysis, **4-11-M** should be more nucleophilic than **4-11** owing to the increased negative charge on the deprotonated oxygen. I looked up our inventory trying to find out which metal salt could be applicable to this design, and $Zn(OTf)_2$ was chosen to be the partner of this gold-catalyzed reaction for three reasons: 1) Zn(II) was a hard Lewis acid which would bind with the two oxygens of **4-11** very tightly; 2) OTf^- is a very week counter ion that enhance the acidity of Zn(II) and would not trap Au(I) to decrease its catalytic activity; 3) it might also assist the last cyclodehydration step.

When $Zn(OTf)_2$ (10 mol %) was added as a cooperative catalyst, the reaction

was drastically accelerated even with 5 mol % gold catalyst, and indole product **4-13c** was formed in 70% yield with 24% intermediate **4-11c'** uncyclized after 3 h at only 60 °C (Scheme 70). This stands for a much more efficient dual-catalysis approach under milder reaction conditions comparing to the previous solo gold catalysis under severe thermal conditions, the best result of which was 66% **4-13c** plus 4% **4-11c'** with 10 mol % gold catalyst at 110 °C (Table 14, entry 11). It's worthy to mention that the most common metal employed in hydrolytic or hydration metalloenzymes (e.g., human carbonic anhydrase II) is Zn(II).

Scheme 70. Zn Effect



Pleasingly, *N*-arylcarbamates **4-11a** and **4-11b** also provided very good results by this strategy, which will be reported later. When the terminal aliphatic alkyne (i.e., 1-dodecyne) served as the substrate, an even better outcome was achieved. Then I began a comprehensive investigation about the reaction conditions by using *tert*-butyl-*N*-hydroxy-*N*-phenylcarbamate **4-11a** and 1-dodecyne as the standard substrates, to see if this dual catalysis was a general method to solve the problems mentioned earlier in this section. The reason why carbamate **4-11a** was chosen instead of hydroxamic acid **4-11c** is that it could be prepared not only via sequential nitrobenzene reduction and protection, but also through Cu-[19] or

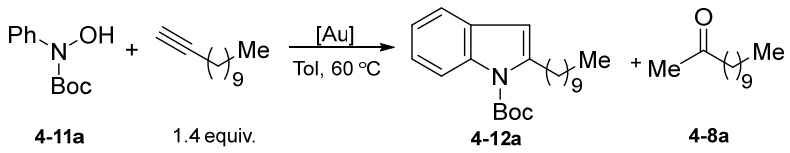
Pd-catalyzed[20] cross coupling reactions.

As shown in Table 15, in the presence of a slight excess of 1-dodecyne and catalytic $(ArO)_3PAuNTf_2$ (Ar = 2,4-di-*tert*-butylphenyl), only a little indole **4-12a** was formed in toluene at 60 °C after 12 h without $Zn(OTf)_2$. Instead, the hydration product, methyl ketone **4-8a**, became significant over time (Table 1, entry 1). This result confirmed our initial concern that heating the reaction might not compensate the diminished nucleophilicity of **4-11a**. After only 5 mol % $Zn(OTf)_2$ was added to the reaction, a satisfying 91% yield was obtained in only 2 hours (entry 2). With $Cu(OTf)_2$ as the co-catalyst, a very disappointing result was gained (entry 4, 18%) possibly due to the oxidative property of Cu(II), but still better than the case without additive (entry 1, 4%). $Sc(OTf)_3$ led to a decent result (entry 3, 75%), and $Dy(OTf)_3$ worked even better (entry 5, 89%), almost as well as $Zn(OTf)_2$.

Subsequent variations of the gold catalyst (entries 6-12) showed that $(ArO)_3PAuNTf_2$ (Ar = 2,4-di-*tert*-butylphenyl) gave the best yield of the desired product once more (Table 15, entry 8). Ph_3AuNTf_2 provided moderate yield (entry 6), and more electron-deficient $(4\text{-}CF_3Ph)_3PAuNTf_2$ offered a better yield (entry 7). Electron-rich $IPrAuNTf_2$ and Et_3AuNTf_2 failed to give good yields just as expected (entries 8, 9), and much less effective dichloro(2-picolinato)Au(III) and $PtCl_2$ only yielded none or 5% product (entries 11, 12). To my surprise, $BrettPhosAuNTf_2$ worked pretty well (entry 10, 83%), which did not deliver satisfactory results in the previous indole synthesis from free *N*-arylhydroxylamines (Table 12, entry 6). $(ArO)_3PAuOTf$ was also tested to see if

the same counter ion to $Zn(OTf)_2$ could offer any improvement compared to NTf_2, but the result was very much alike (entry 13, 91%).

Table 15. Catalysts and Additives Investigation [a]



4-11a 1.4 equiv. **4-12a** **4-8a**

entry	gold catalyst	additive (5 mol %)	time	yield [b]	
				4-12a	**4-8a**
1	$(ArO)_3PAuNTf_2$	-	12 h	4%	76%
2	**$(ArO)_3PAuNTf_2$**	**$Zn(OTf)_2$**	2 h	91% [c]	32%
3	$(ArO)_3PAuNTf_2$	$Sc(OTf)_3$	2 h	75%	50%
4	$(ArO)_3PAuNTf_2$	$Cu(OTf)_2$	12 h	18%	86%
5	$(ArO)_3PAuNTf_2$	$Dy(OTf)_3$	2 h	89%	40%
6	$Ph_3PAuNTf_2$	$Zn(OTf)_2$	6 h	62%	45%
7	$(4\text{-}CF_3Ph)_3PAuNTf_2$	$Zn(OTf)_2$	6 h	77%	37%
8	$IPrAuNTf_2$	$Zn(OTf)_2$	6 h	40%	60%
9	$Et_3PAuNTf_2$	$Zn(OTf)_2$	6 h	41%	11%
10	$BrettphosAuNTf_2$	$Zn(OTf)_2$	6 h	83%	39%
11	dichloro(2-picolinato)gold(III)	$Zn(OTf)_2$	6 h	0%	1%
12	$PtCl_2$	$Zn(OTf)_2$	6 h	5%	24%
13	$(ArO)_3PAuOTf$	$Zn(OTf)_2$	2 h	91%	34%
14	-	$Zn(OTf)_2$	6 h	-	-
15	$(ArO)_3PAuNTf_2$	HOTf (10 %)[h]	3 h	6%	64%
16	$(ArO)_3PAuNTf_2$	$NaHCO_3$ (100 %)	12 h	48%	27%

[a] Reaction run in vials with anhydrous toluene; [**4-11a**] = 0.1 M. Ar = 2,4-di-tert-butylphenyl.

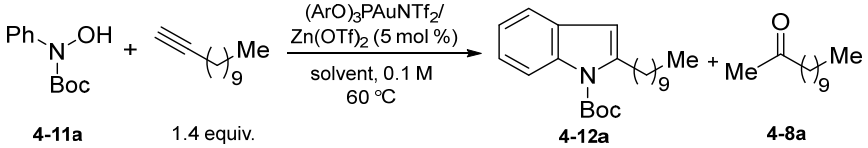
[b] Estimated by 1H NMR using diethyl phthalate as the internal reference. [c] 90% isolated yield.

A control reaction without gold catalyst was run with 5 mol % $Zn(OTf)_2$ present, and no reaction was detected (entry 14). The importance of $Zn(OTf)_2$ was again confirmed by replacing it with HOTf (10 mol %) (entry 15), and only 6%

4-12a was obtained after 3 hours. This result indicates that the Brønsted acid generated in Scheme 69–B is not responsible for the dramatic rate acceleration, but it is critical for catalyst turnover as the reaction was substantially slowed down in the presence of 1 equivalent of $NaHCO_3$ (entry 16).

It is noteworthy that only 5 mol % of $Zn(OTf)_2$ was required, therefore making this strategy an even more interesting cooperation between a gold catalysis and an enzyme-mimicking Zn catalysis. Particularly, this kind of cooperative dual metal catalysis involving gold is rather rare.[21-23]

Table 16. Solvents Screening [a]



entry	solvent	time	yield [b]	
			4-12a	**4-8a**
1	toluene	2 h	91%	32%
2	hexanes	3 h	94%	35%
3	EtOAc	12 h	58%	56%
4	DCE	6 h	59%	51%
5	DCM	6 h	63%	51%
6	Et_2O	6 h	59%	72%
7	CH_3CN	12 h	8%	27%
8	THF	12 h	8%	97%
9	toluene (40 °C)	8 h	76%	61%

[a] Ar = 2,4-di-tert-butylphenyl. [b] Estimated by 1H NMR using diethyl phthalate as the internal reference

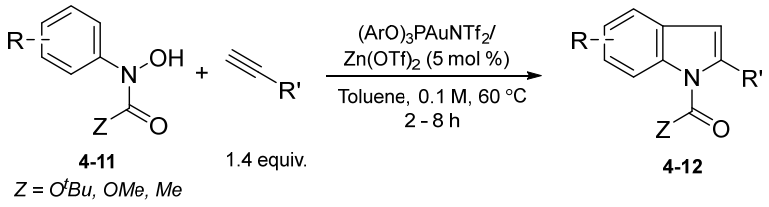
Solvents were then inspected and the results are summarized in Table 16. To

our surprise, extremely non-polar hexanes performed even better than toluene, giving an excellent yield of 94% (entry 1). Relatively polar solvents, including ethyl acetate, 1,2-dichloroethane, dichloromethane and diethylether, provided a moderate yield around 60% (entries 3-6). More polar acetonitrile and THF were the worst solvents investigated, as usual, likely due to their coordinating property thus slowing down the reaction rate. Although hexanes delivered a slightly better outcome than toluene (94% over 91%), toluene was selected to be solvent used in study of substrates scope due to its better solvating property than hexanes.

4.2.3. Substrates Scope

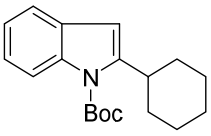
The scope of this methodology was then fully studied after the optimal conditions were figured out. As shown in Table 17, this strategy worked very well with various cycloalkylacetylenes (**4-12a/b/c**) and linear aliphatic terminal alkynes containing various functional/protecting groups, including phenyl (**4-12d**), chloro (**4-12f/j**), benzyl and TIPS protected HO groups (**4-12h/i**), protected amino group (**4-12j**) and an ester group (**4-12k**); the desired *N*-protected-2-alkylindoles were formed regiospecifically in good to excellent yield (82 – 96%). Comparing to our previous indolization based on *N*-arylhydroxylamines, this method necessitates much shorter reaction time (2-8 h vs. ~20 h) and less amount of alkyne (1.4 equiv. vs. 1.8 equiv.), generally results in higher yields and allows much smoother product purification.

Table 17. Formation of *N*-Protected 2-Alkylindoles [a]

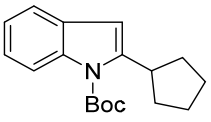


4-11
Z = O^t*Bu, OMe, Me*

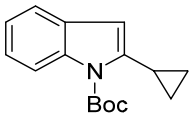
4-12



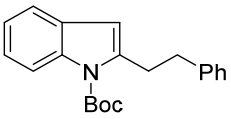
4-12b, 83%,



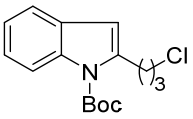
4-12c, 89%



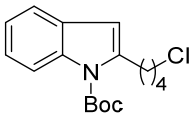
4-12d, 84%



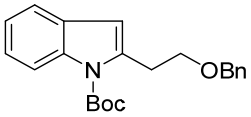
4-12e, 96%



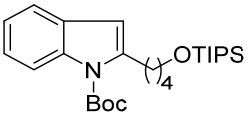
4-12f, 87%



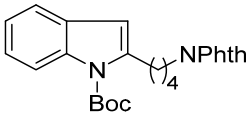
4-12g, 95%



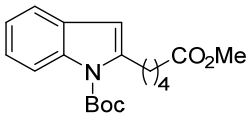
4-12h, 83%



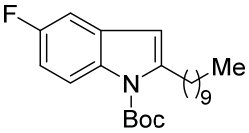
4-12i, 78%



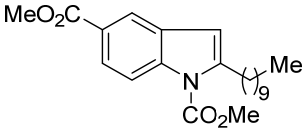
4-12j, 93%



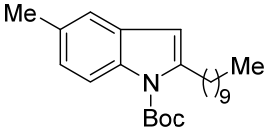
4-12k, 82%



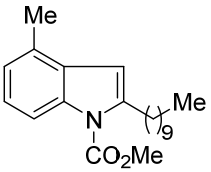
4-12l, 94%

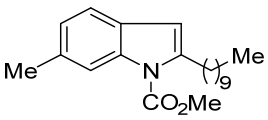


4-12m, 80%

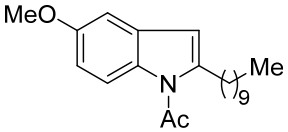


4-12n, 91%,

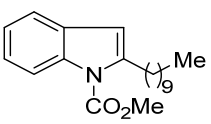




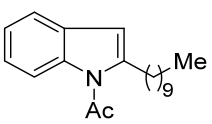
4-12o, 78% (1.25/1) [b]



4-12p, 80% [b,c]



4-12q, 81% [b,d]



4-12r, 90% [b]

[a] Reactions were run in oven-dried vials; isolated yields w reported; Ar = 2,4-di-*tert*-butylphenyl. [b] 2 equivalents of dodecyne. [c] 10% $Zn(OTf)_2$. [d] DCE as the solvent

In spite of the upraised reaction temperature (60 °C) and the use of catalytic Lewis acid $Zn(OTf)_2$, the reaction conditions were still very mild as the Boc group remained untouched. In comparison, the Fischer indolization, in addition to the afore-mentioned issues (i.e., harsh acidic conditions and moderate regioselectivities), could not afford the *N*-unprotected forms of chloro-containing indoles **4-12f** and **4-12g**, due to the interference of the chloro group;[24,25] indole **4-12h** could also be problematic due to the likely elimination of benzyl alcohol from the corresponding methyl ketone substrate under strongly acidic conditions. Thanks to Dr. Lianzhu Liu for helping me finish most cases of Table 17.

Without any surprise, substituents on the benzene ring *para* to the hydroxylamine moiety can vary from electron-withdrawing fluoride and ester (**4-12l/m**) to electron-donating methyl and methoxy groups (**4-12n/o/p**) with good to excellent reaction efficiencies (78 – 94%). With a strong electron-donating *p*-MeO group, the *N*-Boc-hydroxylamine was labile at this reaction temperature, and the obtained yield was only 40%; however, replacing the Boc group with an acetyl permits sufficient substrate stability with good reactivity remaining, and the isolated yield was improved to 80% in the presence of 10% $Zn(OTf)_2$ (**4-12p**). Remarkably, *N*-(4-methoxyphenyl)hydroxylamine, the corresponding free hydroxylamine, is extremely labile even at the ambient temperature and, consequently, could not be employed in our previous indole synthesis. An

ortho-Me group only led to 25 % yield of the desired product, which is probably ascribed to sterics but can be complemented by the Bartoli indolization. A *meta*-Me group led to a good combined yield of 78% though with a very low regioselectivity (**4-12o**, 1.25:1). While this approach delivers *N*-protected indoles with readily removable Boc groups, other protecting groups such as methoxycarbonyl (**4-12m/o/q**) and acetyl (**4-12r**) are also suitable for this chemistry (78 – 90%). Due to the fact that protection of the indole N-H group is often necessary in multi-step synthesis and alkoxycarbonyl or acyl groups are frequently used for this purpose, this strategy, which can directly offer such *N*-protected indoles, can potentially prove to be advantageous and valuable in the total synthesis of indole alkaloids.

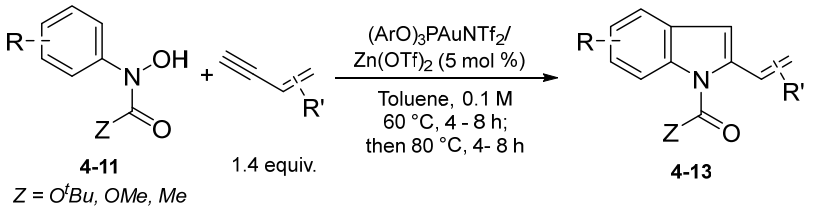
Although the above studies have firmly documented that this novel dual Zn/Au dual catalysis is superior to my previous synthesis of 2-alkylindoles in pretty much every level, counting substrate scope, synthetic efficiency, reaction time and even ease of purification, we still want to assure a categorical supremacy of this new approach by expanding the reaction scope far beyond what the previous chemistry has achieved. Since both terminal enynes and internal alkynes were not suitable substrates in the previous work, consequently, their scope was then further examined.

In the case of terminal enyne substrates, 2-alkenylindoles were the desired products. Remarkably, not only did they fail to be accessed by my previous approach, but also they couldn't be prepared via Fischer indole synthesis, as the

corresponding ketone substrates, which are α,β-unsaturated ketones, typically react with arylhydrazines to form pyrazolines instead of indoles.[26] Bartoli indolization has not been able to access these diene-type indoles either so far.

This type of synthetically useful 2-alkenylinodles were prepared without any trouble based on the push-pull strategy and their scope was shown in Table 18. Different protecting groups on the nitrogens of *N*-arylhydroxylamines were first inspected this time. To our delight, with this cooperative Au/Zn dual catalysis, hydroxylamines protected by *tert*-butoxycarbonyl, methoxycarbonyl and acetyl all reacted very smoothly with sterically demanding 1-cyclohexenylacetylene affording the diene-type indole products **4-13a, 4-13b** and **4-13c** in high yields (83 – 92%). Other diene-type indoles[27] were also readily prepared by using various terminal enynes as the reaction partners; different alkenyl groups (**4-13a/d/e/f/g**) including conjugated β-styryl (**4-13e**) were readily installed at the indole 2-position (68 – 90%). For **4-13d**, due to the low boiling point of 2-methyl-1-buten-3-yne, two equivalents of enynes were required to achieve a decent 68% yield and the efficiency might be improved by using more enynes. For **4-13g**, acid-promoted isomerization might attribute to the increased product *E*/*Z* ratio; another possible reason could be that the *Z*-enyne is sterically less favored toward the nucleophilic attack of **4-11a** compared with the *E*-enyne, hence increasing the product *E*/*Z* ratio.

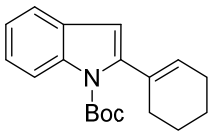
Table 18. Formation of *N*-Protected 2-Alkenylindoles [a]



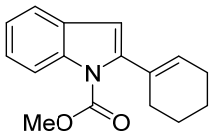
4-11
Z = O^{t}Bu, OMe, Me

1.4 equiv.

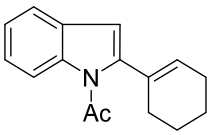
4-13



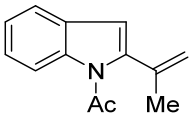
4-13a, 83%,



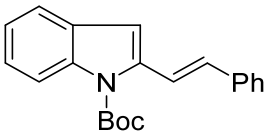
4-13b, 86% [e]



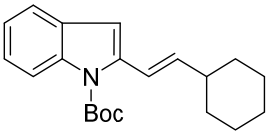
4-13c, 92%



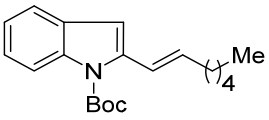
4-13d, 68% [b,c]



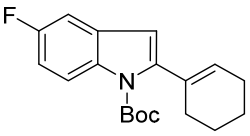
4-13e, 74% [c]



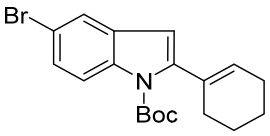
4-13f, 90% [c]



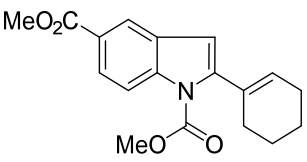
4-13g, 86% [c,d]



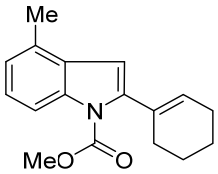
4-13h, 75%

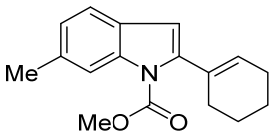


4-13i, 65%

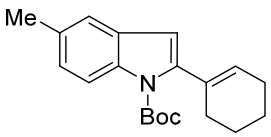


4-13j, 77% [e]

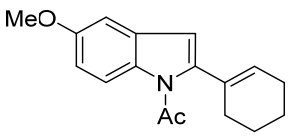




4-13k, 71% (1.5/1) [e]



4-13l, 80%



4-13m, 75% [b,f]

[a] Reactions run in oven-dried vials; isolated yields are reported; Ar = 2,4-di-*tert*-butylphenyl. [b] 2 equiv of the enyne. [c] The reaction was run at 60 °C for 12 h. [d] The enyne E/Z = 9:1, and the product E/Z >19:1. [e] Solvent: DCE. [f] 10 mol % $Zn(OTf)_2$.

Both electron-withdrawing (i.e., F, Br, CO_2Me) and electron-donating substituents (i.e., Me, OMe) on the benzene ring of *N*-protected arylhydroxylamines were readily tolerated (**4-13h/i/j/k/l/m**, 65 – 80%). In the cases of *N*-arylhydroxylamines protected by methoxycarbonyl groups, 1,2-dichloroethane turned out to be a better solvent that toluene (**4-13b/j/k**). Importantly, for all the cases involving more sterically demanding cyclohexenyl groups the last step, cyclodehydration to form indoles, did not go to completion until further heating at a slightly high temperature of 80 °C for 4 - 8 h. Similar to the aliphatic terminal alkynes, the reaction was regiospecific as well, and 2-alkenylindole was the only isomer observed.

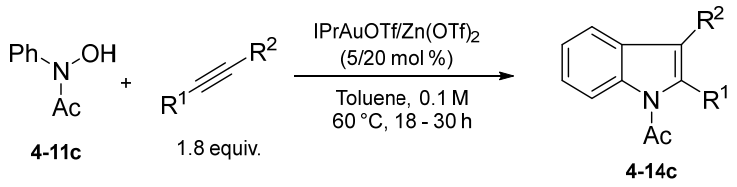
A characteristic problem of the Fischer indole synthesis is the low regioselectivity[28,29] coming with unsymmetrical ketones which fit the following generic formulae, $R^1CH_2C(O)CH_2R^2$ (R^1, $R^2 \neq$ H, Ar). To find out whether this methodology offers a solution to this long standing issue, I surveyed various internal alkynes with *N*-hydroxy-*N*-phenylacetamide (**4-11c**) serving as the nucleophile and the reaction outcomes are summarized in Table 19. First of all, internal alkynes with moderate steric demand were readily allowed; one substituent on one end of the C–C triple bond must be a primary alkyl group, and the other one could be a primary alkyl or phenyl group. Due to their diminished reactivities comparing to the terminal alkynes, the reactions were slower and normally took 18 - 30 h to finish even with increased amount of $Zn(OTf)_2$ (20 mol %); the yields were generally lower as well. Furthermore, a much more

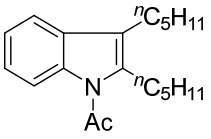
thermostable NHCAu(I) complex, IPrAuOTf, yet less reactive, was a better catalyst than $(ArO)_3PAuNTf_2$ as the reaction could not proceed to completion within the lifetime of the latter catalyst.

For the symmetric 6-dodecyne, the corresponding indole product **4-14a** was isolated in 74% yield. For internal alkynes with a methyl group at one end, the regioisomers with Me at the 2 position were always favored; apparently due to its smaller size the attack from hydroxamic acid **4-11c** preferred to happen at that end. With primary groups at the other end, the selectivities were around 6-8:1 (**4-14b/d/e**, 52 – 68%). Interestingly, a similar regioselectivity of 8:1 was observed with a phenyl group (**4-14g**, 61%), suggesting that steric control is dominating over electronic one.

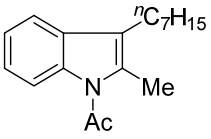
By increasing the steric bulkiness of the substituent (i.e., a cyclohexyl group, **4-14c**), the selectivity was enhanced to >19:1 with a moderate 67% yield. There is a remarkable electronic effect when a strongly inductive phthalimide group (PhthN) is present (**4-14f**), and both the regioselectivity and the reaction yield were synthetically appealing (16.6:1, 80%). While in most cases the 2-methylindole products (**4-14b/c/e/f/g**) mentioned above could be obtained selectively by the Fischer indolization using the corresponding methyl ketones, the ketone-containing indole product **4-14d**, which couldn't be achieved through the Fischer approach, was successful produced in a decent 68% yield by this approach, demonstrating another example of functional group tolerance allowed by this chemistry.

Table 19. Regioselective Formation of *N*-Acetyl-2,3-disubstituted Indoles [a]

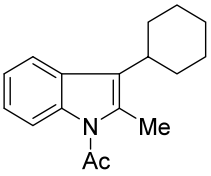




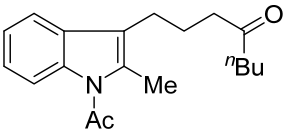
4-14a, 74%,



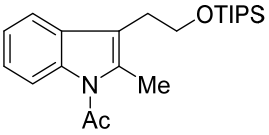
4-14b, 61% (7.1:1) [b]



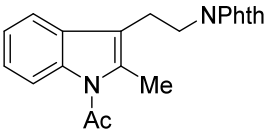
4-14c, 67% (>19:1) [b]



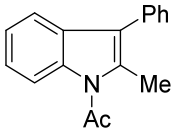
4-14d, 68% (6.8:1) [b]



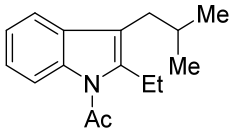
4-14e, 52% (6:1) [b]



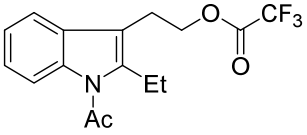
4-14f, 80% (16.6:1) [b]



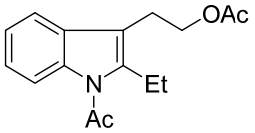
4-14g, 61% (8:1) [b]



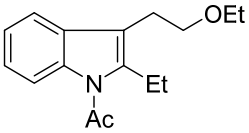
4-14h, 75% (2.5:1) [b,c,d]



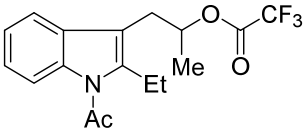
4-14i, 65% (10.3:1) [b,c]



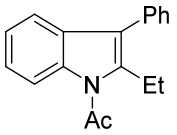
4-14j, 77% (5.6:1) [b,c]



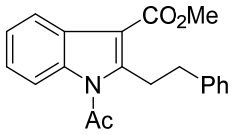
4-14k, 86% (2/1) [b,c]



4-14l, 69% (12/1) [b,c]



4-14m, 70% (2.9:1) [b,c]



4-14n, 66% (>19:1) [b]

[a] Reactions run in oven-dried vials; isolated yields of the major isomers are reported if not specified.; Ar = 2,4-di-*tert*-butylphenyl. [b] Regioselectivity; the major isomer is shown. [c] Overall yields of both isomers are reported. [d] 2 equiv of 6-methylhept-3-yne was used.

For internal alkynes with one end substituted by a primary alkyl group, the other one with a cyclohexyl group on the other end of the alkyne (i.e., but-1-ynylcyclohexane) seemed to be sterically too demanding, and the reaction was so sluggish that only 21% yield was attained. Efforts (gold catalysts, Lewis acids, temperature, time, etc.) spent on this particular reaction did not offer much improvement. With a smaller isobutyl group, the reaction progressed well (**4-14h**, 75%), and the small steric difference between the two alkyne ends (ethyl *vs.* isobutyl) was reflected by a regioselectivity of 2.5/1, favoring the indole product with less hindered ethyl group at the 2 position. With an array of ethyl alkynes with hydroxyethyl differently protected on the other end (**4-14i/j/k**), the trend of regioselectivities apparently correlated to the inductive effect of the electron-withdrawing protecting groups. Therefore, a synthetically useful selectivity and yield (10.3:1, 65%) were achieved by using a trifluoroacetate substrate (**4-14i**); a cooperation between sterics and induction resulted in an even better regioselectivity and efficiency for the indole product **4-14l** (12:1, 69%). It is notable that the trifluoroacetyl group can be easily removed, which permits a convenient and regioselective access to various 2-substituted indole-3-ethanols. In comparison, fully deprotected indole **4-14i** could be obtained according to Patil et al. [12] ($Ph_3PAuNTf_2$/TsOH, toluene, 100 °C) but only as a minor isomer (20%), and the direct Fischer indole synthesis would be very likely to deliver a similar result. These results established, once more, that unreachable regioselectivities in the Fischer indolization could be achieved by judicial choices of protecting groups

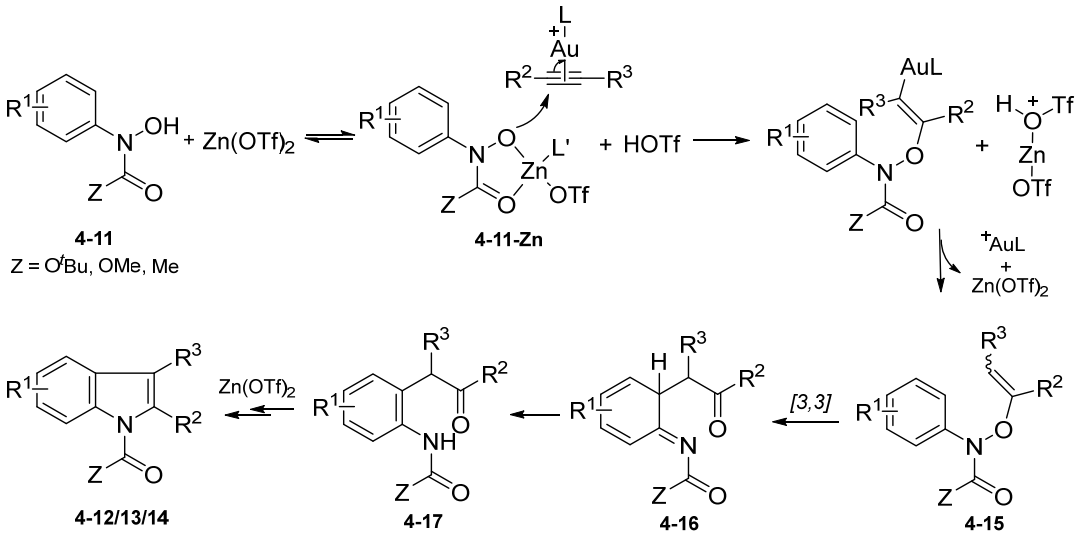
on the alkynes in this operative dual catalysis of gold and Zinc.

Comparing to the methyl group (**4-14g**), the use of a somewhat bulkier Et group (**4-14m**) expectedly afforded a diminished regioselectivity (8:1 *vs.* 2.9:1), but the indole product with the phenyl group at the 3 position was still preferred. Ethyl 3-phenylpropiolate led selectively to the only regioisomer **4-14n** in a yield of 66% through an initial Michael addition due to triple bond being the more electronically biased,[30,31] and the reaction yield could be possibly improved further by using more alkynes since all the alkyne was consumed during the reaction with some hydroxamic acid **4-11c** left.

4.2.4. Mechanism and Discussion

The reaction mechanism is proposed in Scheme 71. First, the hydroxamic acid or related carbamate substrate **4-11** is activated by the hard Lewis acid $Zn(OTf)_2$ via the formation of the zinc chelate **4-11-Zn**, which should be generated in a significant amount during the equilibrium. This more *O*-nucleophilic intermediate can then attack the gold-activated alkyne very efficiently, forming the *N*-aryl-*O*-alkenyl precursor **4-15** after protodeauration. The succeeding key 3,3-sigmatropic rearrangement generates intermediate **4-16**, which then aromatizes to **4-17**, followed by cyclodehydration facilitated by the Lewis acidic $Zn(OTf)_2$, leading to the final indole product **4-12/13/14**.

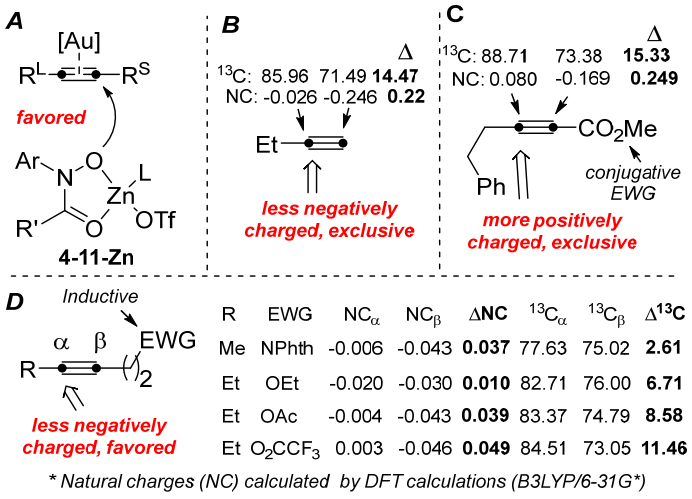
Scheme 71. Proposed Mechanism



The observed regioselectivities are rationalized in Figure 15: first of all, the Zinc hydroxamate **4-11-Zn** is sterically bulky, likely due to additional ligands on the metal, and favors the attacks at the less hindered end of internal alkynes (Figure 15-A). With terminal aliphatic alkynes and enynes, although the internal end of the C–C triple bond is more hindered than the terminus, but it's much less negatively charged than the latter. For example, the difference of the natural charges (NC) of the alkyne ends computed by using DFT calculations (B3LYP/6-31G*) is 0.22 when R is an ethyl group (Figure 15-B), which is also reflected by the ^{13}C chemical shifts of both ends ($\Delta\delta$ = 14.47 ppm). The substantial electronic difference totally overrides the steric disparity and result in an exclusive nucleophilic attack at the more electrophilic internal end, leading to regiospecific formation of indoles. For electronically biased alkynes (i.e., with conjugated electron-withdrawing groups), the polarization of the triple bond is again significant: for example, as shown in Figure 15-C, ΔNC and $\Delta\delta$(^{13}C) between the

two carbons of C–C triple bond are 0.249 and 15.33 ppm, respectively; this electronic difference, quantitatively comparable to that in the terminal alkyne 1-butyne (Figure 15-B, 0.22 and 14.47 ppm), is consistent with the observed excellent regioselectivity (only one isomer was detected).

Figure 15. Rationales for the Reaction Regioselectivity on Alkynes



R	EWG	NC_α	NC_β	**ΔNC**	$^{13}C_\alpha$	$^{13}C_\beta$	$\Delta^{13}C$
Me	NPhth	-0.006	-0.043	**0.037**	77.63	75.02	**2.61**
Et	OEt	-0.020	-0.030	**0.010**	82.71	76.00	**6.71**
Et	OAc	-0.004	-0.043	**0.039**	83.37	74.79	**8.58**
Et	O_2CCF_3	0.003	-0.046	**0.049**	84.51	73.05	**11.46**

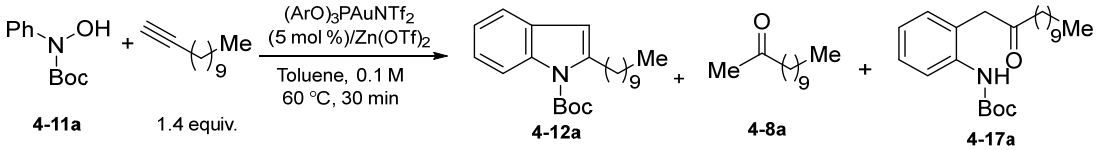
** Natural charges (NC) calculated by DFT calculations (B3LYP/6-31G*)*

For those alkynes without conjugated electron-withdrawing groups, the often overlooked inductive effect[32] can be the key factor. Such an induction results in less electron density at the distal end of the C–C triple bond than the proximal end, which is established by the calculated NCs and the observed ^{13}C chemical shifts of some alkyne substrates in Table 19 (Figure 15-D). In the absence of significant steric discrepancy, this electronic partiality dominates successfully the selective attack by the nucleophilic hydroxamate at the distal end and, furthermore, correlates in a roughly quantitative way with the regioselectivity observed in **4-14f/i/j/k**, Table 19. A matched combination of inductive effect and sterics bias

could lead to a more pleasing outcome (**4-14i/l**).

To validate the view that catalytic $Zn(OTf)_2$ enhances the nucleophilicity of *N*-arylhydroxamic acids/*N*-aryl-*N*-hydroxycarbamates **4-11**, an array of competition reactions between the addition of **4-11a** to and the hydration of 1-dodecyne were run by varying the amount of the Lewis acid. As shown in Table 20, the reactions were stopped before the reactions go to completion (30 min) in order to establish the rate differences at the early stage. When toluene saturated by H_2O was used as the solvent, there was a clear correlation between the amount of $Zn(OTf)_2$ and the ratio of products due to **4-11a** addition (i.e., **4-12a** and **4-17a**) and hydration (i.e., **4-8a**): the more $Zn(OTf)_2$ was used, the higher the ratio was obtained, indicating that $Zn(OTf)_2$ does increase the reaction rate of **4-11a** addition (entries 1-5). Notably, the amount of the hydration product, methyl ketone **4-8a**, did not change much as the amount of the zinc salt increased, suggesting that hydration was not much affected by $Zn(OTf)_2$. In comparison, under anhydrous conditions, a positive correlation was observed when the amount of $Zn(OTf)_2$ was varied from 0% to 5 mol % (entries 6 - 8); additionally, the preference of **4-11a** addition was better than that in the wet toluene as expectedly. The decreased preferences in entries 9 and 10 reflect the significant increase of the amount of byproduct H_2O generated upon the cyclodehydration of **4-17a**, which leads to increasing hydration. The above results do support the role of $Zn(OTf)_2$ we proposed in Scheme 71.

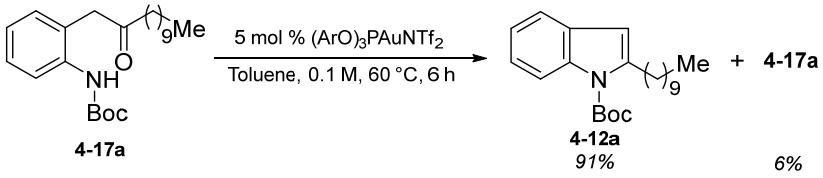
Table 20. Examine the Role of $Zn(OTf)_2$



entry	toluene	$Zn(OTf)_2$	yield [a]			(**4-12a** +	**4-12a/**
			4-12a	**4-8**	**4-17a**	**4-17a**)/**4-8**	**4-17a**
1	wet[b]	0	<1	18%	<1	-	-
2	wet[b]	1 mol%	9%	19%	16%	1.3	0.6
3	wet[b]	5 mol%	29%	21%	27%	2.7	1.1
4	wet[b]	10 mol%	50%	21%	25%	3.6	2.0
5	wet[b]	20 mol%	67%	21%	19%	4.1	3.5
6	dry [c]	0	<1	1.4%	<1	-	-
7	dry [c]	1 mol%	13%	7%	16%	4.1	0.8
8	dry [c]	5 mol%	41%	9%	25%	7.3	1.6
9	dry [c]	10 mol%	57%	11%	20%	7.0	2.9
10	dry [c]	20 mol%	78%	17%	13%	5.4	6

[a] NMR yield estimated by using diethyl phthalate as the internal reference. [b] Saturated with deionized water, and reactions run in vials. [c] Reaction run in Schlenck tubes.

Scheme 72. Control Reaction of Cyclodehydration without $Zn(OTf)_2$



This zinc salt, being Lewis acidic, also facilitated the cyclodehydration: the more $Zn(OTf)_2$ was present in the reaction, the higher ratio of **4-12a/4-17a** was observed. Remarkably, the gold catalyst was found out to be capable to assist this process as well notwithstanding much slower by running a control reaction: carbamate intermediate **4-17a** was converted into indole product **4-12a** in a 91%

yield and 94% conversion with 5 mol % $(ArO)_3PAuNTf_2$ in toluene at 60 °C for 6 h in the absence of $Zn(OTf)_2$ (Scheme 72).

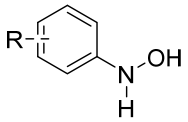
4.2.5. Conclusions

An efficient and general synthesis of *N*-protected indoles via a gold/Zn-catalyzed annulation of easily prepared *N*-arylhydroxamic acids/*N*-aryl-*N*-hydroxycarbamates and readily available alkynes. It is conceptually different from and synthetically much superior to my previous indolization based on free *N*-hydroxyamines. The reaction scope is much broader, yields are generally higher, time is shorter and the reaction conditions are still relatively mild. The indole nitrogens are protected by either acyl or alkoxycarbonyl groups, which could be advantageous as these groups are often used in the multi-step synthesis of complex molecules to offer desirable and flexible *N*-protections. With terminal alkynes, this reaction is regiospecific and offers 2-substituted indoles exclusively and tolerates a range of functional and protecting groups. Particularly, various 2-alkenylindoles, valuable substrates for the Diels-Alder reaction to build up polycyclic structures as dienes but inaccessible via the Fischer or Bartoli indole synthesis, can be readily prepared from terminal enynes. This strategy can also be applied to internal alkynes of moderate steric demand to yield 2,3-disubstituted indoles, and the regioselectivity are controlled by both sterics and/or electronics: the small substituents on the C–C

triple bond ends up selectively at the indole 2-positions, and the electron-withdrawing groups direct the substituents to the indole 3 positions via either inductive effect or conjugation. With judiciary choices of protecting groups, good to excellent regioselectivities with internal alkynes can be achieved. Notably, this strategy is a rare example of cooperative dual catalysis involving gold, and the first example of gold-catalyzed intermolecular addition of hydroxamic acids/*N*-aryl-*N*-hydroxycarbamates to alkynes. Catalytic $Zn(OTf)_2$ not only enhances the nucleophilicity of these hydroxylamine derivatives via the formation of deprotonated metal chelates, which mimics the metal ion catalysis in metalloenzymes, but also facilitates the cyclodehyrative step to form the final indole products.

4.3. Experimental Section

General Procedure A: Preparation of *N*-Arylhydroxylamines 4-1



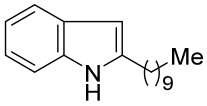
N-Arylhydroxylamines **4-1** were prepared according to literature procedure.[33] To a stirred mixture of nitrobenzene (21 mmol) and NH_4Cl (1.3 g, 24 mmol) in H_2O (40 mL) was slowly added zinc dust (90%, 3.08 g, 42 mmol) while maintaining the temperature below 60 °C. After 15 min's stirring, the reaction mixture was filtered while still warm and the solid was washed with hot water (10 mL). The filtrate was saturated with NaCl and cooled to 0 °C and the resulting

solid was collected and dried. This crude *N*-phenylhydroxylamine **4-1** was recrystallized from hexane-petroleum ether to get the pure compound.

General Procedure B: Preparation of 2-Alkylindoles 4-2

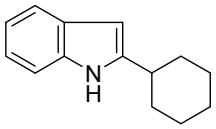
An oven-dried vial was charged with *N*-arylhydroxylamine **4-1** (0.3 mmol, 1 equiv), alkyne (0.54 mmol, 1.8 equiv) and anhydrous DCE (3 mL, 0.1 M); then $(ArO)_3PAuNTf_2$ (Ar = 2,4-di-*tert*-butylphenyl, 16.8 mg, 5 mol %) was added. After being stirred at room temperature for 16 – 24 h until the alkyne was completely consumed, the reaction mixture was concentrated under *vacuum*. The residue was purified via silica gel flash chromatography (eluents: ethyl acetate: hexanes = 1: 100) to give the desired product **4-2**.

4-2a



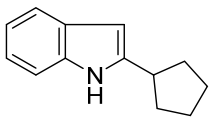
This compound was prepared in 84% yield according to the general procedure B (eluents: ethyl acetate: hexanes = 1: 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (bs, 1H), 7.53 (d, J = 7.6 Hz), 7.30 (d, 1H, J = 7.6 H), 7.12 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.2 Hz), 7.07 (td, 1H, J_1 = 7.2 Hz, J_2 = 1.2 Hz), 6.24 (d, 1H, J = 0.8 Hz), 2.75 (t, 2H, J = 8 Hz), 1.68 – 1.76 (m, 2H), 1.20 – 1.41 (m, 14H), 0.887 (t, 3H, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.0, 135.8, 128.8, 120.9, 119.7, 119.5, 110.2, 99.4, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 28.2, 22.7, 14.1; IR (neat): 3387, 3377, 3052, 2953, 2919, 2849, 1457; MS (ES^+) Calculated for $[C_{18}H_{28}N]^+$: 258.22; Found: 258.16.

4-2b



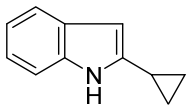
This compound was prepared in 77% yield according to the general procedure B (eluents: ethyl acetate: hexanes = 1: 100). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (bs, 1H), 7.56 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1 Hz), 7.31 (d, 1H, J = 8.5 Hz), 7.14 (td, 1H, J_1 = 7.5 Hz, J_2 = 1.5 Hz), 7.09 (td, 1H, J_1 = 7.5 Hz, J_2 = 1 Hz), 6.25 – 6.26 (m, 1H), 2.72 (tt, 1H, J_1 = 11 Hz, J_2 = 3.5 Hz), 2.08 – 2.11 (m, 2H), 1.86 – 1.90 (m, 2H), 1.76 – 1.81 (m, 1H), 1.39 – 1.55 (m, 4H), 1.29 – 1.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 135.5, 28.6, 120.9, 119.8, 119.5, 110.3, 97.4, 37.3, 32.9, 26.2, 26.1; IR (neat): 3392, 2929, 2851, 1597, 1557, 1444, 1414; MS (ES^+) Calculated for $[C_{14}H_{18}N]^+$: 200.14; Found: 200.16.

4-2c



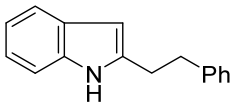
This compound was prepared in 62% yield according to the general procedure B (eluents: ethyl acetate: hexanes = 1: 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (bs, 1H), 7.53 (dd, 1H, J_1 =7.6Hz, J_2 =0.8Hz), 7.30 (d, 1H, J =7.6Hz), 7.12 (td, 1H, J_1 =7.2Hz, J_2 =1.2Hz), 7.04 – 7.09 (m, 1H), 6.24 – 6.2(m, 1H), 3.15 – 3.23 (m, 1H), 2.10 – 2.16 (m, 2H), 1.65 – 1.85 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 135.8, 128.6, 120.9, 119.8, 119.5, 110.2, 97.9, 38.8, 32.8, 25.2; IR (neat): 3584, 3054, 2954, 2868, 1547, 1458, 1289; MS (ES^+) Calculated for $[C_{13}H_{16}N]^+$: 186.13; Found: 186.15.

4-2d



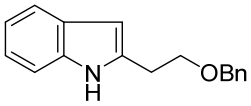
This compound was prepared in 70% yield according to the general procedure B (eluents: ethyl acetate: hexanes = 1: 100). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (bs, 1H), 7.53 (d, 1H, J = 7.5 Hz), 7.28 (d, 1H, J = 8 Hz), 7.14 (td, 1H, J_1 = 7.5 Hz, J_2 = 1 Hz), 7.09 (td, 1H, J_1 = 7.5 Hz, J_2 = 1 Hz), 6.18 (d, 1H, J = 1 Hz), 1.94 – 1.99 (m, 1H), 0.96 – 1.00 (m, 2H), 0.78 – 0.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 135.7, 128.6, 120.9, 119.67, 119.62, 110.2, 97.6, 8.80, 7.29; IR (neat): 3584, 3396, 3086, 3054, 3008, 2916, 2848, 1556, 1458, 1415; MS (ES^+) Calculated for $[C_{11}H_{11}NNa]^+$: 180.08; Found: 180.18

4-2e



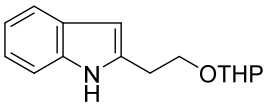
This compound was prepared in 89% yield according to the general procedure B (eluents: ethyl acetate: hexanes = 1: 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (bs, 1H), 7.54 (d, 1H, J = 8 Hz), 7.32 (tt, 2H, J_1 = 6.8 Hz, J_2 = 2 Hz), 7.22 – 7.38 (m, 3H), 7.13 (td, 1H, J_1 = 8 Hz, J_2 = 1.6 Hz), 7.08 (td, 1H, J_1 = 7.2 Hz, J_2 = 1.2 Hz), 6.29 (m, 1H), 3.03 – 3.12 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 140.0, 135.7, 128.6, 128.5, 128.4, 126.8, 121.1, 119.8, 119.6, 110.3, 99.8, 35.6, 30.1; IR (neat): 3584, 3395, 3058, 3021, 2915, 2852, 1553, 1456, 1416; MS (ES^+) Calculated for $[C_{16}H_{16}N]^+$: 222.13; Found: 222.15.

4-2f



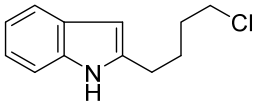
This compound was prepared in 84% yield according to the general procedure B (eluents: ethyl acetate: hexanes = 1: 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (bs, 1H), 7.54 (d, 1H, *J* = 7.6 Hz), 7.26 – 7.41 (m, 5H), 7.13 (t, 1H, *J* = 7.6 Hz), 7.07 (t, 1H, *J* = 7.6 Hz), 6.26 (s, 1H), 4.60 (s, 2H), 3.81 (t, 2H, *J* = 6 Hz), 3.07 (t, 2H, *J* = 6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 137.7, 135.9, 128.5, 128.3, 127.85, 127.78, 121.0, 119.8, 119.4, 110.5, 99.8, 73.3, 69.9, 28.6; IR (neat): 3584, 3407, 3056, 3029, 2914, 2861, 1553, 1456, 1287, 1096; MS (ES^+) Calculated for $[C_{17}H_{17}NNaO]^+$: 274.12; Found: 274.15.

4-2g



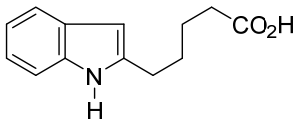
This compound was prepared in 67% yield according to the general procedure B (eluents: ethyl acetate: hexanes = 1: 100). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (bs, 1H), 7.54 (d, 1H, *J* = 7.5 Hz), 7.31 (d, 1H, *J* = 8 Hz), 7.12 (t, 1H, *J* = 7.5 Hz), 7.07 (t, 1H, *J* = 7 Hz), 6.27(s, 1H), 4.66 (t, 1H, *J* = 8.5 Hz), 4.06 – 4.11 (m, 1H), 3.82 – 3.87 (m, 1H), 3.73 (dt, 1H, J_1 = 9.5 Hz, J_2 = 6 Hz), 3.50 – 3.54 (m, 1H), 3.07 (t, 2H, *J* = 6 Hz), 1.85 – 1.90 (m, 1H), 1.76 – 1.82 (m, 1H), 1.52 – 1.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 135.9, 128.4, 120.9, 119.8, 119.4, 110.4, 99.9, 99.3, 67.2, 62.6, 30.8, 28.6, 25.3, 19.8; IR (neat): 3401, 3316, 3055, 2943, 2869, 1553, 1457, 1134, 1030; MS (ES^+) Calculated for $[C_{15}H_{19}NNaO_2]^+$: 268.13; Found: 268.15.

4-2h



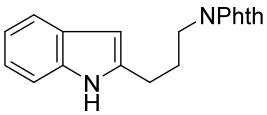
This compound was prepared in 62% yield according to the general procedure B (eluents: ethyl acetate: hexanes = 1: 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (bs, 1H), 7.54 (dd, 1H, J_1 = 7.6 Hz, J_2 = 0.8 Hz), 7.31 (d, 1H, J = 8 Hz), 7.14 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.2 Hz), 7.09 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.2 Hz), 6.27 (d, 1H, J = 0.8 Hz), 3.58 (t, 2H, J = 6 Hz), 2.81 (t, 2H, J = 6.8 Hz), 1.87 – 1.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 135.8, 128.7, 121.1, 119.8, 119.7, 110.3, 99.8, 44.8, 31.9, 27.4, 26.3; IR (neat): 3402, 3056, 2941, 2864, 1551, 1457, 1415, 1286; MS (ES^+) Calculated for $[C_{12}H_{15}ClN]^+$: 208.09; Found: 208.11.

4-2i



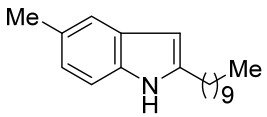
This compound was prepared in 73% yield according to the general procedure B (eluents: ethyl acetate: hexanes = 1: 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (bs, 1H), 7.5 (d, 1H, J = 7.6 Hz), 7.30 (d, 1H, J = 8 Hz), 7.05 – 7.14 (m, 2H), 6.25 (s, 1H), 2.80 (t, 2H, J = 7 Hz), 2.42 (t, 2H, J = 6.8 Hz), 1.70 – 1.83 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.5, 140.0, 135.8, 128.7, 121.1, 119.8, 119.6, 110.3, 99.7, 33.4, 28.4, 27.8, 24.1; IR (neat): 3584, 3390, 3045, 2939, 2861, 1700, 1457, 1412; MS (ES^+) Calculated for $[C_{13}H_{15}NNaO_2]^+$: 240.10; Found: 240.10.

4-2j



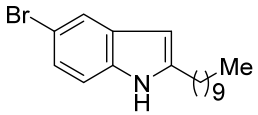
This compound was prepared in 72% yield according to the general procedure B (eluents: ethyl acetate: hexanes = 1: 100). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (bs, 1H), 7.82 – 7.87 (m, 2H), 7.71 – 7.73 (m, 2H), 7.50 (d, 1H, J = 7.5 Hz), 7.35 (d, 1H, J = 8 Hz), 7.11 (td, 1H, J_1 = 7.5 Hz, J_2 = 1 Hz), 7.04 (td, 1H, J_1 = 7.5 Hz, J_2 = 1 Hz), 6.27 (d, 1H, J = 1 Hz), 3.81 (t, 2H, J = 6.5 Hz), 2.80 (t, 2H, J = 7 Hz), 2.07 – 2.13 (m,2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 138.5, 135.9, 134.1, 131.9, 128.7, 123.3, 121.0, 119.7, 119.5, 110.6, 99.8, 37.2, 28.8, 25.1; IR (neat): 3584, 3393, 3058, 2922, 2851, 1769, 1703, 1398; MS (ES^+) Calculated for $[C_{19}H_{16}N_2NaO_2]^+$: 327.11; Found: 327.11.

4-2k



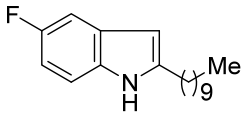
This compound was prepared in 64% yield according to the general procedure B (eluents: ethyl acetate: hexanes = 1: 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (bs, 1H), 7.32 (d, 1H, J = 0.8 Hz), 7.18 (d, 1H, J = 8.4 Hz), 6.94 (dd, 1H, J_1 = 8.4 Hz, J_2 = 0.8 Hz), 6.14 – 6.16 (m, 1H), 2.73 (t, 2H, J = 7.6 Hz), 2.43 (s, 3H), 1.75 – 1.66 (m, 2H), 1.20 – 1.40 (m, 14H), 0.89 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.1, 134.0, 129.1, 128.7, 122.3, 119.5, 109.9, 98.9, 31.9, 29.59, 29.55, 29.4, 29.3, 29.2, 28.3, 22.7, 21.4, 14.1; IR (neat): 3376, 2953, 2918, 2850, 1470, 1412; MS (ES^+) Calculated for $[C_{19}H_{30}N]^+$: 272.24; Found: 272.27.

4-2l



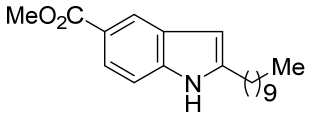
This compound was prepared in 86% yield according to the general procedure B (eluents: ethyl acetate: hexanes = 1: 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (bs, 1H), 7.63 – 7.64 (m, 1H), 7.14 – 7.20 (m, 2H), 2.73 (t, 2H, *J* = 7.6 Hz), 1.66 – 1.74 (m, 2H), 1.22-1.40 (m, 14H), 0.89 (t, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 134.4, 130.6, 123.6, 122.2, 112.7, 111.6, 99.1, 31.9, 29.7, 29.6, 29.6, 29.4, 29.30, 29.27, 29.0, 28.2, 22.7, 14.2; IR (neat): 3403, 3315, 3055, 2943, 2870, 1457, 1418, 1134, 1030; MS (ES^+) Calculated for $[C_{18}H_{27}BrN]^+$: 336.13; Found: 336.08.

4-2m



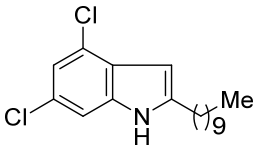
This compound was prepared in 82% yield according to the general procedure B (eluents: ethyl acetate: hexanes = 1: 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (bs, 1H), 7.15 – 7.20 (m, 2H), 6.82 – 6.88 (m, 1H), 6.19 – 6.21 (m, 1H), 2.74 (t, 2H, *J* = 7.6 Hz), 1.67 – 1.75 (m, 2H), 1.22 – 1.40 (m, 14H), 0.89 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9(d, *J* = 231 Hz), 142.0, 132.2, 129.2 (d, *J* = 9 Hz), 110.6 (d, *J* = 10 Hz), 108.9 (d, *J* = 26 Hz), 104.6 (d, *J* = 24 Hz), 99.7 (d, *J* = 4 Hz), 31.9, 29.6, 29.5, 29.4, 29.3, 29.1, 28.3, 22.7, 14.1; IR (neat): 3465, 3417, 2954, 2926, 2854, 1585, 1486, 1452, 1169, 852; MS (ES^+) Calculated for $[C_{18}H_{26}FNNa]^+$: 298.19; Found: 298.16.

4-2n



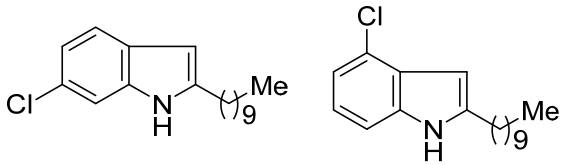
This compound was prepared in 76% yield according to the general procedure B (eluents: ethyl acetate: hexanes = 1: 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 8.27 (bs, 1H), 7.84 (dd, 1H, J_1 = 8.4 Hz, J_2 = 1.2 Hz), 7.29 (d, 1H, J = 8.4 HZ), 6.32 (s, 1H), 3.93 (s, 3H), 2.75 (t, 2H, 8 Hz), 1.68 – 1.76 (m, 2H), 1.20 – 1.40 (m, 14H), 0.89 (t, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 141.6, 138.5, 128.4, 122.6, 112.4, 121.4, 109.9, 100.6, 51.8, 31.9, 29.6, 29.5, 29.4, 29.3, 29.0, 28.2, 22.6, 14.1.

4-2o



This compound was prepared in 63% yield according to the general procedure B (eluents: ethyl acetate: hexanes = 1: 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (bs, 1H), 7.17 (dd, 1H, J_1 = 1.6 Hz, J_2 = 1.2 Hz), 7.09 (d, 1H, J = 1.2 Hz), 6.30 – 6.32 (m, 1H), 2.73 (t, 2H, J = 7.6 Hz), 1.68 - 1.75 (m, 2H), 1.22 – 1.40 (m, 14H), 0.89 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 136.2, 126.4, 126.4, 125.2, 119.7, 109.0, 98.2, 31.9, 29.6, 29.5, 29.4, 29.3, 29.2, 28.9, 28.2, 22.7, 14.1; IR (neat): 2953, 2927, 2854, 1614, 1577, 1468, 1328; MS (ES^+) Calculated for $[C_{18}H_{25}Cl_2NNa]^+$: 348.13; Found: 348.16.

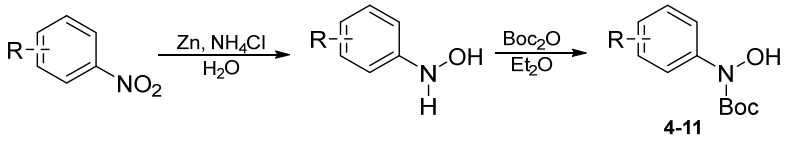
4-2p and **4-2p'** (1.3:1)



1.3:1

These two compound was prepared in 85% yield (1.3: 1) according to the general procedure B (eluents: ethyl acetate: hexanes = 1: 100). **4-2p:** ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (bs, 1H), 7.41 (d, 1H, *J* = 9 Hz), 7.27 (t, 1H, *J* = 0.8 Hz), 7.02 – 7.05 (m, 1H), 6.20 – 6.21 (m, 1H), 2.73 (t, 2H, *J* = 7.5 Hz), 1.68 – 1.72 (m, 1H), 1.20 – 1.40 (m, 14H), 0.89 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 136.1, 127.4, 126.6, 120.4, 120.2, 110.2, 99.5, 31.9, 29.6, 29.5, 29.4, 29.31, 29.28, 29.0, 28.2, 22.7, 14.1; IR (neat): 3584，3403, 2954, 2924, 1543, 1467, 1397; MS (ES^+) Calculated for $[C_{18}H_{27}ClN]^+$: 292.18; Found: 292.18. **4-2p':** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (bs, 1H), 7.19 (dt, 1H, J_1 =8Hz, J_2 =0.8Hz), 7.02 – 7.08 (m, 2H), 6.34 – 6.35 (m, 1H), 2.76 (t, 2H, *J* = 8 Hz), 1.69 – 1.77 (m, 2H), 1.23 – 1.43 (m, 14H), 0.88 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 136.4, 127.6, 125.0, 121.5, 119.3, 108.8, 98.1, 31.9, 29.6, 29.5, 29.4, 29.30, 29.28, 29.1, 28.2, 22.7, 14.1; IR (neat): 3584, 3410, 2922, 2851, 1608, 1433; MS (ES^+) Calculated for $[C_{18}H_{27}ClN]^+$: 292.18; Found: 292.19.

General Procedure C: Preparation of *N*-Arylhydroxylcarbamates 4-11

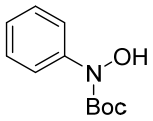


4-11

The precursor *N*-phenylhydroxylamine was synthesized according to literature

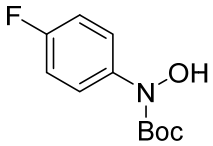
procedures.[33] To a solution of *N*-phenylhydroxylamine (10 mmol) in dry diethyl ether (50 mL) was added di-*t*-butyl dicarbonate (2.8 g, 10 mmol) at room temperature. After 12 h, the reaction was concentrated and the residue was purified through silica gel flash chromatography to give the desired product *tert*-butyl hydroxy(aryl)carbamate **4-11**.

4-11a



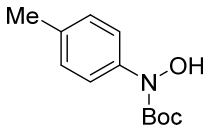
This compound was prepared in 70% yield according to the general procedure C (eluents: ethyl acetate: hexanes = 1:20). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (bs, 1H), 7.47 (dt, 2H, J_1 = 8.5 Hz, J_2 = 1.5 Hz), 7.35 (t, 2H, J = 8 Hz), 7.16 (t, 1H, J = 7.5 Hz), 1.52 (S, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 140.7, 128.3, 125.1, 121.4, 83.4, 28.2; IR (neat): 3218, 2979, 2933, 1682, 1596, 1495, 1368, 1125.

4-11b



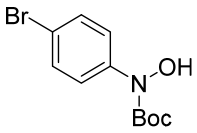
This compound was prepared in 66% yield according to the general procedure C (eluents: ethyl acetate: hexanes = 1:15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (bs, 1H), 7.37 – 7.42 (m, 2H), 6.99 – 7.05 (m, 2H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2 (d, J = 243 Hz), 154.7, 137.1, 124.0 (d, J = 9 Hz), 115.1 (d, J = 23 Hz), 83.4, 28.2; IR (neat): 3238, 3232, 2980, 2934, 1695, 1683, 1507, 1369, 1230, 1126, 836; 250.09; HRMS-(ESI+) calculated for $[C_{11}H_{14}FNNaO_3]^+$: 250.0855, found 250.0853.

4-11c



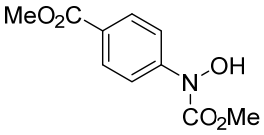
This compound was known and prepared in 70% yield according to the general procedure C (eluents: ethyl acetate: hexanes = 1:15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (bs, 1H), 7.32 (d, 2H, *J* = 8.8 Hz), 7.14 (d, 2H, *J* = 8Hz), 2.34 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 138.3, 135.1, 128.9, 121.9, 28.2, 20.9; IR (neat): 3194, 3130, 2975, 2925, 1694, 1667, 1509, 1367, 1161, 1122, 1106.

4-11d



This compound was prepared in 60% yield according to the general procedure C (eluents: ethyl acetate: hexanes = 1:25). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (bs, 1H), 7.44 (dt, 2H, J_1 = 9.2 Hz, J_2 = 2.4 Hz), 7.34 (dt, 2H, J_1 = 9.2 Hz, J_2 = 2.4 Hz), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0, 139.9, 131.3, 122.7, 118.0, 83.9, 28.2; IR (neat): 3239, 2978, 2931, 1691, 1486, 1370, 1340, 1130; HRMS-(ESI+) calculated for $[C_{11}H_{14}BrNNaO_3]^+$: 310.0055, found 310.0046.

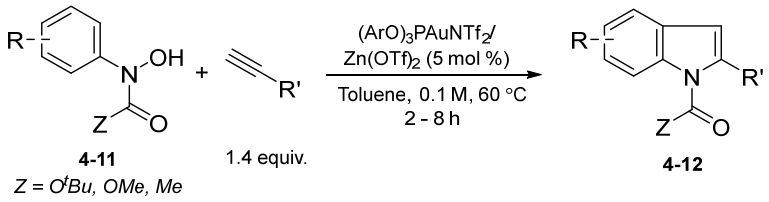
4-11e



This compound was prepared in 70 % yield according to literature procedures. [2]

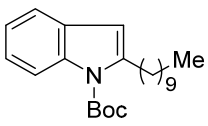
(eluents: ethyl acetate: hexanes = 1:8). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, 2H, *J* = 8.4 Hz), 7.60 (d, 2H, *J* = 8.8 Hz), 3.90 (s, 3H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 154.9, 144.3, 130.2, 126.0, 119.0, 54.1, 52.2; IR (neat): 3582, 3304, 3007, 2955, 2847, 1717, 1606, 1439, 1338, 1282, 1113; HRMS-(ESI+) calculated for $[C_{10}H_{11}NNaO_5]^+$: 248.0535, found 248.0523.

General Procedure D: Preparation of *N*-Protected-2-alkyl Indoles 4-12



To a solution of *N*-protected hydroxylamine **4-11** (0.3 mmol, 1 equiv) in dry toluene (3 mL, 0.1 M) was added the corresponding alkyne (0.42 mmol, 1.4 equiv), $Zn(OTf)_2$ (0.015 mol%) and $(ArO)_3PAuNTf_2$ (Ar = 2,4-di-*tert*-butylphenyl, 0.015 mmol, 5 mol%) at room temperature. The reaction mixture was stirred at 60 °C for 2 – 8 h. Once the reaction finished by TLC, it was concentrated and the residue was purified through silica gel flash chromatography to give the pure desired product **4-12**.

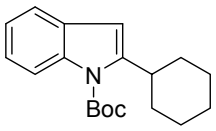
4-12a



This compound was prepared in 90% yield according to the general procedure D (eluents: ethyl acetate: hexanes = 1:80). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, 1H, *J* = 8.5 Hz), 8.46 – 8.48 (d, 1H, *J* = 8 Hz), 7.19 – 7.27 (m, 2H), 6.36 (d, 1H, *J* = 1 Hz),

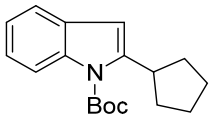
3.02 (t, 2H, J = 8 Hz), 1.69 – 1.74 (m, 11 H), 1.41 – 1.48 (m, 2H), 1.30 – 1.39 (m, 12H), 0.91 (t, 3H, J = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5, 142.5, 136.6, 129.3, 123.0, 122.4, 119.5, 115.5, 106.9, 83.5, 31.9, 30.2, 29.7, 29.6, 29.5, 29.4, 29.0, 28.3, 22.7, 14.2; IR (neat): 3051, 2954, 2925, 2854, 1734, 1454, 1369, 1327, 1166, 1118, 1086; HRMS-(ESI+) calculated for $[C_{23}H_{35}NNaO_2]^+$: 380.2565, found 380.2562.

4-12b



This compound was prepared in 83% yield according to the general procedure D (eluents: ethyl acetate: hexanes = 1:100). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, 1H, J = 8.0 Hz), 7.45 (dd, 1H, J_1 = 7.6 Hz, J_2 = 0.8 Hz), 7.15 – 7.23 (m, 2H), 6.37 (s, 1H), 3.35 (m, 1H, Hz), 2.10 (d, 1H, J = 12.8 Hz), 1.83 – 1.87 (m, 2H), 1.69 (s, 9H), 1.24 – 1.50 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 147.9, 136.7, 129.4, 123.1, 122.4, 119.7, 115.5, 104.8, 83.5, 37.4, 33.7, 28.3, 26.7, 26.4; IR (neat): 2977, 2929, 2852, 1730, 1454, 1369, 1324, 1158, 1113, 1084; HRMS-(ESI+) calculated for $[C_{19}H_{25}NNaO_2]^+$: 322.1783, found 322.1774.

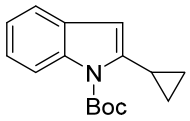
4-12c



This compound was prepared in 89% yield according to the general procedure D (eluents: ethyl acetate: hexanes = 1:100). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, 1H, J = 8.0 Hz), 7.45 (dd, 1H, J_1 = 7.2 Hz, J_2 = 0.8 Hz), 7.16-7.24 (m, 2H), 6.37 (d, 1H, J =

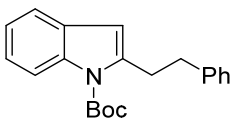
0.8 Hz), 3.74 (m, 1H, J = 7.6 Hz), 2.13 – 2.17 (m, 2H), 1.71 – 1.77 (m, 2H), 1.56 – 1.70 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 146.5, 136.8, 129.2, 123.1, 122.4, 119.7, 115.4, 104.6, 83.5, 39.4, 33.0, 28.2, 24.8. IR (neat): 3050, 2959, 2869, 2852, 1732, 1454, 1369, 1327, 1159, 1115, 1089; HRMS-(ESI+) calculated for $[C_{18}H_{23}NNaO_2]^+$: 308.1626, found 308.1616.

4-12d



This compound was prepared in 84% yield according to the general procedure D (eluents: ethyl acetate: hexanes = 1:100). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, 1H, J = 8.0 Hz), 7.43 (dd, 1H, J_1 = 7.6 Hz, J_2 = 0.8 Hz), 7.17 – 7.24 (m, 2H), 6.24 (s, 1H), 2.34 – 2.40 (m, 1H), 1.70 (s, 9H), 0.94 – 1.00 (m, 2H), 0.72 – 0.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 143.9, 136.8, 129.0, 123.3, 122.5, 119.8, 115.3, 105.6, 83.4, 28.3, 11.2, 7.6; IR (neat): 3050, 2979, 2930, 2851, 1730, 1454, 1369, 1335, 1165, 1118, 1096; HRMS-(EI+) calculated for $[C_{16}H_{19}NO_2]^+$: 257.1416, found 257.1425.

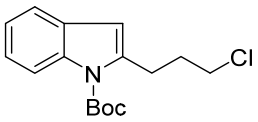
4-12e



This compound was prepared in 96% yield according to the general procedure D (eluents: ethyl acetate: hexanes = 1:100). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, 1H, J = 8.4 Hz), 7.47 (dd, 1H, J_1 = 7.2 Hz, J_2 = 0.8 Hz), 7.21 – 7.34 (m, 7H), 6.38 (d, 1H, J = 0.8 Hz), 3.37 (d, 2H, J = 7.2 Hz), 3.05 (d, 2H, J = 7.2 Hz), 1.71 (s, 9H); ^{13}C NMR

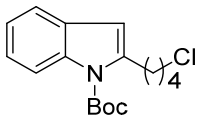
(100 MHz, $CDCl_3$) δ 150.6, 141.7, 141.5, 136.5 129.3, 128.4, 128.3, 126.0, 123.3, 122.6, 119.8, 115.6, 107.4, 83.8, 35.3, 31.9, 28.4; IR (neat): 3051, 2977, 2925, 2851, 1732, 1460, 1369, 1328, 1158, 1115, 1086; HRMS-(ESI+) calculated for $[C_{21}H_{23}NNaO_2]^+$: 344.1626, found 344.1623.

4-12f



This compound was prepared in 87% yield according to the general procedure D (eluents: ethyl acetate: hexanes = 1:100). ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, 1H, *J* = 8.0 Hz 7.46 (dd, 1H, J_1 = 7.8 Hz, J_2 = 1.2 Hz), 7.19 – 7.25 (m, 2H), 6.40 (s, 1H), 3.62 (t, 2H, *J* = 6.4 Hz), 3.20 (t, 2H, *J* = 7.2 Hz), 2.10 – 2.25 (m, 2H), 1.70 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4 140.1, 136.6, 129.1, 123.5, 122.7, 119.8, 115.6, 107.9, 83.9, 44.4, 31.7, 31.5, 30.6, 28.3, 27.3; IR (neat): 3050, 2977, 2925, 2851, 1732, 1460, 1369, 1328, 1158, 1115, 1086; HRMS-(ESI+) calculated for $[C_{16}H_{20}ClNNaO_2]^+$: 316.1080, found 316.1085.

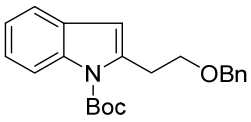
4-12g



This compound was prepared in 95% yield according to the general procedure D (eluents: ethyl acetate: hexanes = 1:100). ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, 1H, *J* = 8.4 Hz 7.45 (dd, 1H, J_1 = 6.8 Hz, J_2 = 1.6 Hz), 7.18 – 7.23 (m, 2H), 6.37 (s, 1H), 3.60 (t, 2H, *J* = 6.4 Hz), 3.20 (t, 2H, *J* = 6.8 Hz), 1.86 – 1.90 (m, 2H), 1.70 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 141.5, 136.6, 129.2, 123.3, 122.6, 119.7, 115.6,

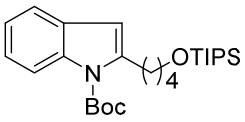
107.3, 83.8, 45.0, 32.3, 29.5, 28.3, 26.3; IR (neat): 3050, 2977, 2925, 2851, 1732, 1454, 1370, 1327, 1158, 1115, 1087; HRMS-(ESI+) calculated for $[C_{17}H_{22}ClNNaO_2]^+$: 330.1237, found 330.1259.

4-12h



This compound was prepared in 83% yield according to the general procedure D (eluents: ethyl acetate: hexanes = 1:100). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, 1H, *J* = 8.2 Hz 7.47 – 7.49 (m, 1H), 7.19 – 7.36 (m, 7H), 6.45 (d, 1H, *J* = 0.8 Hz), 4.59 (s, 2H), 3.83 (t, 2H, *J* = 7.2 Hz), 3.38 (td, 2H, J_1 = 6.4 Hz, J_2 = 0.8 Hz), 1.68 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 138.4, 138.2, 136.5, 129.2, 128.3, 127.7, 127.5, 123.4, 122.6, 119.8, 115.5, 108.3, 83.8, 72.9, 69.0, 30.6, 28.1; IR (neat): 3050, 2977, 2930, 2858, 1732, 1454, 1370, 1328, 1158, 1118, 1092; HRMS-(ESI+) calculated for $[C_{22}H_{25}NNaO_3]^+$: 374.1732, found 374.1732.

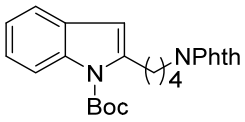
4-12i



This compound was prepared in 78% yield according to the general procedure D (eluents: ethyl acetate: hexanes = 1:200). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, 1H, J_1 = 8.8 Hz, J_2 = 0.8 Hz), 7.35 – 7.37 (m, 1H), 7.08 – 7.16 (m, 2H), 6.28 (d, 1H, *J* = 0.8 Hz), 3.67 (t, 2H, *J* = 6.0 Hz), 2.95 (t, 2H, *J* = 7.6 Hz), 1.69 – 1.74 (m, 2H), 1.57 – 1.62 (m, 12H), 0.95 – 0.99 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 142.3, 136.6, 129.4, 123.1, 122.5, 119.6, 115.5, 107.0, 83.6, 63.2, 32.7, 29.9, 28.2, 25.2, 18.0,

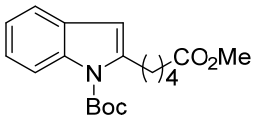
11.9; IR (neat): 3050, 2977, 2941, 2865, 1734, 1454, 1369, 1303, 1165, 1116, 1095; HRMS-(ESI+) calculated for $[C_{26}H_{43}NNaSiO_3]^+$: 468.2910, found 468.2897.

4-12j



This compound was prepared in 93% yield according to the general procedure D (eluents: ethyl acetate: hexanes = 1:40). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, 1H, *J* = 8.0 Hz), 7.83 – 7.85 (m, 2H), 7.69-7.2 (m, 2H), 7.42-7.44 (m, 2H), 7.16-7.21 (m, 2H), 6.34 (s, 1H), 3.75 (t, 2H, *J* = 7.2 Hz), 3.04 (t, 2H, *J* = 7.2 Hz), 1.75-1.82 (m, 4H), 1.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 150.4, 141.5, 136.6, 133.8, 132.1, 129.2, 123.2, 123.1, 122.5, 119.7, 115.6, 107.3, 83.7, 37.9, 29.8, 28.4, 28.3, 26.3; IR (neat): 3050, 2977, 2925, 2851, 1707, 1460, 1369, 1328, 1158, 1116, 1086; HRMS-(ESI+) calculated for $[C_{25}H_{26}N_2NaO_4]^+$: 441.1790, found 441.1784.

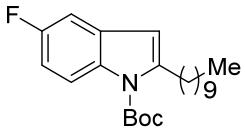
4-12k



This compound was prepared in 82% yield according to the general procedure D (eluents: ethyl acetate: hexanes = 1:80). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, 1H, *J* = 8.5 Hz), 7.17 – 7.23 (m, 2H), 6.36 (d, 1H, *J* = 0.5 Hz), 3.69 (s, 3H), 3.03 (t, 2H, *J* = 7.5 Hz), 2.40 (t, 2H, *J* = 7.5 Hz), 1.75 – 1.78 (m, 4H), 1.70 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 150.5, 141.7, 136.6, 129.3, 123.2, 122.6, 119.7, 115.5, 107.2, 83.7, 51.6, 34.0, 29.9, 28.4, 28.3, 24.7. IR (neat): 3050, 2977, 2925, 2851, 1732, 1455, 1369, 1328, 1161, 1115, 1086; HRMS-(ESI+) calculated for $[C_{19}H_{25}NNaO_4]^+$:

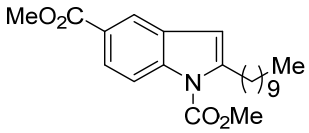
354.1681, found 354.1684.

4-12l



This compound was prepared in 94% yield according to the general procedure D (eluents: ethyl acetate: hexanes = 1:80). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (dd, 1H, J_1 = 9.2 Hz, J_2 = 4.8 Hz), 7.09 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.8 Hz), 6.93 (td, 1H, J_1 = 8.8 Hz, J_2 = 2.4 Hz), 6.30 (s, 1H), 2.97 (t, 2H, J = 7.6 Hz), 1.68 (s, 9H), 1.21 – 1.44 (m, 16H), 0.89 (t, 3H, J = 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1, 158.2, 150.3, 144.2, 132.9, 132.0 (d, J = 10.3 Hz), 116.4 (d, J = 9.0 Hz), 110.6 (d, J = 9.0 Hz), 106.6 (d, J = 3.4 Hz), 105.0 (d, J = 23.1 Hz), 83.8, 32.0, 30.4, 29.7, 29.6, 29.5, 29.48, 29.41, 28.9, 28.3, 22.8, 14.2. IR (neat): 3050, 2977, 2925, 2851, 1732, 1460, 1369, 1327, 1158, 1115, 1086; HRMS-(EI+) calculated for $[C_{23}H_{34}NFO_2]^+$: 375.2574, found 375.2570.

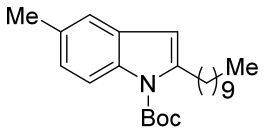
4-12m



This compound was prepared in 80% yield according to the general procedure D (eluents: ethyl acetate: hexanes = 1:40). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, 1H, J = 1.6 Hz), 8.09(d, 1H, J = 8.8 Hz), 7.92 (dd, 1H, J_1 = 8.8 Hz, J_2 = 1.6 Hz), 7.42 (d, 1H, J = 0.8 Hz), 4.06 (s, 3H), 3.93 (s, 3H), 2.99 (t, 2H, J = 7.6 Hz), 1.67-1.71 (m, 2H), 1.27-1.42 (m, 14H), 0.88 (t, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5,

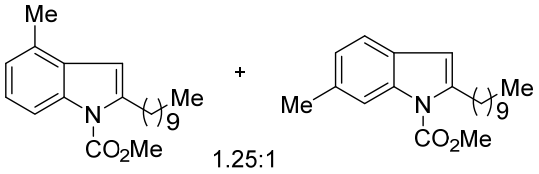
152.2, 144.0, 139.1, 129.3, 124.8, 124.7, 121.9, 115.2, 107.7, 53.7, 52.0, 31.9, 29.9, 29.6, 29.5, 29.3, 28.6, 22.7, 14.1; IR (neat): 3050, 2977, 2925, 2851, 1732, 1707, 1441, 1369, 1328, 1158, 1115, 1086; HRMS-(EI+) calculated for $[C_{22}H_{31}NNaO_4]^+$: 396.2151, found 396.2153.

4-12n



This compound was prepared in 91% yield according to the general procedure D (eluents: ethyl acetate: hexanes = 1:100). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, 1H, *J* = 8.8 Hz), 7.23-7.26 (m, 1H), 7.04 (d, 1H, *J* = 8.8 Hz), 6.27 (s, 1H), 2.98 (t, 2H, *J* = 7.6 Hz), 2.42 (s, 3H), 1.68-1.70 (m, 11H), 1.27-1.41 (m, 14H), 0.89 (t, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 142.6, 134.8, 131.9, 129.6, 124.3, 119.6, 115.2, 106.7, 83.4, 76.8, 43.9, 31.9, 30.3, 29.7, 29.6, 29.5, 29.48, 29.42, 29.0, 28.3, 22.8, 21.3, 14.2; IR (neat): 3050, 2977, 2925, 2851, 1732, 1460, 1369, 1327, 1158, 1116, 1086; HRMS-(ESI+) calculated for $[C_{24}H_{37}NNaO_2]^+$: 394.2722, found 394.2713.

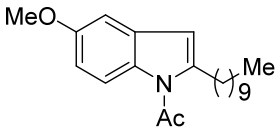
4-12o and **4-12o'** (1.25:1)



These two compounds were prepared as a pair of inseparable mixtures in 78% yield according to the general procedure D (eluents: ethyl acetate: hexanes = 1:100). The position of the methyl group is determined by 1H nosey; ^{1}H NMR (400 MHz, $CDCl_3$)

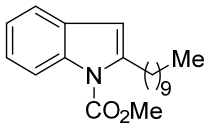
δ 7.90-7.92 (m, 1H), 7.32 (d, 0.44 H, *J* = 8.4 Hz), 7.12-7.16 (m, 0.63H), 7.00-7.12 (m, 1H), 6.40 (d, 0.54 H, *J* = 0.4 Hz), 6.40 (d, 0.43 H, *J* = 0.8 Hz), 4.04 (s, 3H), 2.97-3.02 (m, 2H), 2.47-2.49 (m, 3H), 1.68-1.71 (m, 2H), 12.8-14.6 (m, 16H), 0.87.-0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 142.0, 141.8, 136.8, 136.1, 133.2, 129.0, 128.9, 127.2, 124.2, 123.4, 123.3, 119.3, 115.8, 113.1, 107.4, 105.9, 53.34, 53.31, 43.8, 31.9, 29.99, 29.91, 29.84, 29.62, 29.53, 29.47, 29.39, 29.35, 29.30, 29.17, 28.89, 28.79, 23.84, 22.69, 21.98, 18.39, 14.17 IR (neat): 3050, 2977, 2925, 2851, 1732, 1460, 1369, 1328, 1158, 1115, 1086; HRMS-(EI+) calculated for $[C_{21}H_{31}NO_2]^+$: 329.2355, found 329.2362.

4-12p



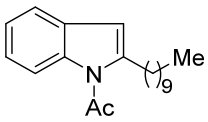
This compound was prepared in 80% yield according to the general procedure D (eluents: ethyl acetate: hexanes = 1:100). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, 1H, *J* = 8.8 Hz), 6.95 (d, 1H, *J* = 2.8 Hz), 6.84 (dd, 1H, J_1 = 9.2 Hz, J_2 = 2.4 Hz), 6.34 (s, 1H), 3.85 (s, 3H), 2.97 (t, 2H, *J* = 7.6 Hz), 2.72 (s, 3H), 1.66 – 1.74 (m, 2H), 1.20 – 1.43 (m, 14H), 0.88 (t, 3H, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 155.9, 143.7, 131.04, 130.96, 115.7, 150.5, 11.5, 108.2, 102.9, 5.6, 31.9, 30.6, 29.6, 29.5, 29.3, 28.8, 27.5, 22.7, 14.2; IR (neat): 2995, 2925, 2853, 1704, 1614, 1478, 1371, 1308, 1206; HRMS-(ESI+) calculated for $[C_{21}H_{31}NNaO_2]^+$: 352.2252, found 352.2241.

4-12q



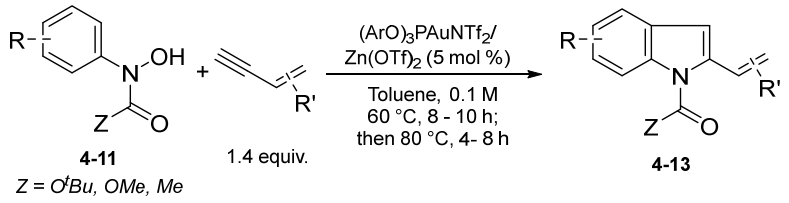
This compound was prepared in 81% yield according to the general procedure D (2 equiv of 1-dodecyne was used; reaction solvent was DCE; eluents: ethyl acetate: hexanes = 1:75). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (dd, 1H, J_1 = 8 Hz, J_1 = 0.8 Hz), 7.46 (dd, 1H, J_1 = 8 Hz, J_2 = 0.8 Hz), 7.19 – 7.27 (m, 2H), 6.38 (s, 1H), 4.05 (s, 3H), 3.00 (t, 2H, J = 7.6 Hz), 1.66 – 1.74 (m, 2H), 1.28 – 1.46 (m, 14H), 0.89 (t, 3H, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 142.6, 136.4, 129.5, 123.3, 122.9, 119.7, 115.5, 53.4, 31.9, 29.9, 29.6, 29.5, 29.3, 28.7, 22.7, 14.1; HRMS-(ESI+) calculated for $[C_{20}H_{29}NNaO_2]^+$: 338.2096, found 338.2102.

4-12r



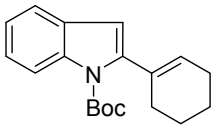
This compound was prepared in 90% yield according to the general procedure D (eluents: ethyl acetate: hexanes = 1:40). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, 1H, J = 8.0 Hz), 7.47-7.50 (m, 1H), 7.21-7.26 (m, 2H), 6.41 (d, 1H, J = 0.8 Hz), 2.99 (t, 2H, J = 7.2 Hz), 2.76 (s, 3H), 1.68-1.74 (m, 2H), 1.20-1.43 (m, 14H), 0.89 (t, 3H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 70.3, 143.0, 136.3, 129.9, 123.4, 122.9, 120.1, 114.7, 108.1, 31.9, 30.5, 29.6, 29.5, 29.3, 28.9, 27.7, 22.7, 14.1; IR (neat): 3050, 2954, 2925, 2851, 1707, 1460, 1369, 1301, 1208; HRMS-(ESI+) calculated for $[C_{20}H_{29}NNaO]$ 322.2147, found 322.2153.

General Procedure E: Preparation of *N*-Protected-2-alkenyl Indoles 4-13



To a solution of *N*-protected hydroxylamine **4-11** (0.3 mmol, 1 equiv) in dry toluene (3 mL, 0.1 M) was added the corresponding 1,3-enyne (0.42 mmol, 1.4 equiv), $Zn(OTf)_2$ (0.015 mmol, 5 mol%) and $(ArO)_3PAuNTf_2$ (Ar = 2,4-di-*tert*-butylphenyl, 0.015 mmol, 5 mol%) at room temperature. The reaction mixture was stirred at 60 °C for 4 – 8 h. Once TLC indicated there was no starting material left, the reaction was raised up to 80 °C, stirred for additional 4 - 8 h, and then concentrated. The residue was purified through silica gel flash chromatography to give the desired product **4-13**.

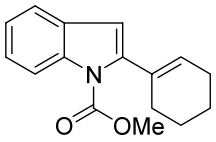
4-13a



This compound was prepared in 83% yield according to the general procedure E (eluents: ethyl acetate: hexanes = 1:50). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (dd, 1H, J_1 = 8.5 Hz, J_2 = 1 Hz), 7.50 (d, 1H, J = 7.5 Hz), 7.26 – 7.29 (m, 1H), 7.21 (td, 1H, J_1 = 7.5 Hz, J_1 = 1 Hz), 6.39 (s, 1H), 5.89 – 5.92 (m, 1H), 2.27 – 2.30 (m, 2H), 2.21 – 2.25 (m, 2H), 1.78 – 1.83 (m, 2H), 1.70 – 1.75 (m, 2H), 1.67 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.3, 143.7, 136.9, 132.5, 129.3, 126.5, 123.6, 122.6, 120.1, 115.1, 107.8, 83.4, 29.1, 28.2, 25.4, 22.7, 21.9; IR (neat): 3051, 2979, 2932, 2859, 2834, 1731, 1453, 1369, 1326, 1161, 1126; HRMS-(ESI+) calculated for $[C_{19}H_{23}NNaO_2]^+$:

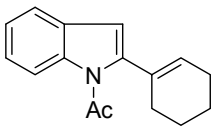
320.1626, found 320.1627.

4-13b



This compound was prepared in 86% yield according to the general procedure E (reaction solvent: DCE, eluents: ethyl acetate: hexanes = 1:50). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, 1H, J = 8.5 Hz), 7.50 (dt, 1H, J_1 =7.5 Hz, J_2 = 1 Hz), 7.22 – 7.31 (m, 2H), 6.40 (s, 1H), 5.88 – 5.90 (m, 1H), 4.09 (S, 3H), 2.22 – 2.27 (m, 4H), 1.72 – 1.75 (m, 2H), 1.77 – 1.81 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 125 152.0, 143.5, 136.4, 132.5, 129.5, 127.1, 123.8, 122.9, 120.2, 115.4, 108.3, 53.5, 29.4, 25.5, 22.8, 22.1; IR (neat): 3027, 2932, 2856, 2834, 1744, 1455, 1324, 1213; HRMS-(ESI+) calculated for $[C_{16}H_{17}NNaO_2]^+$: 278.1157, found 278.1146.

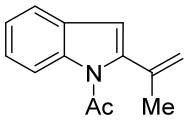
4-13c



This compound was prepared in 92% yield according to the general procedure E (eluents: ethyl acetate: hexanes = 1:30). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, 1H, J = 8.5 Hz), 7.50 (d, 1H, J = 7.5 Hz), 7.31 (td, 1H, J_1 = 7 Hz, J_2 = 1.5 Hz), 7.25 (td, 1H, J_1 = 7.5 Hz, J_2 = 1.5 Hz), 6.46 (S, 1H), 5.98 – 6.00 (m, 1H), 2.30 – 2.33 (m, 2H), 2.23 – 2.27 (m, 2H), 1.78 – 1.83 (m, 2H), 1.71 – 1.75 (m, 2H); ^{13}C NMR (125MHz, $CDCl_3$) δ 171.2, 142.3, 137.1, 131.8, 129.8, 129.0, 124.4, 123.3, 120.0, 115.6, 109.0, 30.0, 26.4, 25.6, 22.7, 21.8; IR (neat): 3049, 2930, 2857, 2834, 1701, 1450, 1367, 1303;

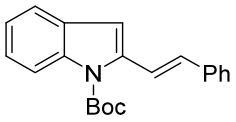
HRMS-(ESI+) calculated for $[C_{16}H_{17}NNaO]^+$: 262.1208, found 262.1195.

4-13d



This compound was prepared in 68% yield according to the general procedure E (2 equiv enyne was used; eluents: ethyl acetate: hexanes = 1:30, 60 °C, 12 h). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (ddd, 1H, J_1 = 8.5 Hz, J_2 = 2 Hz, J_3 = 1 Hz), 7.52 (ddd, 1H, J_1 = 8 Hz, J_2 = 2 Hz, J_3 = 1 Hz,), 7.31 – 7.34 (m, 1H), 7.24 – 7.27 (m, 1H), 6.56 (d, 1H, J = 1 Hz), 5.31 – 5.32 (m, 1H), 5.26 (s, 1H), 2.62 (s, 3H), 2.15 (dd, 3H, J_1 = 1.5 Hz, J_2 = 1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.0, 141.6, 138.0, 137.3, 128.9, 124.8, 123.4, 120.4, 117.3, 115.3, 109.8, 26.8, 23.3; IR (neat): 3084, 3050, 2954, 2923, 2854, 1706, 1451, 1368, 1299, 1187; HRMS-(ESI+) calculated for $[C_{13}H_{13}NNaO]^+$: 222.0895, found 222.0887.

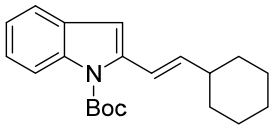
4-13e



This compound was prepared in 74% yield according to the general procedure E (eluents: ethyl acetate: hexanes = 1: 50). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, 1H, J = 8.5 Hz), 7.78 (d, 1H, J = 16.5 Hz), 7.56 (d, 3H, J = 7.5 Hz), 7.39 (t, 2H, J = 7.5 Hz), 7.28 – 7.32 (m, 2H), 7.24 – 7.27 (m, 1H), 7.08 (d, 1H, J = 16.5 Hz), 6.88 (S, 1H), 1.73 (S, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5, 139.5, 137.1, 136.8, 130.5, 129.3, 128.6, 127.7, 126.6, 124.1, 122.9, 120.7, 120.2, 115.7, 106.7, 84.1, 28.4; IR (neat): 3058, 3023, 2976, 2931, 1730, 1450, 1370, 1327, 1157; HRMS-(ESI+) calculated for

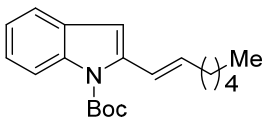
$[C_{21}H_{21}NNaO_2]^+$: 342.1470, found 342.1468.

4-13f



This compound was prepared in 90% yield according to the general procedure E (pent-2-en-4-yn-1-ylcyclohexane (E/Z> 30:1) was used; eluents: ethyl acetate: hexanes = 1:50). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, 1H, *J* = 8.5 Hz), 8.48 (d, 1H, *J* = 8 Hz), 7.25 (td, 1H, J_1 = 7.5 HZ, J_2 = 1.5 Hz), 7.20 (td, 1H, J_1 = 7.5 Hz, J_2 = 1.0 Hz), 6.91 (d, 1H, *J* = 16 Hz), 6.64 (S, 1H), 6.16 (dd, 1H, J_1 = 15.5 Hz, J_2 = 2 Hz), 2.18 – 2.21 (m, 1H), 1.87 (dd, 1H, J_1 = 14 Hz, J_2 = 2 Hz), 1.80 (dt, 2H, J_1 = 13 Hz, J_2 = 3.5 Hz), 1.71 (S, 9H), 1.31 – 1.39 (m, 3H), 1.19 – 1.27 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5, 140.0, 139.1, 136.5, 129.4, 123.5, 122.7, 119.87, 119.81, 115.5, 105.8, 83.8, 41.2, 32.8, 28.4, 26.2, 26.1; IR (neat): 2927, 2853,1731, 1451, 1370, 1328, 1159; HRMS-(EI+) calculated for $[C_{21}H_{27}NO_2]^+$: 325.2042, found 325.2040.

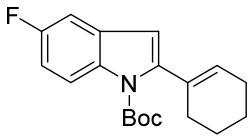
4-13g



This compound was prepared in 86% yield (E/Z> 15:1) according to the general procedure E (non-3-en-1-yne (E/Z = 9:1) was used; eluents: ethyl acetate: hexanes = 1:50). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, 1H, *J* = 8 Hz), 7.49 (d, 1H, *J* = 8 Hz), 7.19 – 7.27 (m, 2H), 6.64 (s, 1H), 6.20 (dt, 1H, J_1 = 16 Hz, J_2 = 7 Hz), 2.24 – 2.29 (m, 2H), 1.71 (s, 9H), 1.51 – 1.57 (m, 2H), 1.36 – 1.40 (m, 4H), 0.94 (t, 3H, *J* = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.5, 139.8, 136.4, 133.7, 129.4, 123.5, 122.7, 122.1,

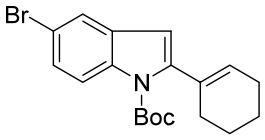
119.9, 115.5, 105.9, 83.8, 33.1, 31.5, 28.9, 28.3, 22.6, 14.1; IR (neat): 3051, 2957, 2856, 1731, 1451, 1327, 1159, 1116, 962; HRMS-(EI+) calculated for $[C_{20}H_{27}NO_2]^+$: 313.2042, found 325.2041.

4-13h



This compound was prepared in 75% yield according to the general procedure E (eluents: ethyl acetate: hexanes = 1:50). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, 1H, J_1 = 8.8 Hz, J_2 = 4.4 Hz), 7.12 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.8 Hz), 6.97 (td, 1H, J_1 = 8.8 Hz, J_2 = 2.8 Hz), 6.31 (s,1H), 5.87 – 5.89 (m, 1H), 2.18 – 2.27 (m, 4H), 1.75 – 1.80 (m, 2H), 1.68 – 1.73 (m, 2H), 1.64 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (d, J = 236 Hz), 150.1, 145.3, 133.2, 132.3, 130.1 (d, J = 11 Hz), 127.0, 116.1 (d, J = 11 Hz), 111.2 (d, J = 24 Hz), 107.5, 105.5 (d, J = 24 Hz), 83.7, 29.1, 28.1, 25.3, 22.6, 21.9; IR (neat): 2979, 2970, 2933, 2860, 2834, 1732, 1471, 1370, 1314, 1115; HRMS-(ESI+) calculated for $[C_{19}H_{22}NNaO_2]^+$: 338.1532, found 338.1523.

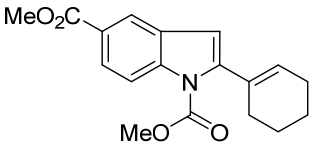
4-13i



This compound was prepared in 65% yield according to the general procedure E (eluents: ethyl acetate: hexanes = 1:50). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, 1H, J = 9 Hz), 7.60 (d, 1H, J = 2 Hz), 7.33 (dd, 1H, J_1 =9 HZ, J_2 = 2 Hz), 6.29 (S, 1H), 5.87 – 5.89 (m, 1H), 2.23 – 2.26 (m, 2H), 2.18 – 2.22 (m, 2H), 1.75 – 1.79 (m, 2H), 1.68 –

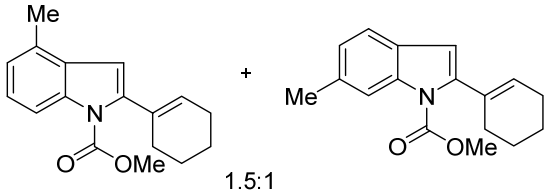
1.72 (m, 2H), 1.64 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.9, 144.8, 135.6, 132.0, 131.0, 127.2, 126.3, 122.6, 116.6, 115.8, 106.9, 83.9, 29.1, 28.2, 25.4, 22.7, 21.9; IR (neat): 3111, 2965, 2932, 2859, 2834, 1733, 1446, 1348, 1155, 1013; HRMS-(ESI+) calculated for $[C_{19}H_{22}BrNNaO_2]^+$: 398.0732, found 398.0738.

4-13j



This compound was prepared in 77% yield according to the general procedure E (reaction solvent: DCE; eluents: ethyl acetate: hexanes = 1:30). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, 1H, J = 1.6 Hz), 8.10 (d, 1H, J = 8.8 Hz), 7.96 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2 Hz), 6.43 (s, 1H), 5.87 – 5.89 (m, 1H), 4.02 (s, 3H), 3.93 (s, 3H), 2.19 – 2.22 (m,4H), 1.68 – 1.77 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 151.8, 144.8, 139.2, 132.1, 129.3, 127.9, 125.2, 124.9, 122.4, 115.1, 108.5, 53.8, 52.0, 29.3, 25.4, 22.7, 21.9; IR (neat): 3022, 2933, 2856, 1741, 1722, 1444, 1338, 1210; HRMS-(ESI+) calculated for $[C_{18}H_{19}NNaO_4]^+$: 336.1212, found 336.1205.

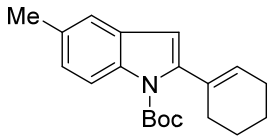
4-13k



These two compounds were prepared as a pair of inseparable mixtures in 71% yield according to the general procedure E (reaction solvent: DCE; eluents: ethyl acetate: hexanes = 1:40). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.94 (m, 0.75H), 7.37 (d, 0.39H, J = 8 Hz), 7.19 (t, 0.48H, J = 8 Hz), 7.03 – 7.07 (m, 0.83H), 6.45 (d, 0.47H, J

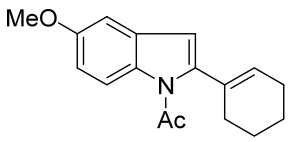
= 0.8 Hz), 6.34 (d, 0.34H, *J* = 0.8 Hz), 5.86 – 5.91(m, 0.86H), 4.01 (s, 2.70H), 2.51 (s, 1.5H), 2.50 (s, 1.2H), 2.21 – 2.25 (m, 4H), 1.60 – 1.79 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 152.1, 143.04, 142.95, 136.9, 136.2, 133.8, 132.7, 129.6, 129.0, 127.2, 127.0, 126.9, 124.3, 123.9, 123.4, 119.8, 115.6, 112.9, 108.2, 106.9, 53.50, 53.47, 29.42, 29.39, 25.4, 22.8, 22.1, 22.0, 18.4; IR (neat): 3025, 2931, 2856, 2834, 1734, 1441, 1327, 1129; HRMS-(ESI+) calculated for $[C_{17}H_{19}NNaO_2]^+$: 292.1313, found 292.1293.

4-13l



This compound was prepared in 80% yield according to the general procedure E (eluents: ethyl acetate: hexanes = 1:50). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, 1H, *J* = 8.4 Hz), 7.27 (s, 1H), 7.07 (d, 1H, *J* = 8.8 Hz), 6.29 (s, 1H), 5.87 – 5.89 (m, 1H), 2.42 (s, 3H), 2.23 – 2.26 (m, 2H), 2.19 – 2.21 (m, 2H), 1.75 – 1.81 (m, 2H), 1.67 – 1.73 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 143.8, 135.1, 132.6, 132.0, 129.5, 126.3, 124.9, 120.1, 114.8, 107.6, 83.2, 29.1, 28.2, 25.3, 22.7, 21.9, 21.2; IR (neat): 2978, 2932, 2857, 2834,1731, 1474, 1352, 1134; HRMS-(ESI+) calculated for $[C_{20}H_{25}NNaO_2]^+$: 334.1783, found 334.1779.

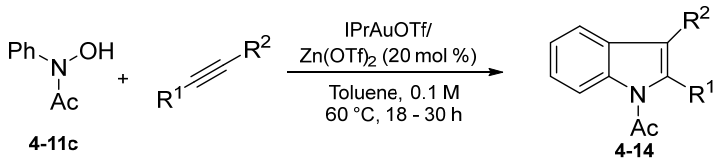
4-13m



This compound was prepared in 75% yield according to the general procedure E

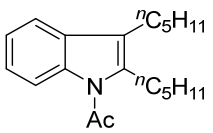
(eluents: ethyl acetate: hexanes = 1:60). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, 1H, *J* = 8.8 Hz), 6.95 (d, 1H, *J* = 2.8 Hz), 6.89 (dd, 1H, J_1 = 9.2 Hz, J_2 = 2.8 Hz), 6.36 (s, 1H), 5.94 – 5.97 (m, 1H), 3.84 (s, 3H), 2.55 (s, 3H), 2.26 – 2.30 (m, 2H), 2.20 – 2.25 (m, 2H), 1.75 – 1.81 (m, 2H), 1.68 – 1.73 (m, 2H); ^{13}C NMR (100MHz, $CDCl_3$) δ 170.9, 156.3, 143.1, 132.0, 130.0, 129.9, 116.7, 112.7, 109.1, 102.9, 55.7, 30.1, 26.1, 25.6, 22.7; IR (neat): 2996, 2927, 2856, 2832, 1697, 1609, 1472, 1368, 1305, 1212, 1141; HRMS-(ESI+) calculated for $[C_{17}H_{19}NNaO_2]^+$: 292.1313, found 292.1300.

General Procedure F: Preparation of *N*-Acetyl-2,3-disubstituted Indoles 4-14



To a solution of **4-11c** (0.3 mmol, 1 equiv) in dry toluene (3 mL, 0.1 M) was added corresponding internal alkyne (0.54 mmol, 1.8 equiv), $Zn(OTf)_2$ (0.06 mmol, 20 mol%) and IPrAuOTf (0.015 mmol, 5 mol%) at room temperature. The reaction mixture was stirred at 60 °C for 18 - 30 h. Once TLC indicated there was no starting material left, the reaction was concentrated. The residue was purified through silica gel flash chromatography to give the desired product **4-14**.

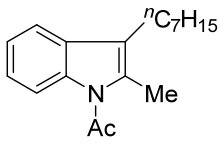
4-14a



This compound was prepared in 74% yield according to the general procedure F. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 – 7.72 (m, 1H), 7.52 – 7.45 (m, 1H), 7.29 – 7.20 (m,

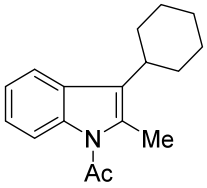
2H), 2.99 (t, J = 8.0 Hz, 2H), 2.77 (s, 3H), 2.65 (t, J = 8.0 Hz, 2H), 1.66 – 1.54 (m, 4H), 1.44 – 1.31 (m, 8H), 0.98 – 0.85 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.00, 138.26, 135.60, 130.87, 123.27, 122.53, 120.10, 118.66, 114.45, 31.97, 31.91, 30.03, 29.91, 27.67, 27.01, 23.93, 22.56, 22.48, 14.04, 14.02. IR (neat): 2957, 2930, 2859, 1705, 1463, 1368, 1216; HRMS-(EI+) calculated for $[C_{20}H_{29}NO]^+$: 299.2249, found 299.2257.

4-14b



This compound was prepared in 61% yield (regioselectivity 7.4: 1) according to the general procedure F. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 – 7.93 (m, 1H), 7.49 – 7.44 (m, 1H), 7.28 – 7.21 (m, 2H), 2.73 (s, 3H), 2.64 (t, J = 7.5 Hz, 2H), 2.56 (s, 3H), 1.63 – 1.53 (m, 2H), 1.41 – 1.23 (m, 8H), 0.89 (dd, J = 7.1, 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.19, 135.70, 132.49, 130.64, 123.50, 122.74, 120.38, 118.24, 115.00, 31.84, 29.94, 29.56, 29.20, 29.15, 27.55, 23.87, 22.64, 14.38, 14.07; IR (neat): 2956, 2929, 2856, 1701, 1458, 1368, 1311, 1216745; HRMS-(EI+) calculated for $[C_{18}H_{25}NO]^+$: 271.1926, found 271.1948.

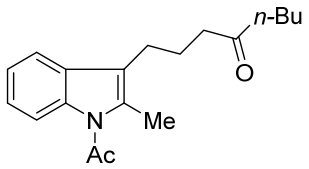
4-14c



This compound was prepared in 67% yield (regioselectivity > 19: 1) according to the general procedure F. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 – 7.93 (m, 1H), 7.75 – 7.69

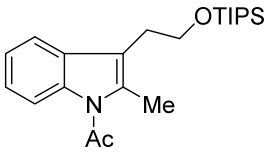
(m, 1H), 7.26 – 7.19 (m, 2H), 2.80 (tt, J = 12.4, 3.7 Hz, 1H), 2.73 (s, 3H), 2.58 (s, 3H), 2.02 – 1.86 (m, 4H), 1.86 – 1.79 (m, 1H), 1.79 – 1.71 (m, 2H), 1.49 – 1.31 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.40, 135.99, 131.49, 129.44, 124.37, 123.11, 122.27, 119.95, 114.90, 36.45, 31.80, 27.74, 27.12, 26.22, 14.42. IR (neat): 2928, 2853, 1699,1449, 1375, 1314, 1212, 1034, 756; HRMS-(EI+) calculated for $[C_{17}H_{21}NO]^+$: 255.1623, found 255.1628.

4-14d



This compound was prepared in 68% yield (regioselectivity 6.8:1) according to the general procedure F. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 – 7.90 (m, 1H), 7.51 – 7.44 (m, 1H), 7.27 – 7.20 (m, 2H), 2.71 (s, 3H), 2.66 (t, J = 7.5 Hz, 2H), 2.55 (s, 3H), 2.44 (t, J = 7.0 Hz, 2H), 2.35 (t, J = 7.5 Hz, 2H), 1.90 – 1.81 (m, 2H), 1.57 – 1.48 (m, 3H), 1.32 – 1.23 (m, 2H), 0.91 – 0.86 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.87, 170.16, 135.61, 132.91, 130.40, 123.62, 122.84, 119.29, 118.20, 114.96, 42.51, 41.75, 27.51, 25.83, 23.60, 23.01, 22.27, 14.34, 13.79; IR (neat): 2958, 2933, 2873, 1707, 1458, 1369, 1311, 748; HRMS-(ESI+) calculated for $[C_{19}H_{25}NNaO_2]^+$: 322.1783, found 322.1781.

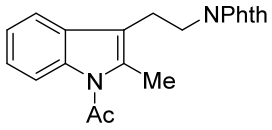
4-14e



This compound was prepared in 52% yield (regioselectivity 6:1) according to the

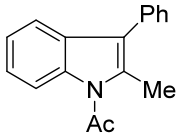
general procedure F. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 – 7.94 (m, 1H), 7.52 – 7.46 (m, 1H), 7.29 – 7.22 (m, 2H), 3.85 (t, *J* = 7.5 Hz, 2H), 2.95 (t, *J* = 7.3 Hz, 2H), 2.73 (s, 3H), 2.60 (s, 3H), 1.10 – 1.00 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.22, 135.68, 133.78, 130.65, 123.62, 122.85, 118.17, 116.76, 115.01, 62.91, 27.94, 27.54, 17.98, 17.93, 14.53, 11.92; IR (neat): 2944, 2867, 1704, 1463, 1367, 1310, 1102, 742; HRMS-(ESI+) calculated for $[C_{22}H_{35}NNaO_2Si]^+$: 396.2349, found 396.2342.

4-14f



This compound was prepared in 80% yield (regioselectivity 16.6:1) according to the general procedure F. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 – 7.89 (m, 1H), 7.82 (m, 2H), 7.73 – 7.67 (m, 2H), 7.66 – 7.60 (m, 1H), 7.27 – 7.21 (m, 2H), 3.85 (t, *J* = 7.8 Hz, 2H), 3.02 (t, *J* = 7.8 Hz, 2H), 2.71 (s, 3H), 2.59 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.20, 168.15, 135.61, 134.03, 133.94, 132.04, 130.06, 123.87, 123.19, 123.11, 118.10, 115.90, 115.00, 37.29, 27.57, 23.19, 14.30. IR (neat): 3061, 2945, 1772, 1713, 1436, 1368, 1311, 1011, 722; HRMS-(EI+) calculated for $[C_{21}H_{18}N_2O_3]^+$: 346.1317, found 346.1321.

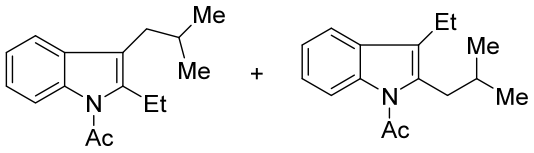
4-14g



This compound was prepared in 61% yield (regioselectivity 8:1) according to the general procedure F. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.3 Hz, 1H), 7.51 (m,

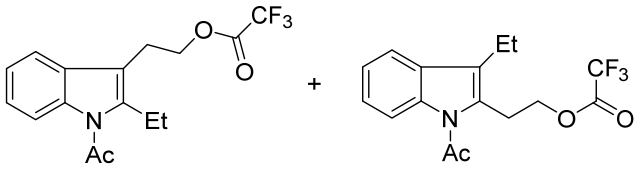
3H), 7.45 (m, 2H), 7.44 – 7.38 (m, 1H), 7.35 – 7.30 (m, 1H), 7.28 – 7.22 (m, 1H), 2.80 (s, 3H), 2.63 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.47, 135.70, 133.45, 133.08, 130.11, 129.95, 128.53, 127.17, 124.07, 123.21, 122.49, 119.13, 115.04, 27.58, 15.25; IR (neat): 3052, 2929, 1701, 1367, 1309, 747; HRMS-(EI+) calculated for $[C_{17}H_{15}NO]^+$: 249.1154, found 249.1155.

4-14h and **4-14h'** (2.5:1)



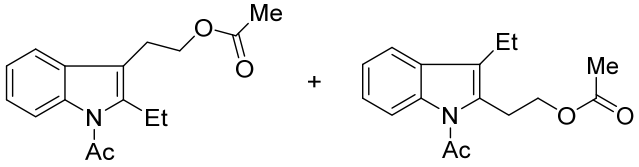
These two compounds were prepared in 75 % overall yield (regioselectivity 2.5:1) according to the general procedure F. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 – 7.73 (m, 1H, **4-14h** + **4-14h'**), 7.55 – 7.51 (m, 1H, **4-14h'**), 7.46 – 7.50 (m, 1H, **4-14h**), 7.28 – 7.20 (m, 2H, **4-14h** + **4-14h'**), 3.05 (q, *J* = 7.3 Hz, 2H, **4-14h**), 2.89 (d, *J* = 7.0 Hz, 2H, **4-14h'**), 2.79 (s, 3H, **4-14h**), 2.77 (s, 3H, **4-14h'**), 2.70 (q, *J* = 7.5 Hz, 2H, **4-14h'**), 2.54 (d, *J* = 7.4 Hz, 2H, **4-14h**), 2.03 – 1.90 (m, 1H, **4-14h** + **4-14h'**), 1.26 – 1.20 (m, 3H, **4-14h** + **4-14h'**), 0.97 (d, *J* = 6.6 Hz, 6H, **4-14h**), 0.93 (d, *J* = 6.7 Hz, 6H, **4-14h'**); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.20, 169.93, 140.20, 136.63, 135.82, 135.54, 131.29, 130.43, 123.35, 123.27, 122.51, 122.49, 122.39, 119.04, 118.75, 114.43, 114.34, 35.60, 33.07, 29.20, 28.95, 27.75, 27.68, 22.84, 22.44, 20.36, 17.40, 14.63, 14.47; IR (neat): 2958, 2933, 2870, 1705, 1463, 1367, 1312, 1204, 743; HRMS-(EI+) calculated for $[C_{16}H_{21}NO]^+$: 243.1623, found 243.1631.

4-14i and **4-14i'** (10:1)



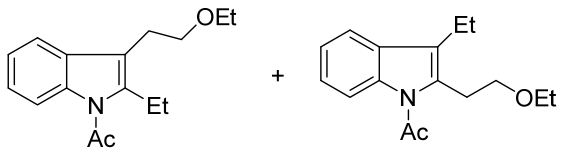
These two compounds were prepared in 65% overall yield (regioselectivity 10:1) according to the general procedure F. **4-14i**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 – 7.74 (m, 1H), 7.55 – 7.51 (m, 1H), 7.32 – 7.27 (m, 2H), 4.52 (t, *J* = 7.0 Hz, 2H), 3.15 (t, *J* = 7.0 Hz, 2H), 3.07 (q, *J* = 7.4 Hz, 2H), 2.80 (s, 3H), 1.25 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.91, 157.45, (q, *J* = 43.1 Hz)141.68, 135.43, 129.96, 123.88, 122.95, 118.16, 114.51, 113.08, 67.04, 27.62, 23.00, 20.27, 14.82; IR (neat): 2968, 2930, 1785, 1707, 1464, 1352, 745; HRMS-(ESI+) calculated for $[C_{16}H_{16}F_3NaNO_3]^+$: 350.0980, found 350.0970.

4-14j and **4-14j'** (4.6:1)



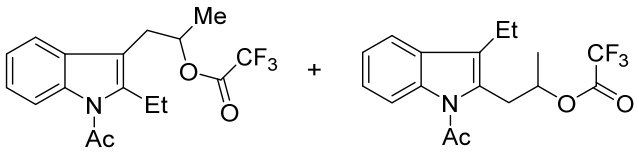
These two compounds were prepared in 77% overall yield (regioselectivity 4.6:1) according to the general procedure F. **4-14j**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 – 7.71 (m, 1H), 7.56 – 7.51 (m, 1H), 7.29 – 7.24 (m, 3H), 4.25 (t, *J* = 7.0 Hz, 2H), 3.06 (q, *J* = 7.0 Hz, 2H), 3.01 (t, *J* = 7.0 Hz, 2H), 2.79 (s, 3H), 2.04 (s, 3H), 1.24 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.98, 169.92, 141.20, 135.45, 130.47, 123.65, 122.80, 118.51, 114.77, 114.45, 77.25, 77.00, 76.75, 63.74, 27.66, 23.49, 20.99, 20.30, 14.90; IR (neat): 2968, 2937, 1739, 1704, 1464, 1368, 1312, 1241, 1034, 745; HRMS-(ESI+) calculated for $[C_{16}H_{19}NNaO_3]^+$: 296.1263, found 296.1257.

4-14k and **4-14l'** (2:1)



These two compounds were prepared in 88% overall yield (regioselectivity 2:1) according to the general procedure F. **4-14k**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 – 7.72 (m, 1H), 7.54 – 7.49 (m, 1H), 7.28 – 7.21 (m, 2H), 3.58 (t, *J* = 7.6 Hz, 2H), 3.55 – 3.47 (q, *J* = 7.6 Hz, 2H), 3.05 (q, *J* = 7.3 Hz, 2H), 2.96 (t, *J* = 7.6 Hz, 2H), 2.77 (s, 3H), 1.23 (t, *J* = 7.6 Hz, 3H), 1.21 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.88, 140.79, 135.47, 130.70, 123.46, 122.64, 118.53, 115.75, 114.44, 70.11, 66.30, 27.60, 24.71, 20.29, 15.18, 14.91; **4-14k'**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 – 7.67 (m, 1H), 7.51 (m, 1H), 7.28 – 7.21 (m, 2H), 3.65 (t, *J* = 7.0 Hz, 2H), 3.49 (q, *J* = 7.0 Hz, 2H), 3.30 (t, *J* = 7.0 Hz, 2H), 2.77 (s, 3H), 2.71 (q, *J* = 7.6 Hz, 2H), 1.22 (t, *J* = 7.6 Hz, 3H), 1.18 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.13, 135.55, 134.15, 130.44, 123.55, 123.13, 122.60, 118.79, 114.36, 70.26, 66.21, 27.84, 27.83, 17.10, 15.23, 14.81. IR (neat): 2973, 1935, 2872, 1702, 1463, 1368, 1310, 1108, 943; HRMS-(EI+) calculated for $[C_{16}H_{21}NO_2]^+$: 259.1572, found 259.1574.

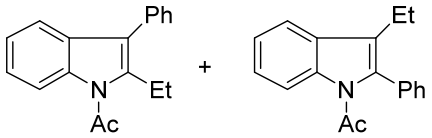
4-14l and **4-14l'** (12:1)



These two compounds were prepared in 69% overall yield (regioselectivity 12:1) according to the general procedure F. **4-14l**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 – 7.71 (m, 1H), 7.59 – 7.52 (m, 1H), 7.33 – 7.24 (m, 2H), 5.34 (h, *J* = 6.4 Hz, 1H), 3.14

(dd, J = 14.4, 6.6 Hz, 1H), 3.08 (ddd, J = 14.6, 7.3, 2.9 Hz, 2H), 2.99 – 2.91 (dd, J = 14.4, 6.6 Hz, 1H), 2.80 (s, 3H), 1.40 (t, J = 7.0 Hz, 3H), 1.26 – 1.21 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.95, 157.06 (q, J = 41.8 Hz), 141.73, 135.43, 130.24, 123.83, 122.92, 118.64, 114.47 (q, J = 41.8 Hz), 114.40, 113.52, 75.85, 30.00, 27.66, 20.32, 19.39, 14.59; IR (neat): 2985, 2943, 1783, 1717, 1383, 1338, 1221, 1167, 778; HRMS-(ESI$^+$) calculated for $[C_{17}H_{18}F_3NNaO_3]^+$: 364.1136, found 364.1121.

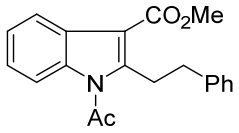
4-14m and **4-14m'** (2.9:1)



These two compounds were prepared in 70% overall yield (regioselectivity 2.9: 1) according to the general procedure F. **4-14m**: ^{1}H NMR (600 MHz, CDC_3) δ 7.83 (d, J = 8.4 Hz, 1H), 7.52 - 7.46 (m, 2H), 7.45 – 7.38 (m, 4H), 7.32 – 7.28 (m, 1H), 7.24 – 7.19 (m, 1H), 3.05 (q, J = 7.3 Hz, 2H), 2.85 (s, 3H), 1.23 (t, J = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.27, 140.27, 135.50, 133.61, 130.53, 130.08, 128.56, 127.26, 123.89, 123.03, 121.98, 119.61, 114.45, 27.72, 20.76, 15.19. **4-14m':** ^{1}H NMR (600 MHz, cdcl$_3$) δ 8.45 (d, J = 8.3 Hz, 1H), 7.58 (d, J = 7.4 Hz, 1H), 7.51 – 7.45 (m, 3H), 7.42 – 7.36 (m, 3H), 7.34 – 7.30 (m, 1H), 2.56 (q, J = 7.6 Hz, 2H), 1.95 (s, 3H), 1.21 – 1.17 (t, J = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.07, 136.95, 134.39, 133.59, 130.22, 129.27, 128.69, 128.57, 125.18, 124.30, 123.38, 118.71, 116.52, 27.65, 17.60, 14.95. IR (neat): 3054, 2974, 2935, 2875, 1706, 1454, 1314, 1209, 1186, 747; HRMS-(EI$^+$) calculated for $[C_{18}H_{17}NO]^+$: 263.1310, found

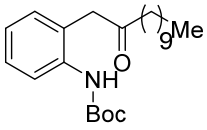
263.1313.

4-14n



This compound was prepared in 66% yield (regioselectivity > 19: 1) according to the general procedure F. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 – 8.15 (m, 1H), 7.67 – 7.59 (m, 1H), 7.37 – 7.29 (m, 6H), 7.25 – 7.19 (m, 1H), 3.99 (s, 3H), 3.74 – 3.67 (t, 2H), 3.07 – 3.00 (t, 2H), 2.76 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.87, 165.30, 149.20, 141.34, 134.65, 128.61, 128.38, 127.50, 126.05, 124.17, 123.71, 122.14, 113.47, 110.35, 51.30, 36.05, 29.74, 27.62. IR (neat): 3027, 2951, 2861, 1726, 1706, 1560, 1435, 1280, 1194, 1088, 751; HRMS-(ESI+) calculated for $[C_{20}H_{19}NnaO_3]^+$: 344.1263, found 344.1269.

4-17a



This compound was obtained by quenching the reaction to prepare **4-12a** right after 20 min according to the general procedure D (eluents: ethyl acetate: hexanes = 1:10). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, 1H, J = 8 Hz), 7.51 (bs, 1H), 7.17 – 7.21 (m, 1H), 7.06 (dd, 1H, J_1 = 7.5 Hz, J_2 = 1.5 Hz), 6.97 (td, 1H, J_1 = 7.5 Hz, J_2 = 1 Hz), 3.68 (s, 2H), 2.55 (t, 2H, J = 7.5 Hz), 1.53 – 1.58 (m, 2H), 1.52 (s, 9H), 1.20 – 1.30 (m, 14H), 0.87 (t, 3H, J = 7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.5, 153.6, 137.4, 130.5, 128.2, 125.4, 124.1, 123.4, 80.2, 46.9, 42.7, 31.9, 29.5, 29.4, 29.31, 29.27, 29.0,

28.3, 23.5, 22.7, 14.1; IR (neat): 3340, 2954, 2925, 2854, 1731, 1708, 1452, 1239, 1159; HRMS-(ESI+) calculated for $[C_{23}H_{37}NNaO_3]^+$: 398.2671, found 398.2667.

4.4. References

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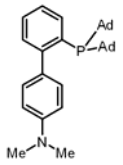
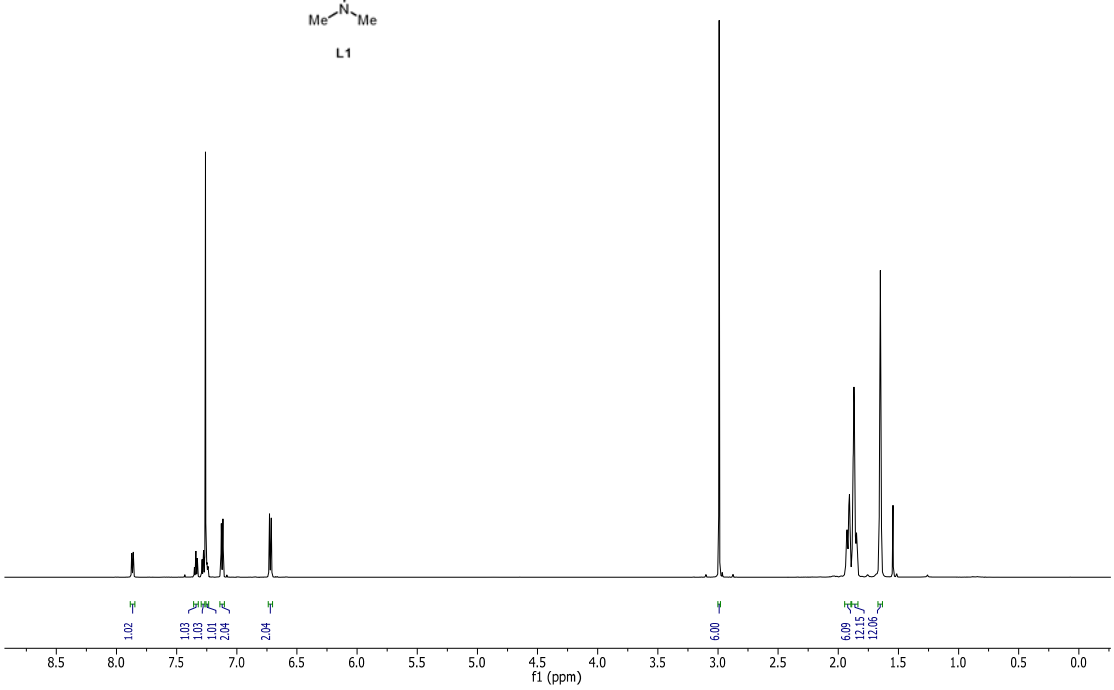
5. Appendix: Selected NMR Spectra

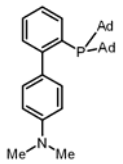
Parameter	Value
Title	zhixun-3-L2
Solvent	cdcl3
Spectrometer Frequency	599.64



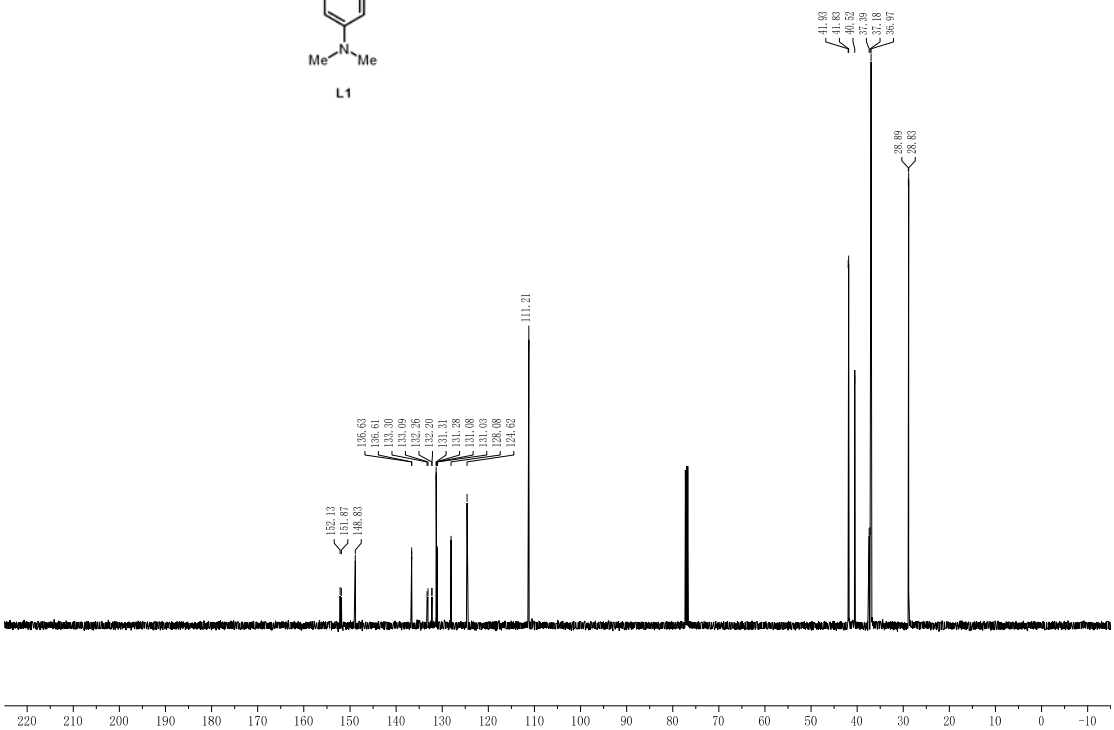
L1



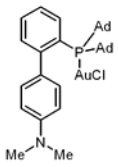
Parameter	Value
Title	wyz7-296-10-C13
Solvent	CDCl3
Spectrometer Frequency	125.70
Nucleus	13C



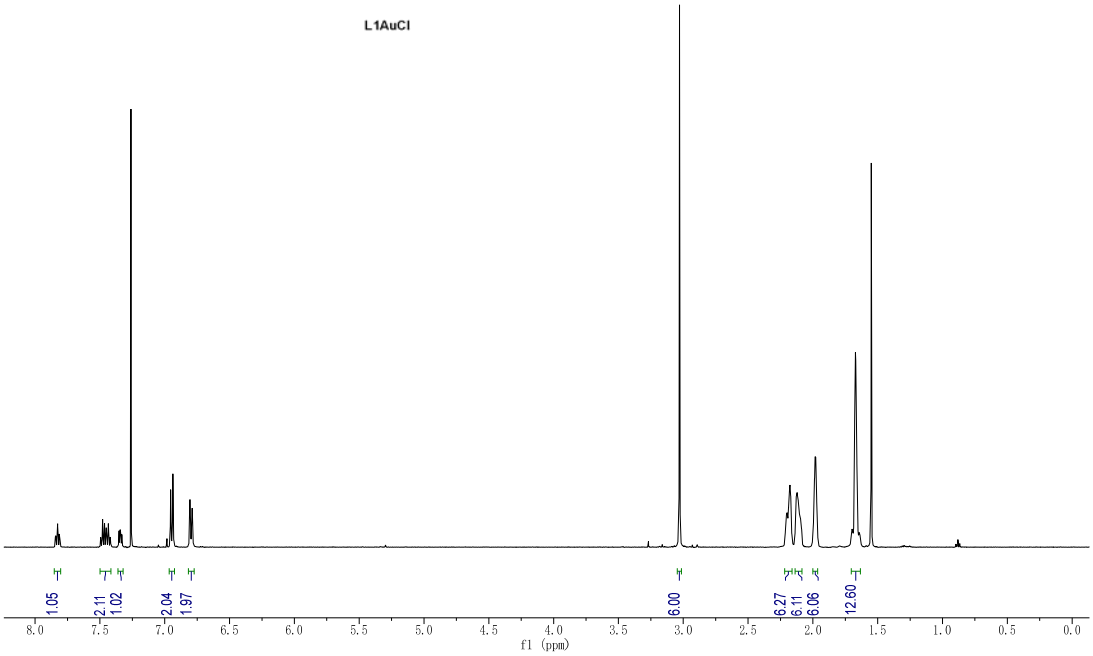
L1



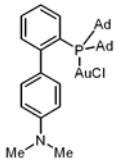
Parameter	Value
1 Title	zhixun-3-L2AuCl
2 Solvent	CDCl3
3 Spectrometer Frequency	499.86



L1AuCl

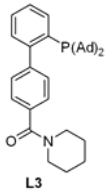


Parameter	Value
Title	wyz8-L2AuCl-C13-2500
Solvent	cdcl3
Spectrometer Frequency	150.79
Nucleus	13C

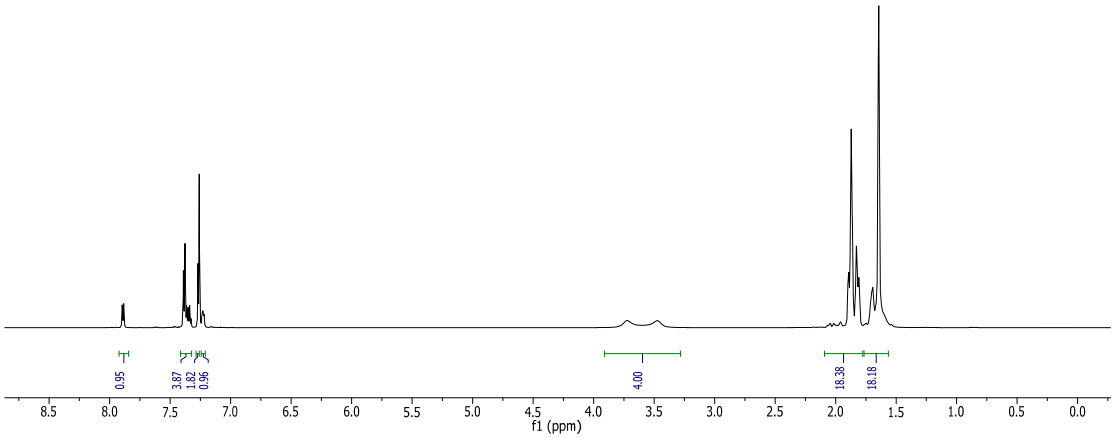


L1AuCl

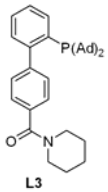
Parameter	Value
Title	zhixun-3-L3-1
Solvent	cdcl3
Spectrometer Frequency	599.64



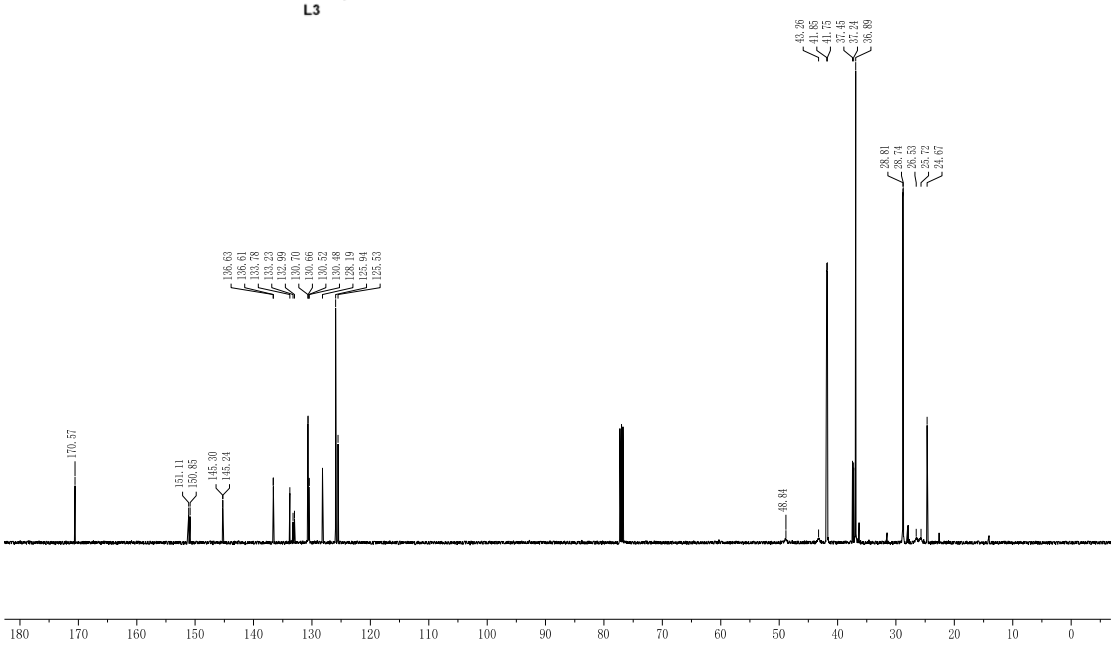
L3



Parameter	Value
Title	wyz7-296-9-C13
Solvent	CDCl3
Spectrometer Frequency	125.70
Nucleus	13C

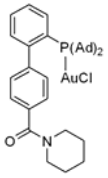


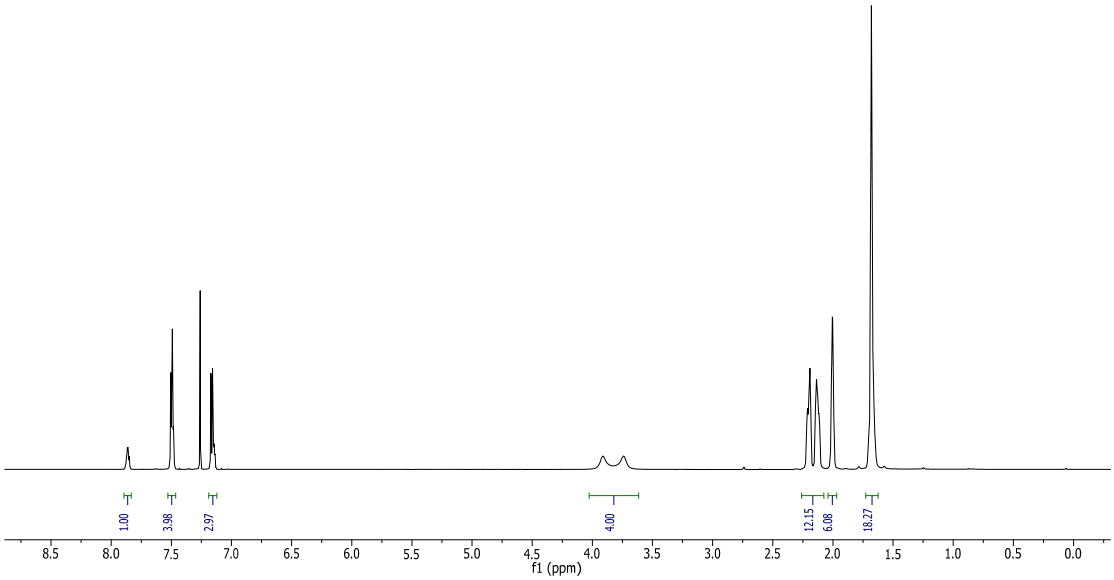
L3



Parameter	Value
Title	zhixun-3-L3AuCl
Solvent	cdcl3
Spectrometer Frequency	599.64

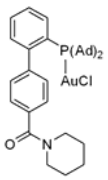
L3AuCl

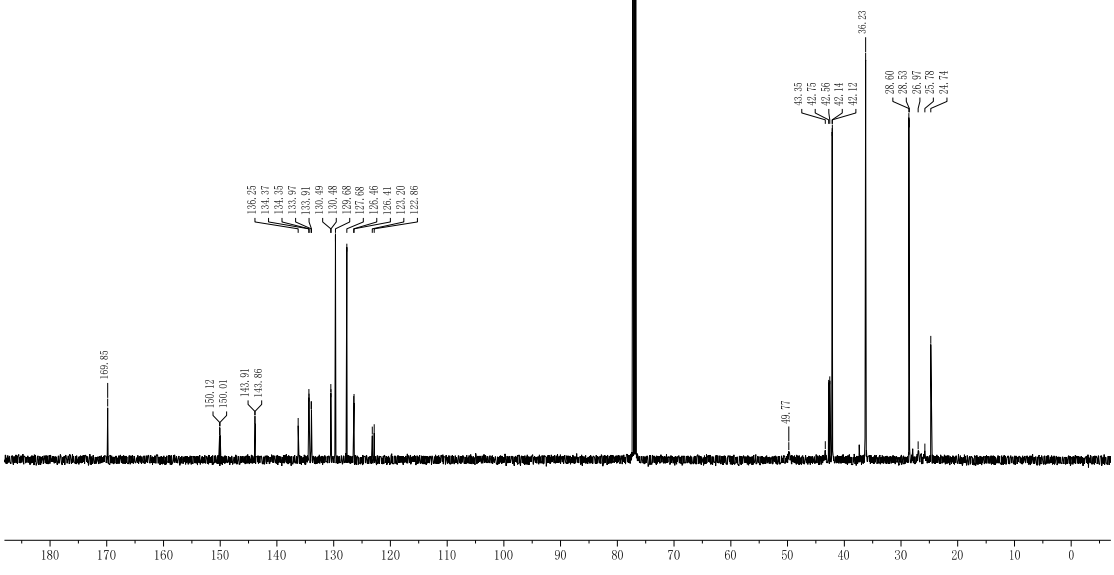




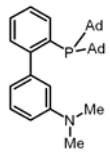
Parameter	Value
Title	wyz8-L3AuCl-C13
Solvent	CDCl3
Spectrometer Frequency	125.70
Nucleus	13C

L3AuCl

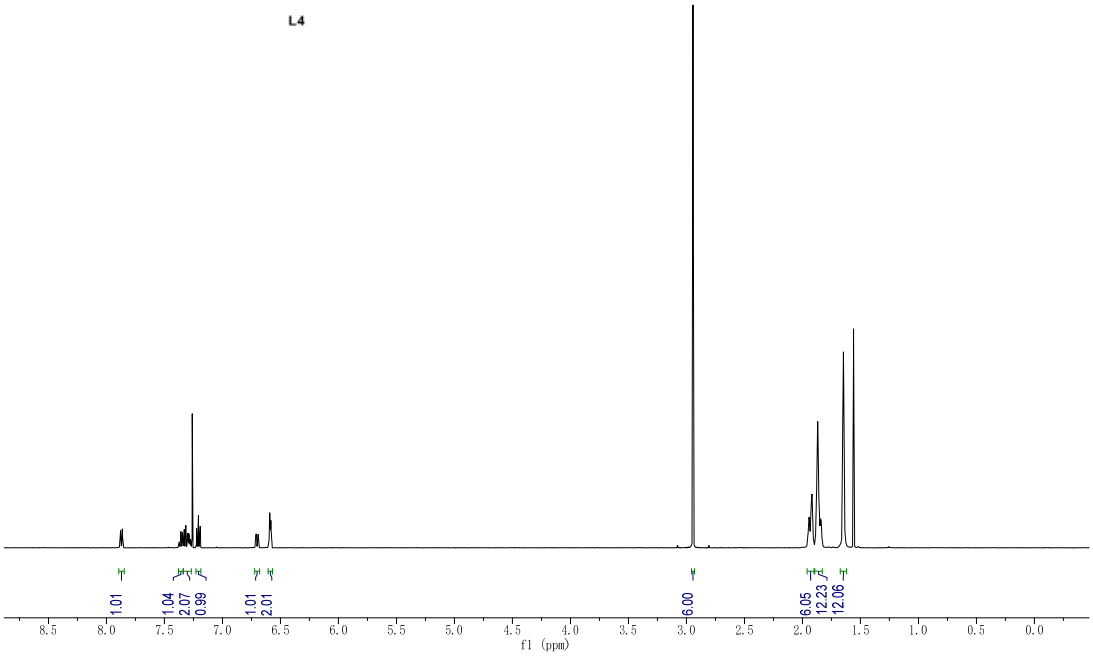




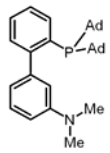
Parameter	Value
1 Title	zhixun-3-L1
2 Solvent	CDCl3
3 Spectrometer Frequency	499.86



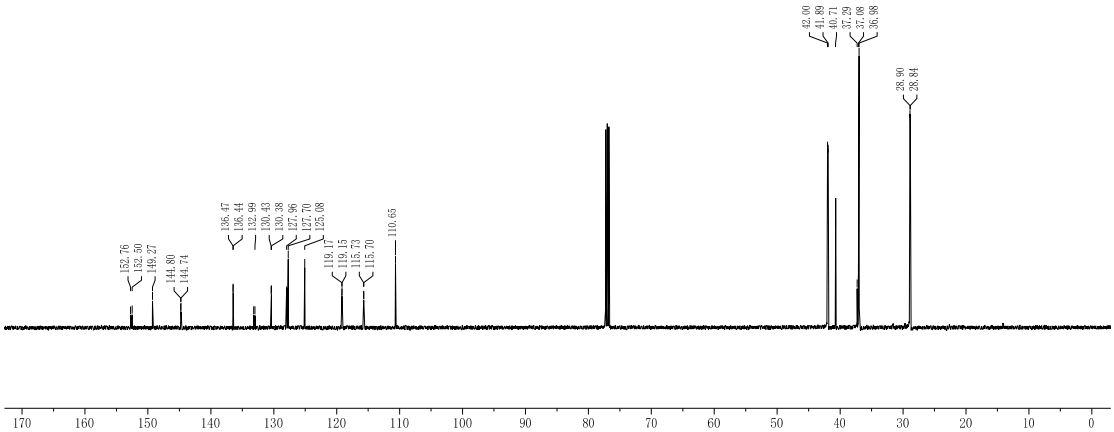
L4



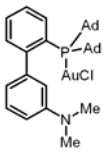
Parameter	Value
Title	wyz7-296-7-C13
Solvent	CDCl3
Spectrometer Frequency	125.70
Nucleus	13C



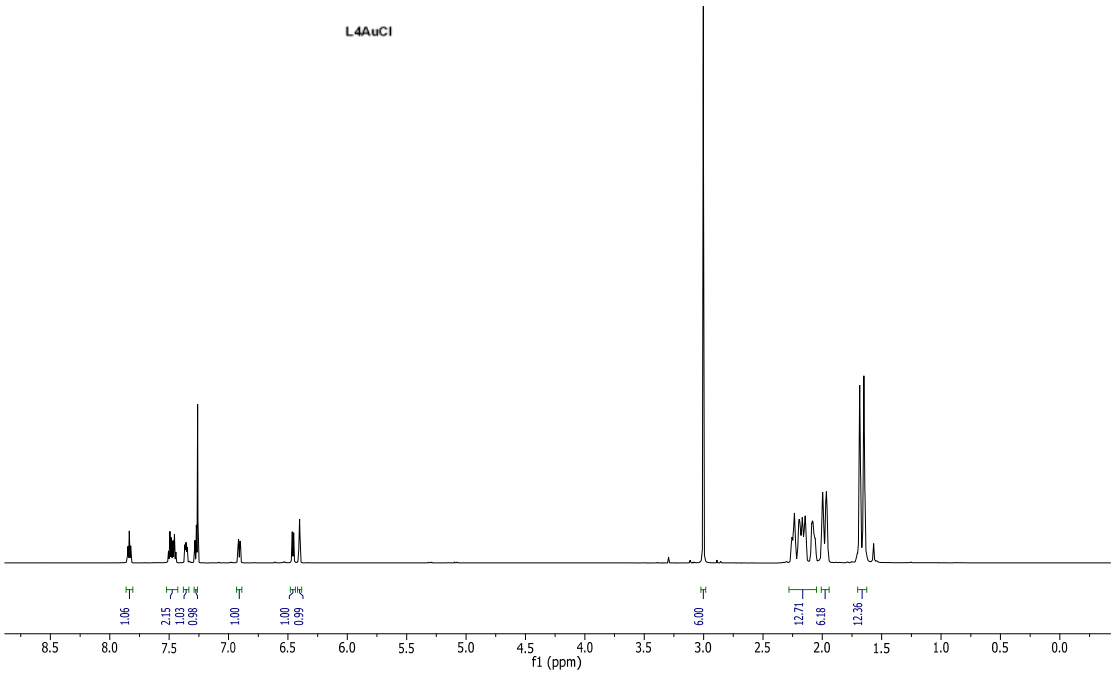
L4



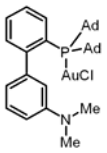
Parameter	Value
Title	zhixun-3-L1AuCl-4
Solvent	cdcl3
Spectrometer Frequency	599.64



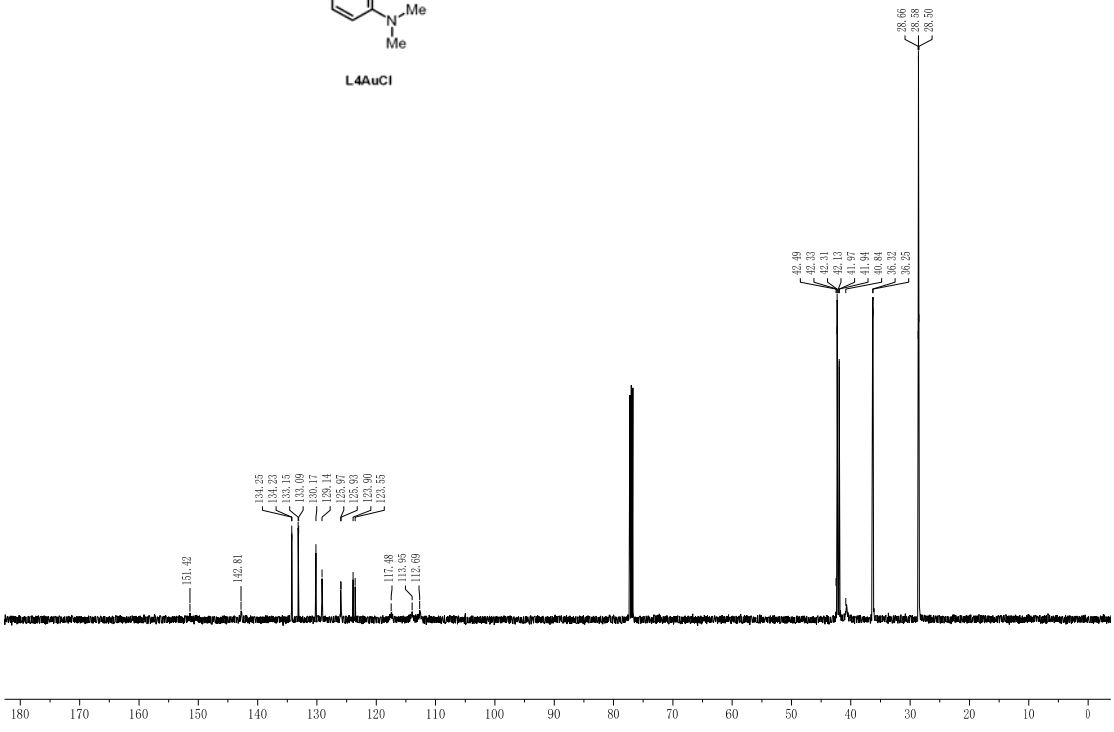
L4AuCl

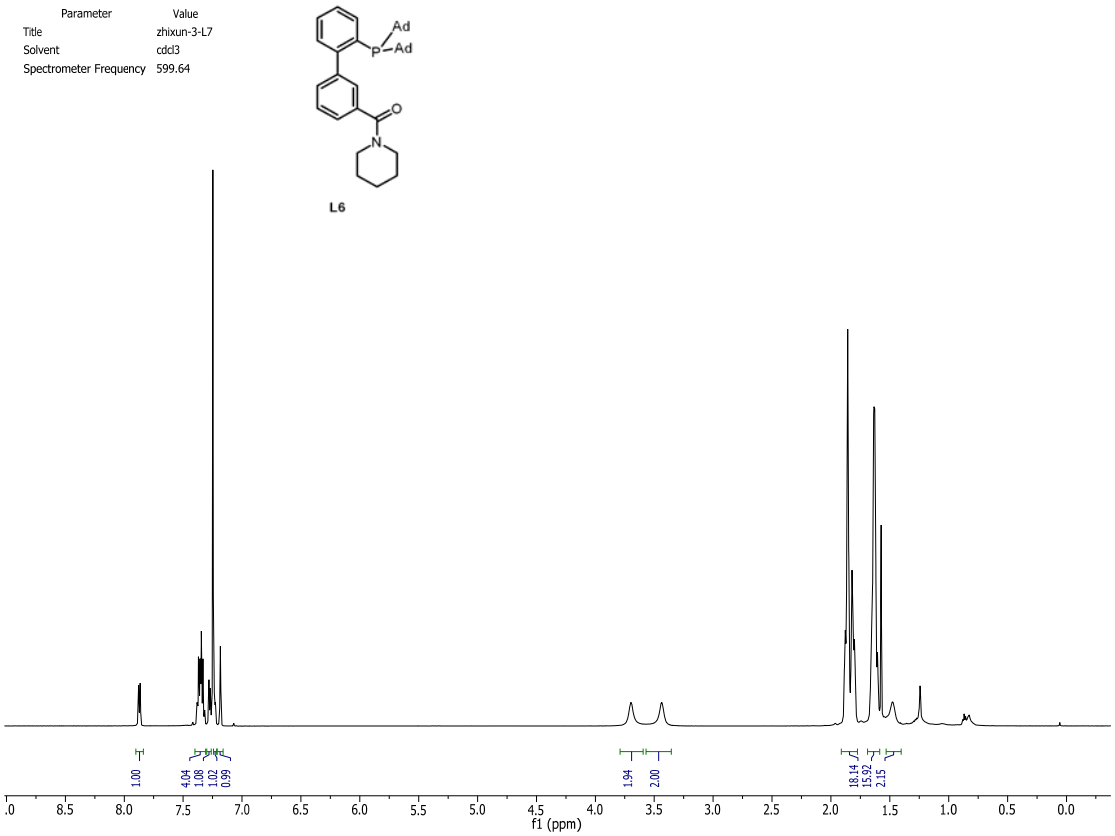


Parameter	Value
Title	wyz8-L1AuCl-C13
Solvent	CDCl3
Spectrometer Frequency	125.70
Nucleus	13C



L4AuCl




Parameter Value
Title zhixun-3-L7
Solvent cdcl3
Spectrometer Frequency 599.64
Ad
P
Ad
O
N
L6
1.00
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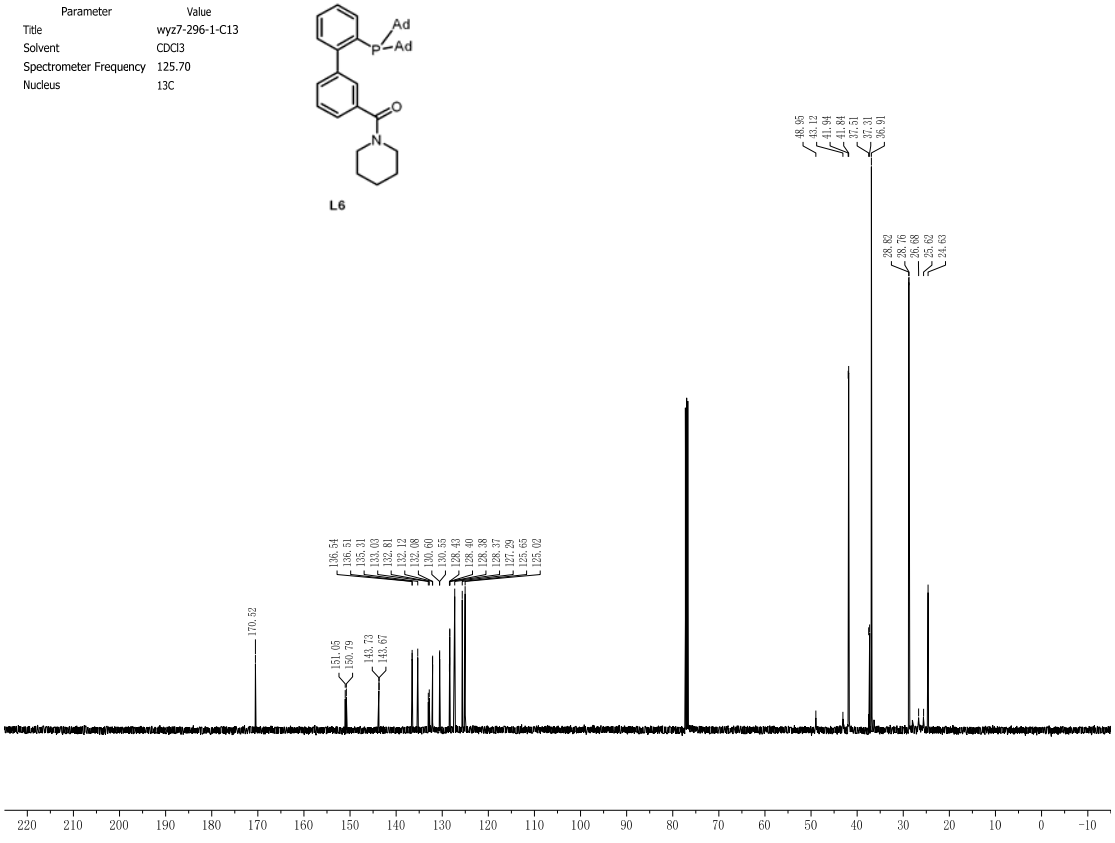
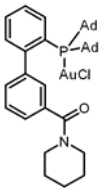
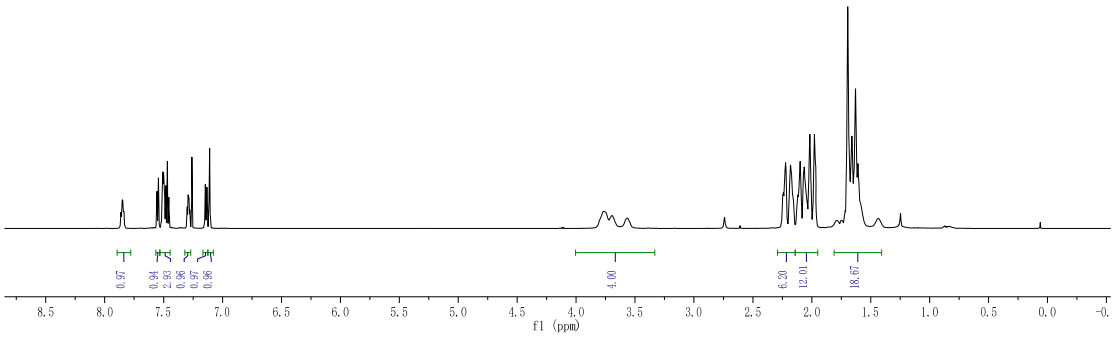
1.08
1.02
0.99
1.94
2.00
18.14
15.92
2.15
f1 (ppm)


Parameter Value
Title wyz7-296-1-C13
Solvent CDCl3
Spectrometer Frequency 125.70
Nucleus 13C
Ad
P
Ad
O
N
L6
48.95
43.12
41.94
41.84
37.51
37.31
36.91
28.82
28.76
26.68
25.62
24.63
136.54
136.51
135.31
133.03
132.81
132.12
132.08
130.60
130.55
128.43
128.40
128.38
128.37
127.29
125.65
125.02
170.52
151.05
150.79
143.73
143.67

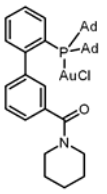
Parameter	Value
1 Data File Name	C:/ Users/ zhang laptop/ Desktop/ NMR/ ywang/ wyz8-L5AuCl.fid/ fid
2 Title	wyz8-L5AuCl
3 Solvent	cdcl3
4 Spectrometer Frequency	599.64



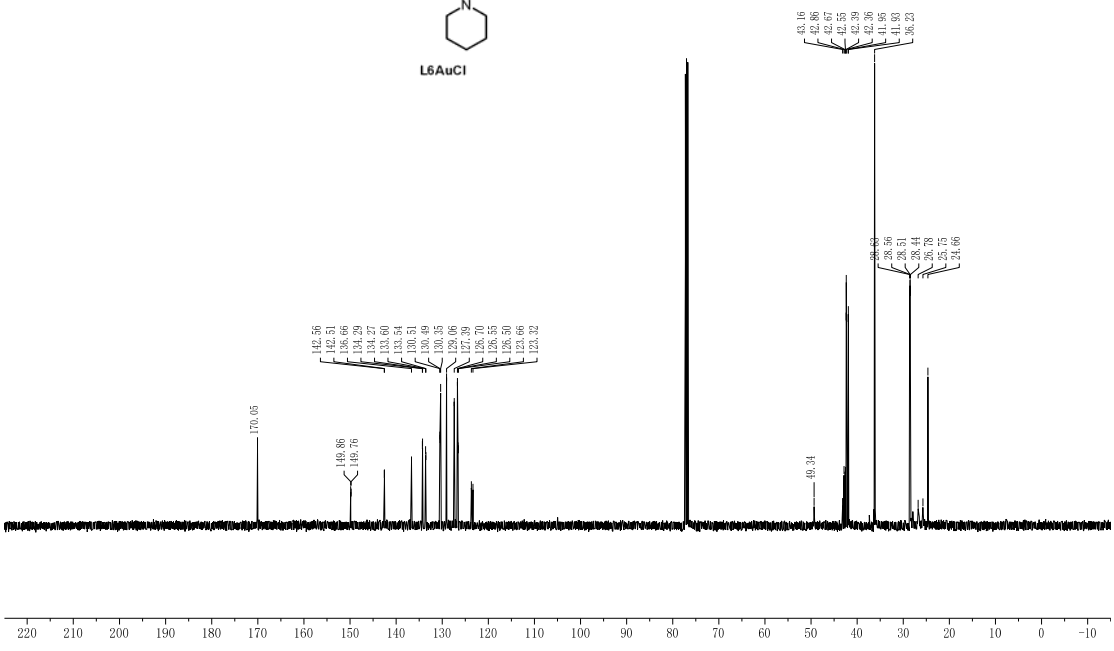
L6AuCl



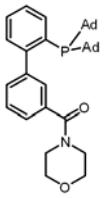
Parameter	Value
Title	wyz8-L5AuCl-C13
Solvent	CDCl3
Spectrometer Frequency	125.70
Nucleus	13C



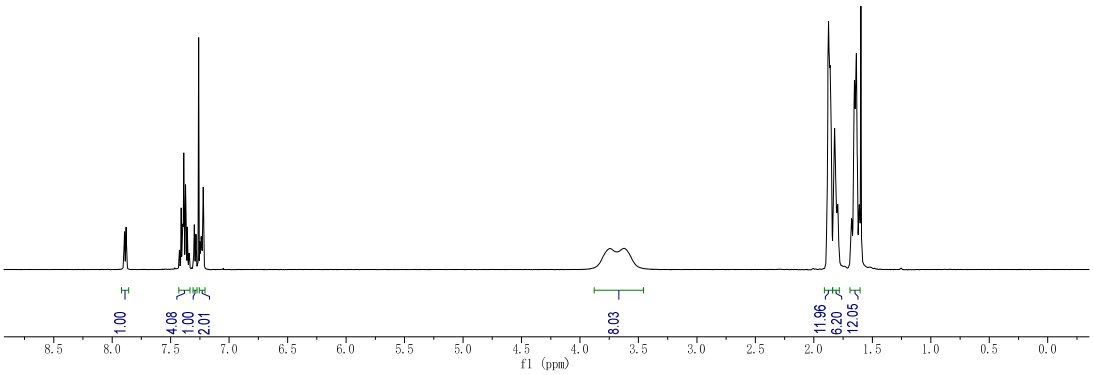
L6AuCl



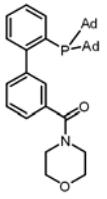
Parameter	Value
1 Title	zhixun-3-L4
2 Solvent	CDCl3
3 Spectrometer Frequency	499.86



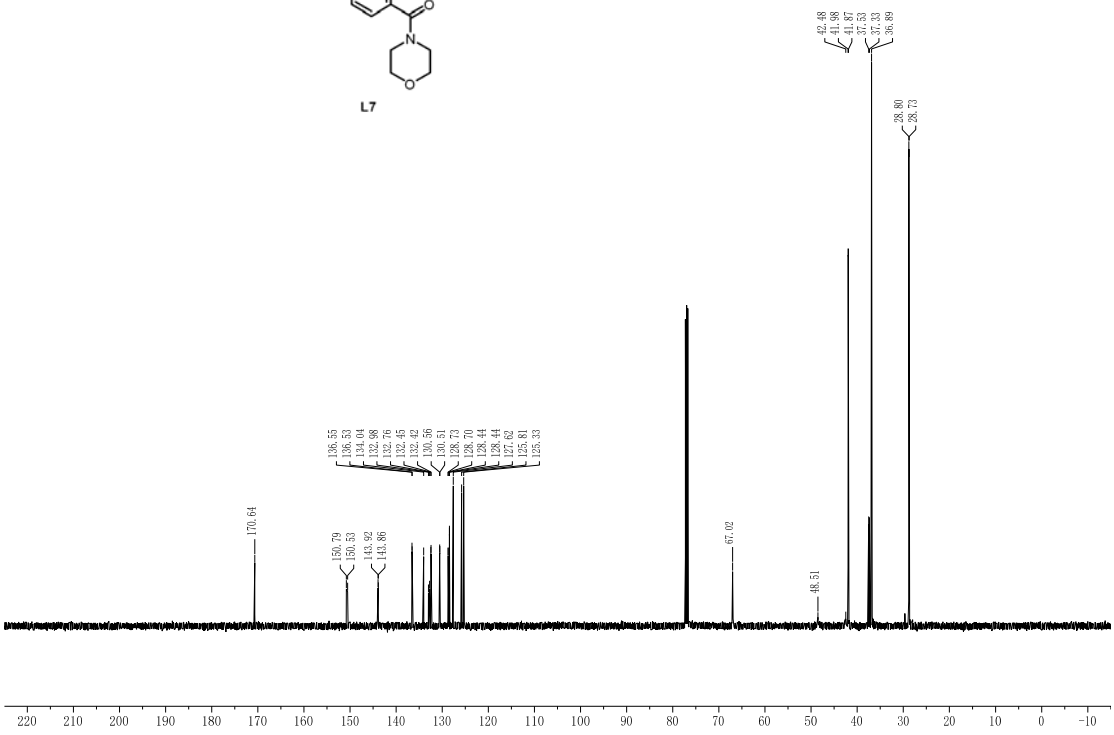
L7



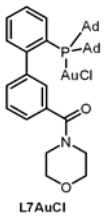
Parameter	Value
Title	wyz7-296-4-C13
Solvent	CDCl3
Spectrometer Frequency	125.70
Nucleus	13C



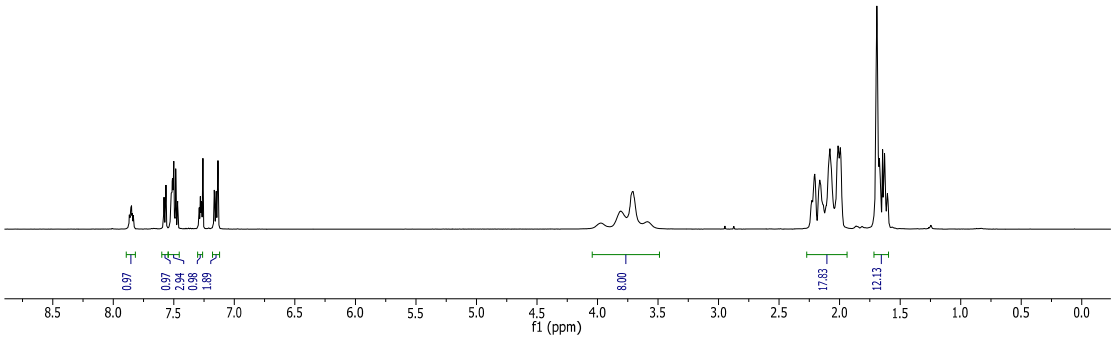
L7



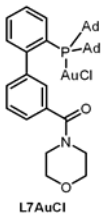
Parameter	Value
Title	zhixun-3-L4AuCl
Solvent	CDCl3
Spectrometer Frequency	499.86



L7AuCl

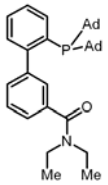


Parameter	Value
Title	wyz8-L8AuCl-C13
Solvent	cdcl3
Spectrometer Frequency	150.79
Nucleus	13C

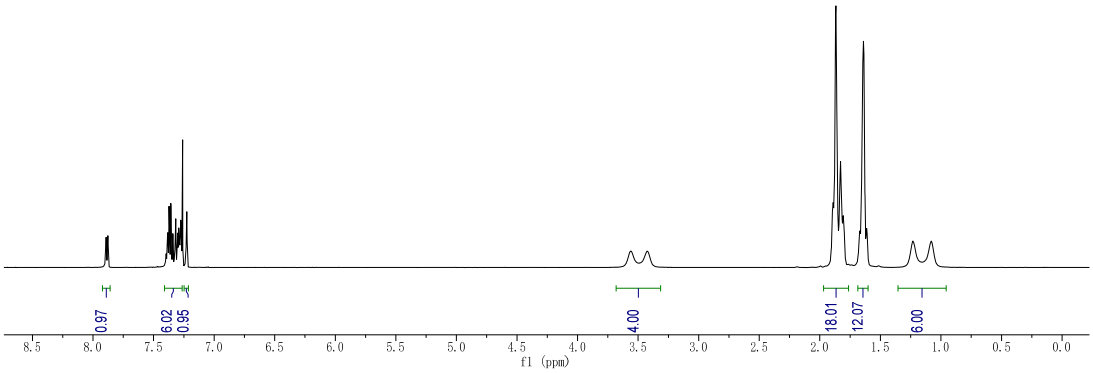


L7AuCl

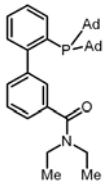
	Parameter	Value
1	Title	zhixun-3-L5
2	Solvent	CDCl3
3	Spectrometer Frequency	499.86



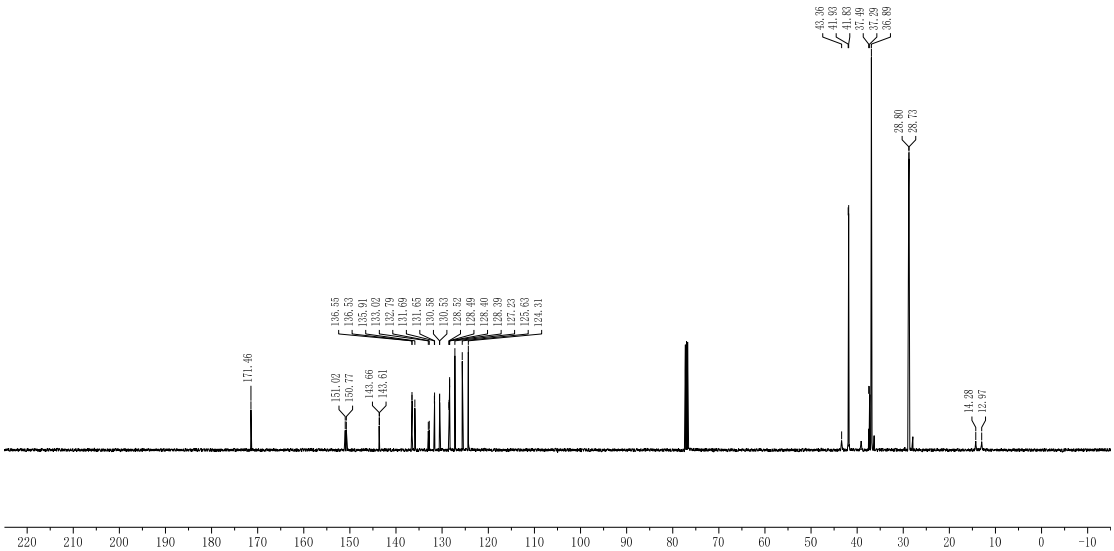
L8



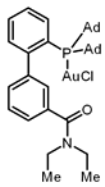
Parameter	Value
Title	wyz7-296-2-C13
Solvent	CDCl3
Spectrometer Frequency	125.70
Nucleus	13C



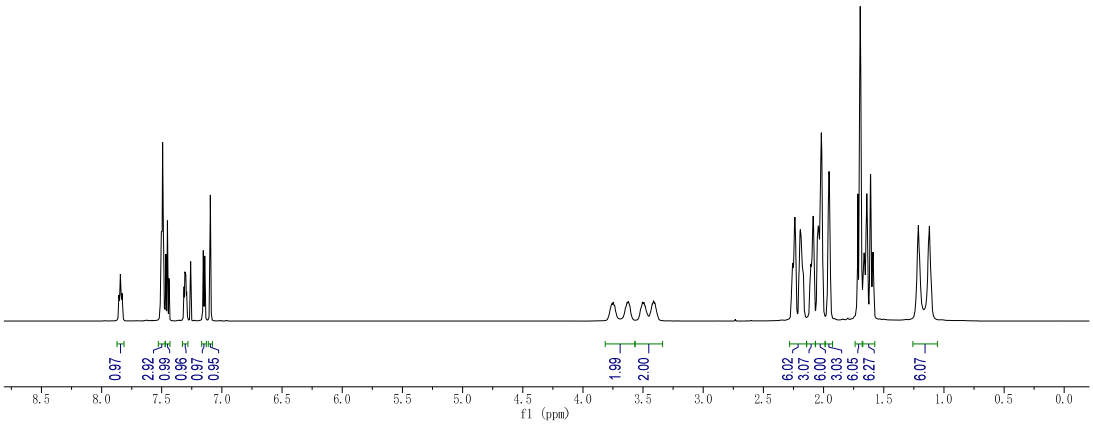
L8



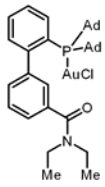
Parameter	Value
1 Title	zhixun-3-L5AuCl
2 Solvent	cdcl3
3 Spectrometer Frequency	599.64



L8AuCl

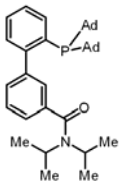


Parameter	Value
Title	wyz8-L6AuCl-C13
Solvent	CDCl3
Spectrometer Frequency	125.70
Nucleus	13C

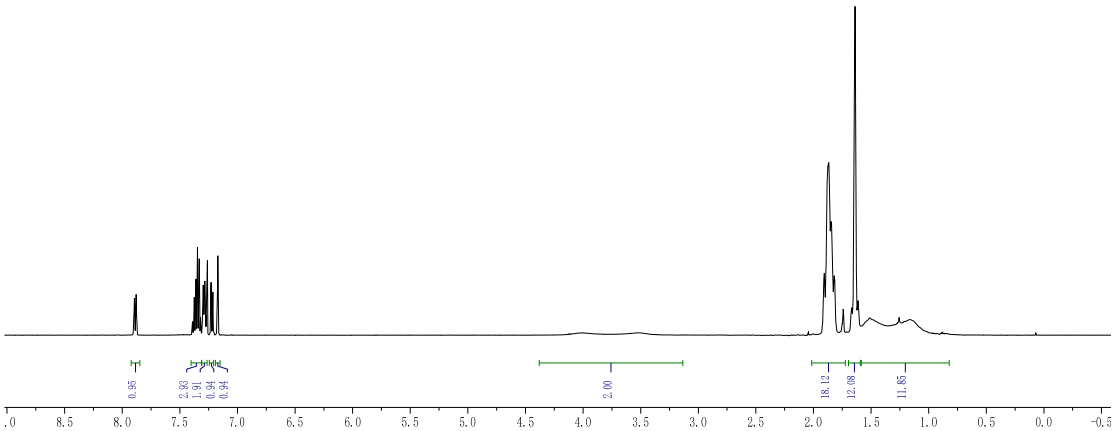


L8AuCl

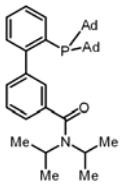
Parameter	Value
Title	wyz7-296-3-H1-again
Solvent	CDCl3
Spectrometer Frequency	499.86
Nucleus	1H



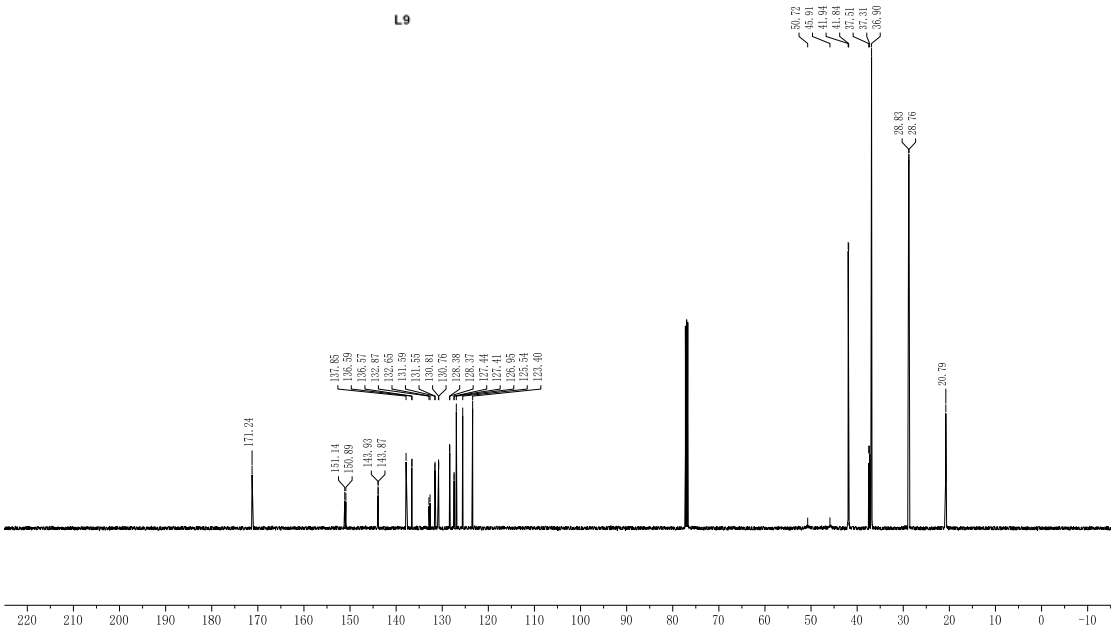
L9



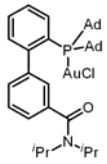
Parameter	Value
Title	wyz7-296-3-C13
Solvent	CDCl3
Spectrometer Frequency	125.70
Nucleus	13C



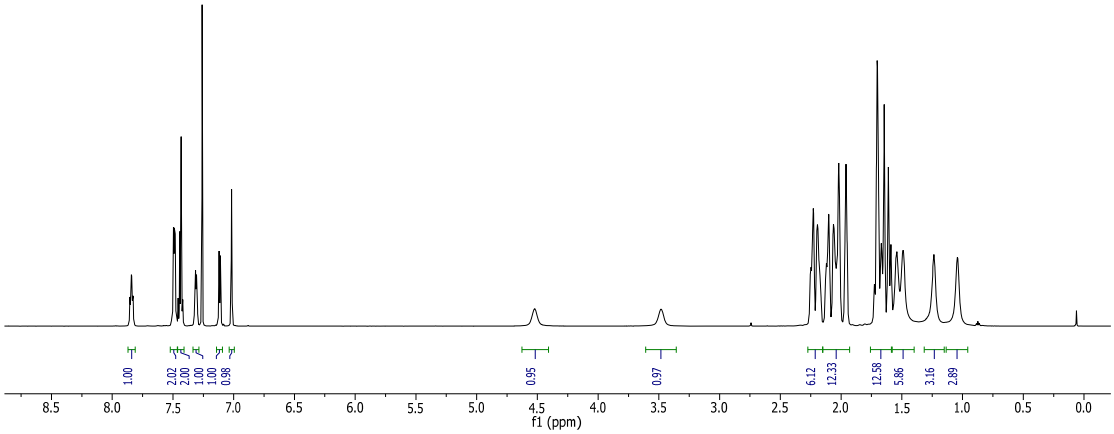
L9



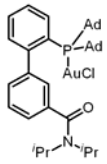
Parameter	Value
Title	zhixun-3-L6AuCl
Solvent	cdcl3
Spectrometer Frequency	599.64



L9AuCl

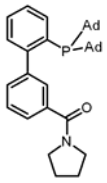


Parameter	Value
Title	wyz8-L7AuCl-C13
Solvent	cdcl3
Spectrometer Frequency	150.79
Nucleus	13C

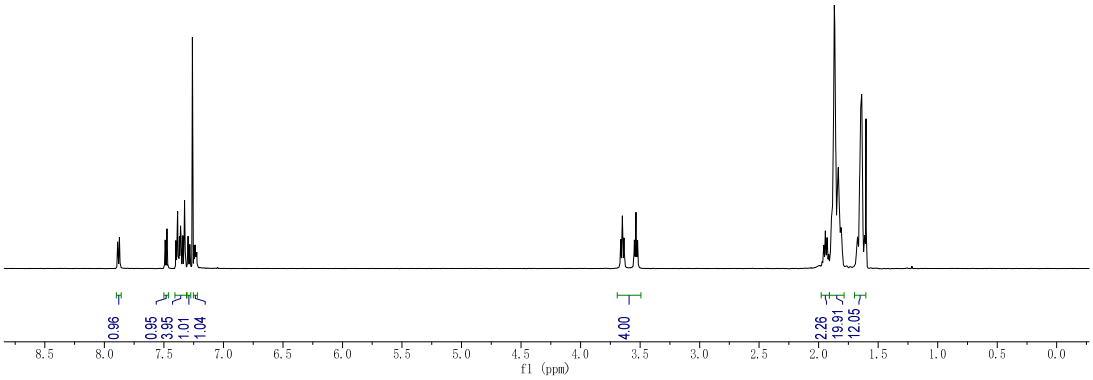


L9AuCl

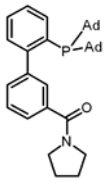
Parameter	Value
1 Title	zhixun-3-L8
2 Solvent	CDCl3
3 Spectrometer Frequency	499.86



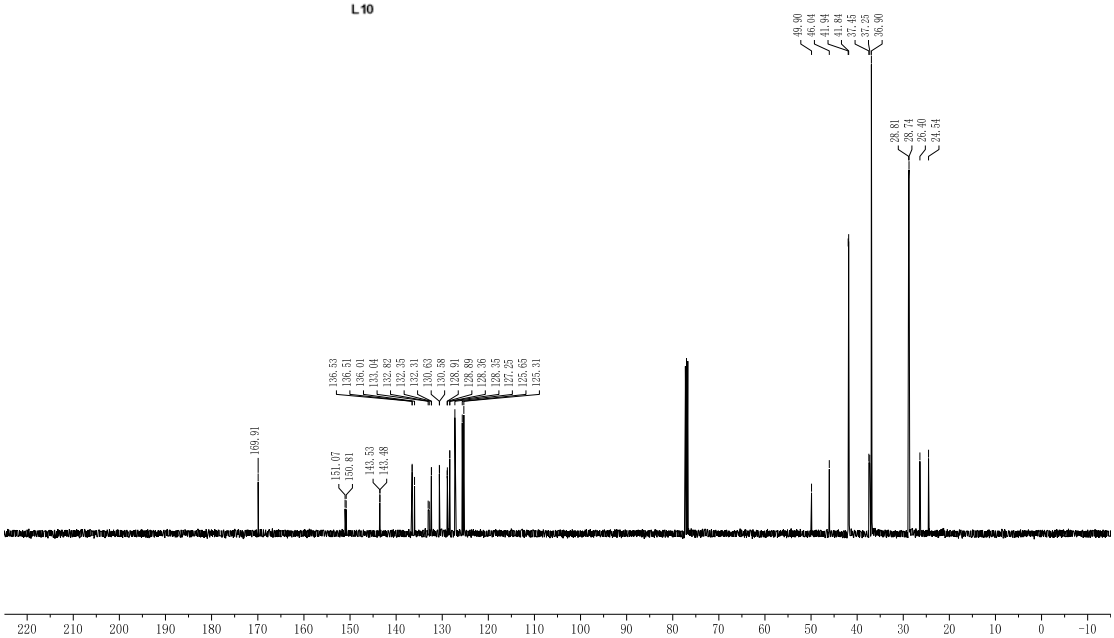
L10



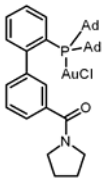
Parameter	Value
Title	wyz7-296-5-c13
Solvent	CDCl3
Spectrometer Frequency	125.70
Nucleus	13C



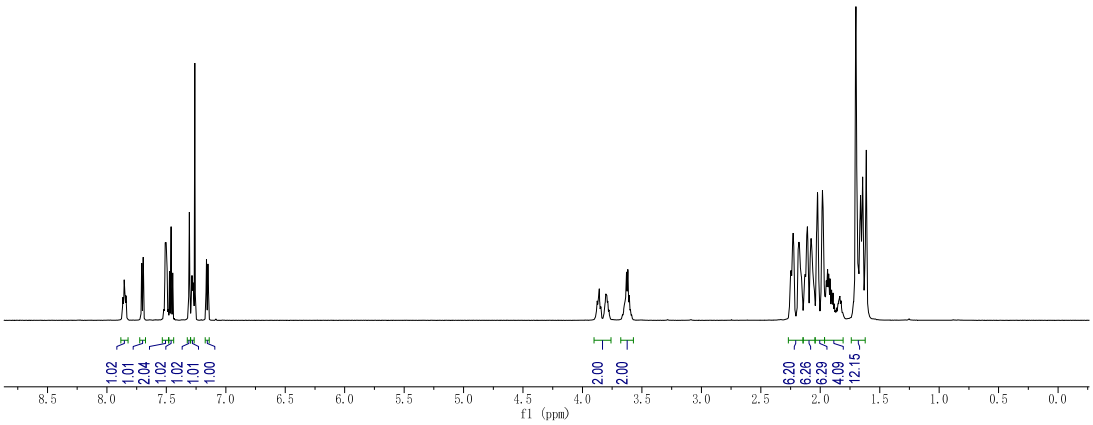
L10



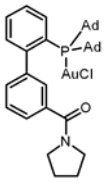
Parameter	Value
1 Title	zhixun-3-L8AuCl
2 Solvent	cdcl3
3 Spectrometer Frequency	599.64



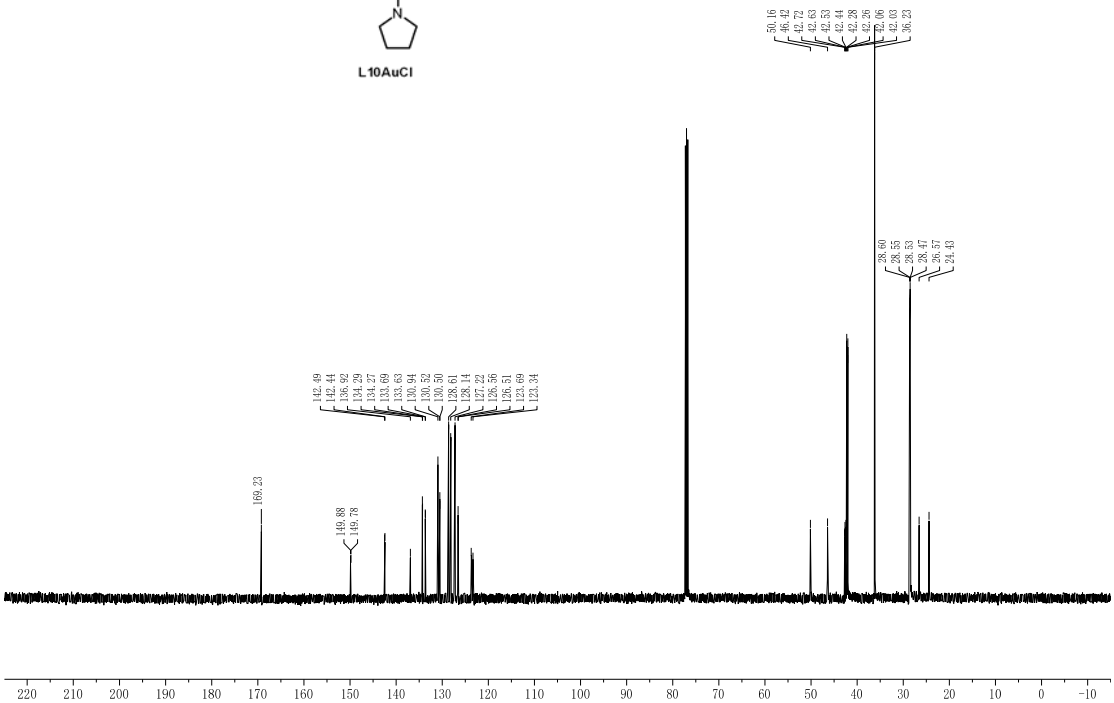
L10AuCl



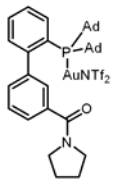
Parameter	Value
Title	wyz8-L9AuCl-C13
Solvent	CDCl3
Spectrometer Frequency	125.70
Nucleus	13C



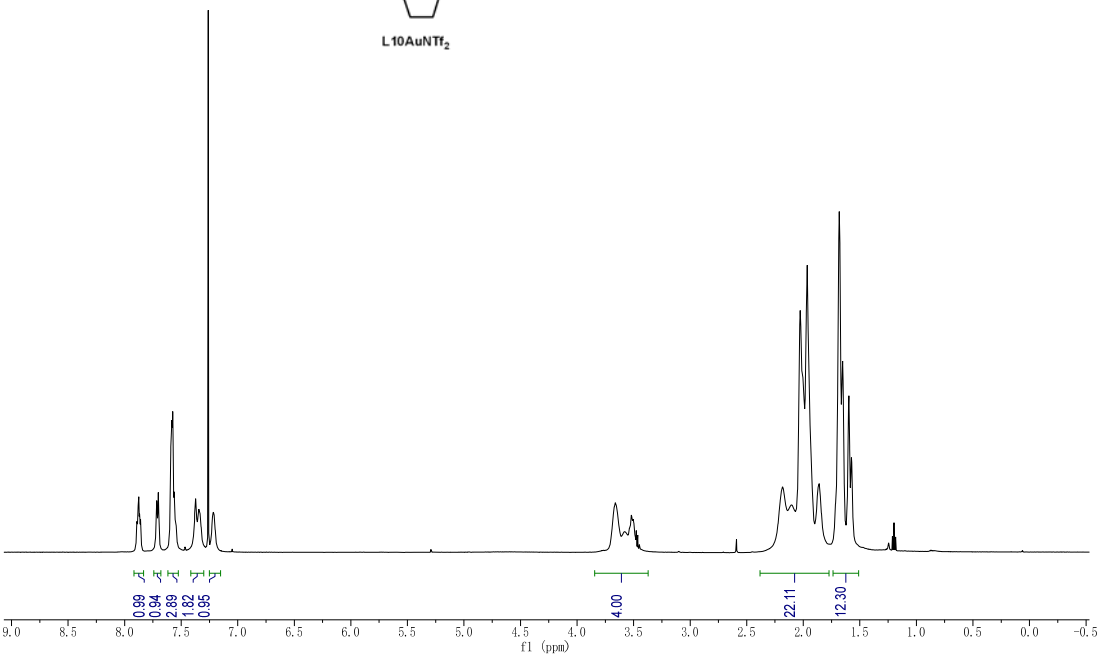
L10AuCl



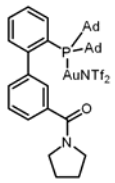
Parameter	Value
1 Title	zhixun-3-L8AuNTf2
2 Solvent	CDCl3
3 Spectrometer Frequency	499.86



L10AuNTf$_2$

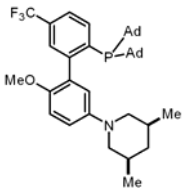


Parameter	Value
Title	wyz8-L9AuNTf2-C13
Solvent	cdcl3
Spectrometer Frequency	150.79

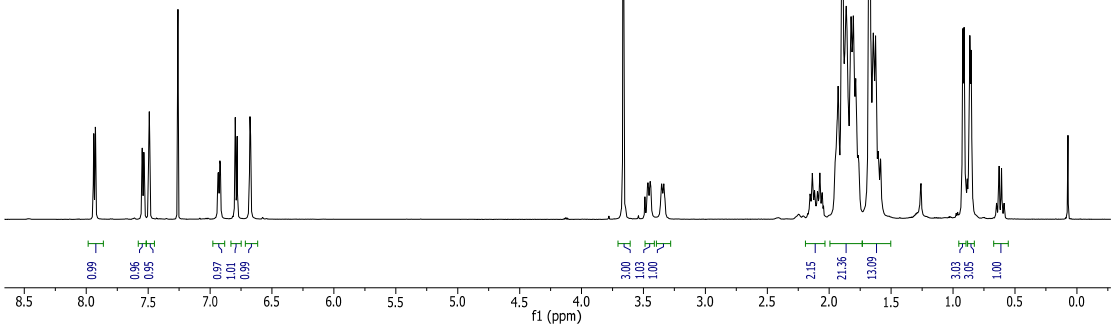


L10AuNTf$_2$

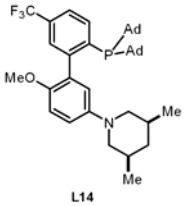
Parameter	Value
Title	wyz8-142-H1
Solvent	cdcl3
Relaxation Delay	4.8000
Spectrometer Frequency	599.64



L14

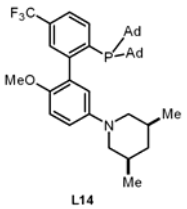


Parameter	Value
Title	wyz8-142-C13
Solvent	CDCl3
Relaxation Delay	1.0000
Spectrometer Frequency	125.70

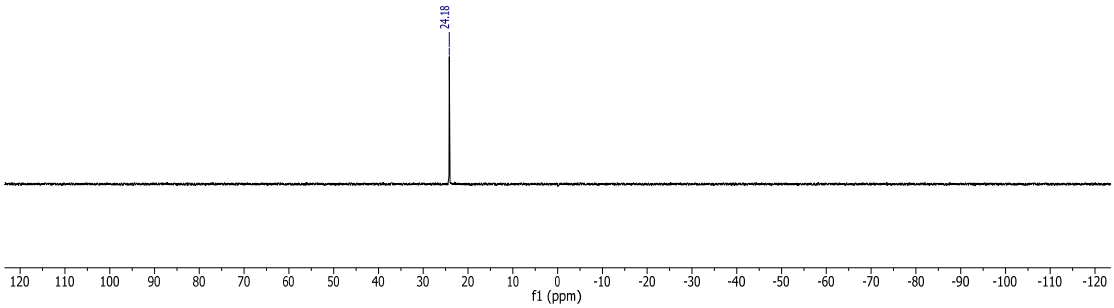


L14

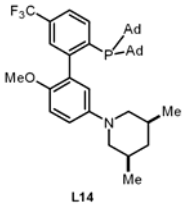
Parameter	Value
Title	wyz8-142-P31
Solvent	cdcl3
Spectrometer Frequency	161.90



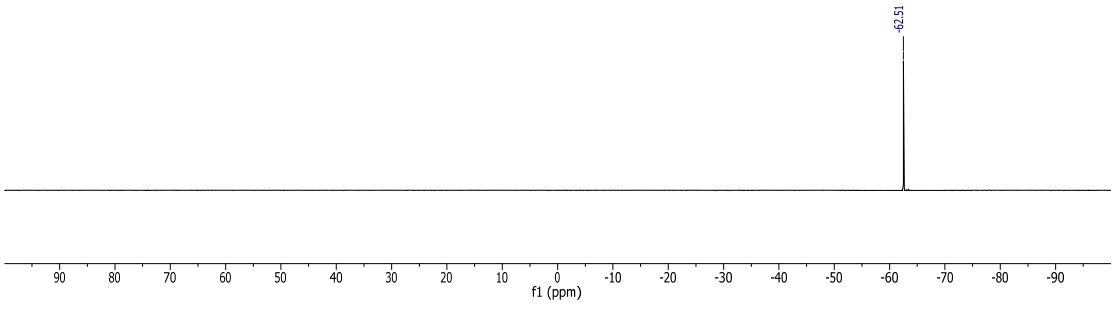
L14



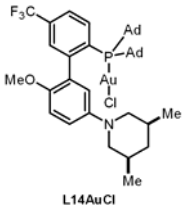
Parameter	Value
Title	wyz8-142-F19
Solvent	cdcl3
Spectrometer Frequency	376.33



L14

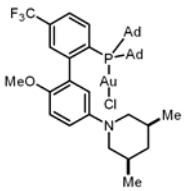


Parameter	Value
Title	wyz8-143-pro-H1
Solvent	cdcl3
Spectrometer Frequency	599.63



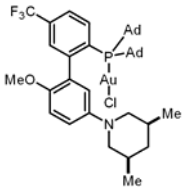
L14AuCl

Parameter	Value
Title	wyz8-143-pro-C13
Solvent	cdcl3
Spectrometer Frequency	150.79

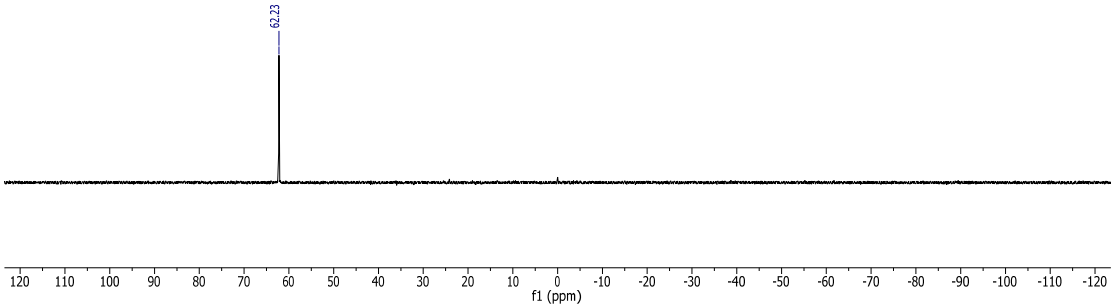


L14AuCl

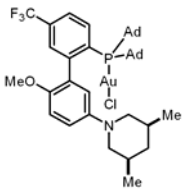
Parameter	Value
Title	wyz8-143-P31
Solvent	cdcl3
Spectrometer Frequency	161.90



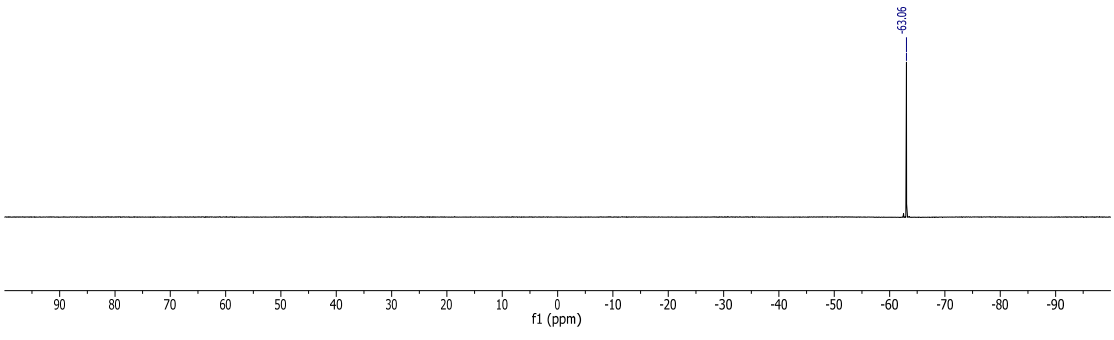
L14AuCl



Parameter	Value
Title	wyz8-143-F19
Solvent	cdcl3
Spectrometer Frequency	376.33

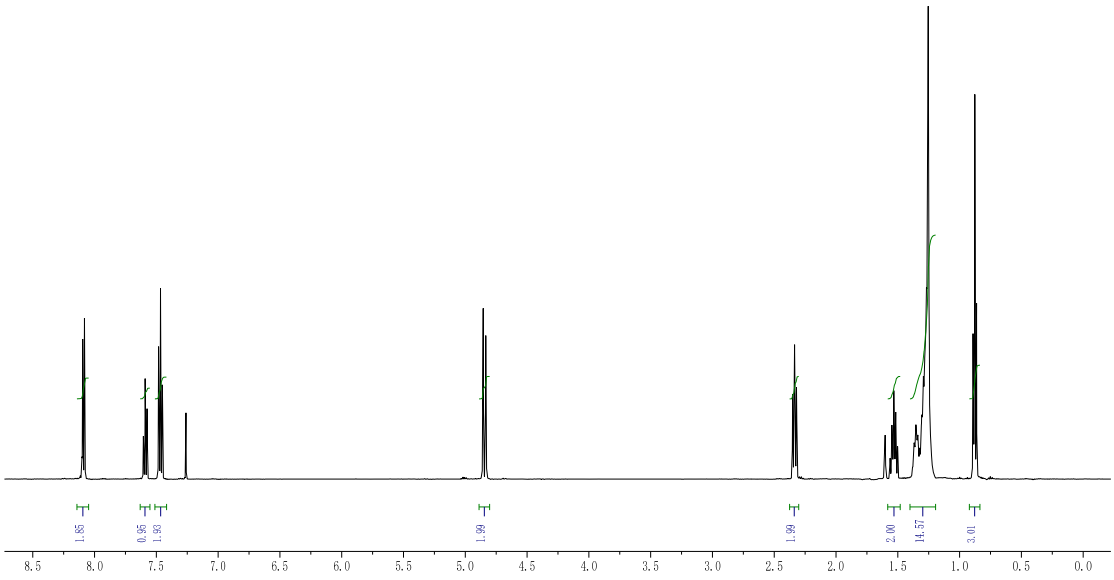


L14AuCl



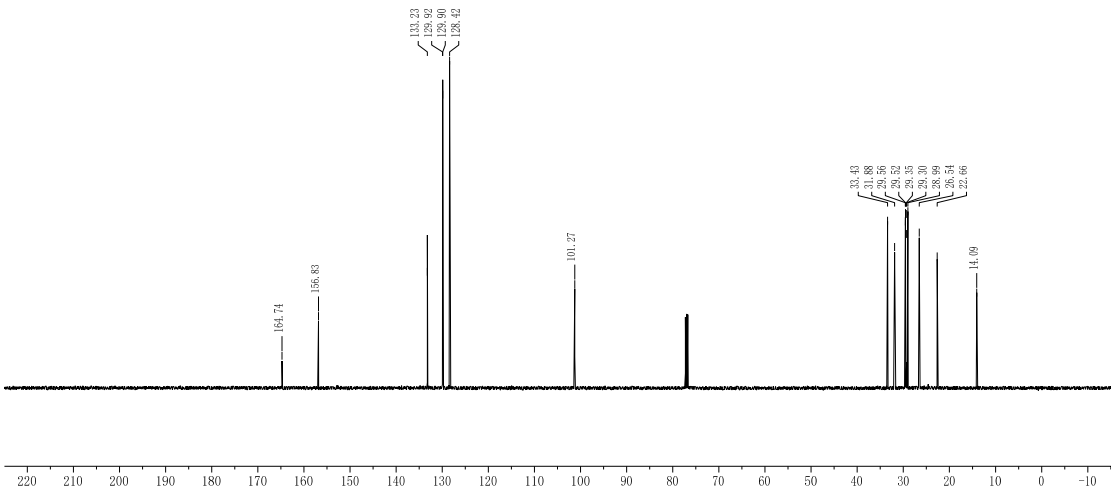
Parameter	Value
Title	wyz8-33-H1
Solvent	CDCl3
Spectrometer Frequency	499.86
Nucleus	1H

2-1a

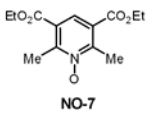


Parameter	Value
Title	wyz8-33-c13
Solvent	CDCl3
Spectrometer Frequency	125.70
Nucleus	13C

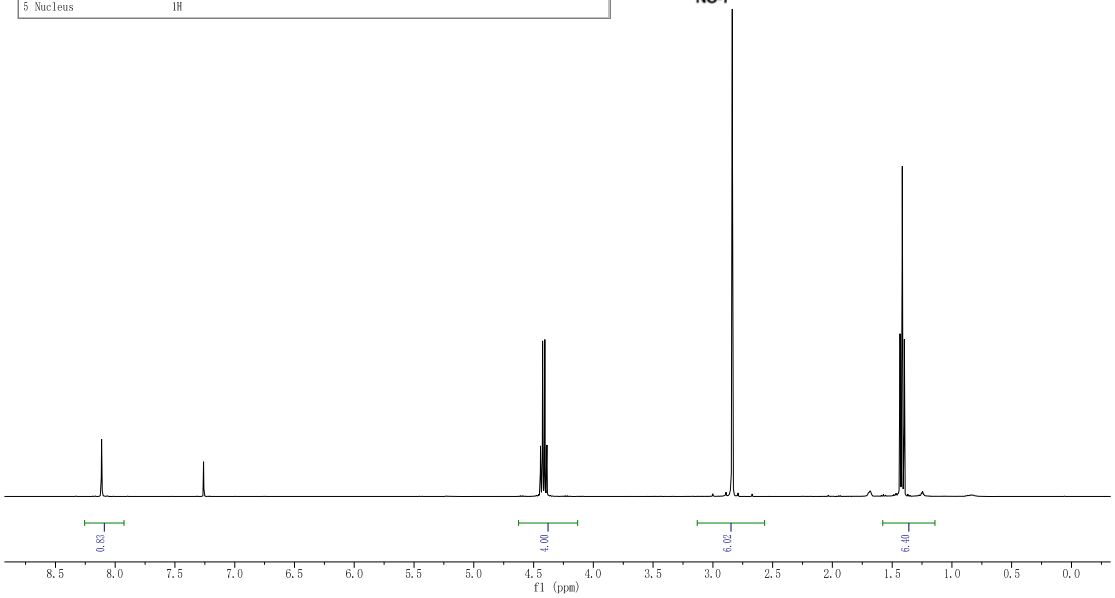
2-1a



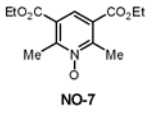
Parameter	Value
1 Data File Name	C:/ Users/ Yanzhao Wang/ Desktop/ proj 4/ NMR/ wyz4-248-pro-h1.fid/ fid
2 Title	wyz4-248-pro-h1
3 Solvent	cdcl3
4 Spectrometer Frequency	399.95
5 Nucleus	1H



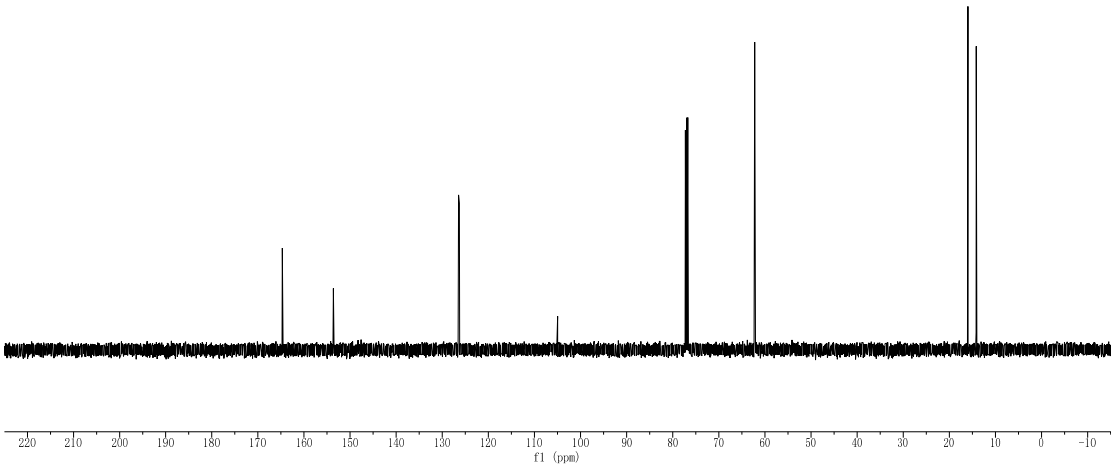
NO-7



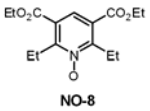
Parameter	Value
1 Data File Name	C:/ Users/ Yanzhao Wang/ Desktop/ proj 4/ NMR/ wyz4-248-pro-c13.fid/ fid
2 Title	wyz4-248-pro-c13
3 Solvent	CDCl3
4 Spectrometer Frequency	125.70
5 Nucleus	13C



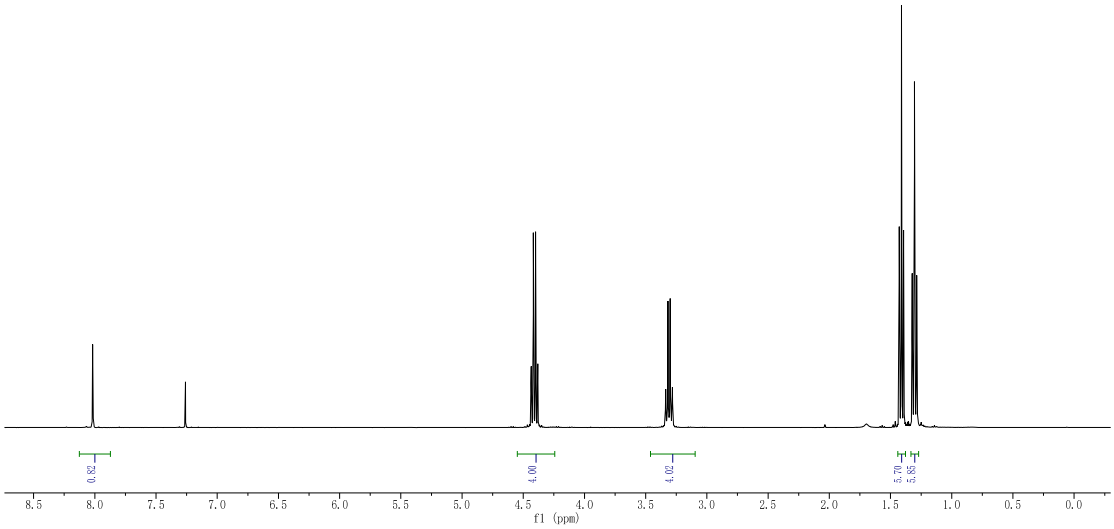
NO-7



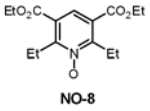
Parameter	Value
1 Data File Name	C:/ Users/ Yanzhao Wang/ Desktop/ proj 4/ NMR/ wyz4-249-pro-h1.fid/ fid
2 Title	wyz4-249-pro-h1
3 Solvent	cdcl3
4 Spectrometer Frequency	399.95
5 Nucleus	1H



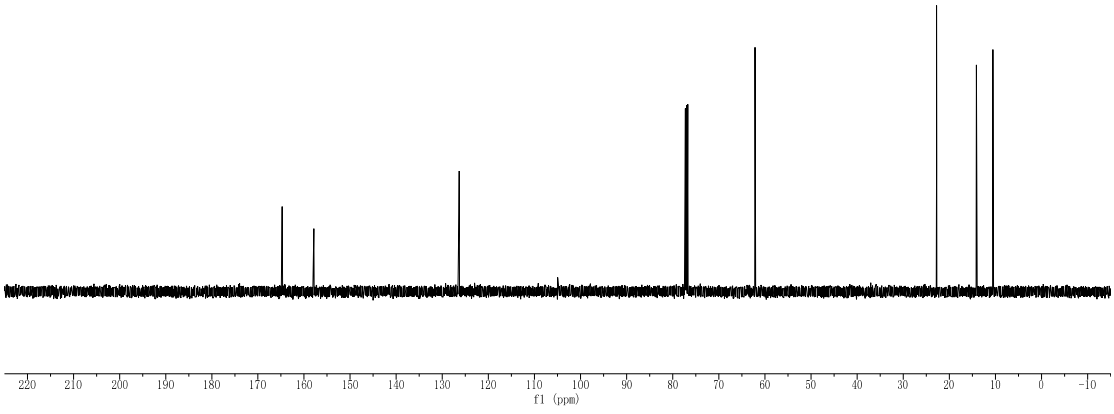
NO-8



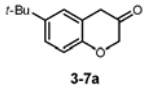
Parameter	Value
1 Data File Name	C:/ Users/ Yanzhao Wang/ Desktop/ proj 4/ NMR/ wyz4-249-pro-c13.fid/ fid
2 Title	wyz4-249-pro-c13
3 Solvent	CDCl3
4 Spectrometer Frequency	125.70
5 Nucleus	13C



NO-8

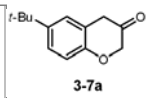


Parameter	Value
1 Data File Name	C:/ Users/ Yanzhao Wang/ Desktop/ proj 4/ NMR/ wyz4-253-pro-h1.fid/ fid
2 Title	wyz4-253-pro-h1
3 Solvent	cdcl3
4 Spectrometer Frequency	599.63
5 Nucleus	1H

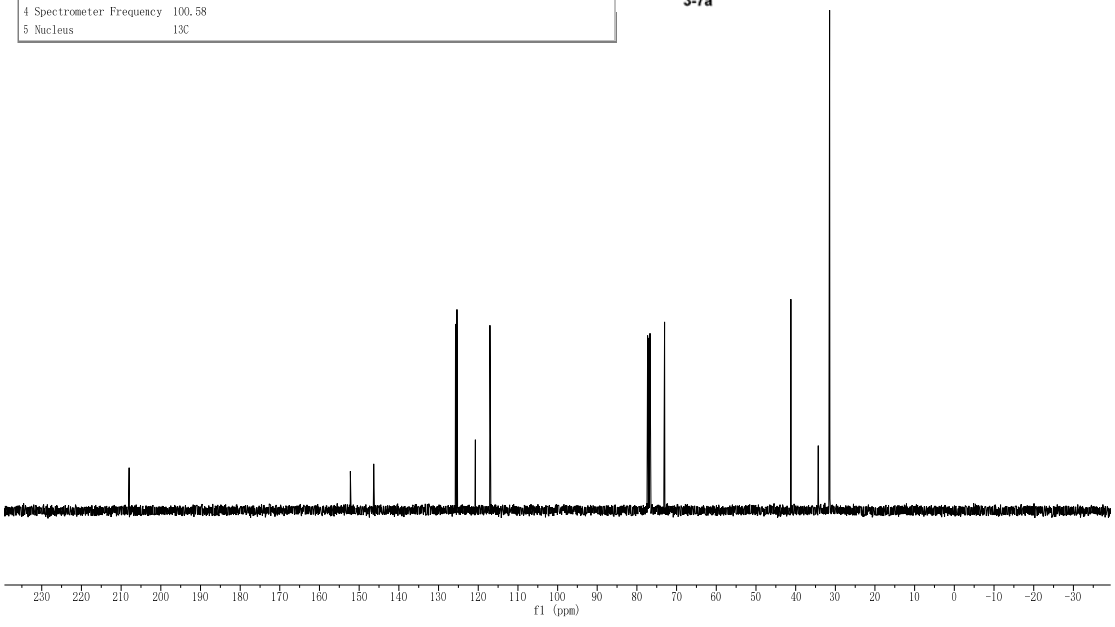


3-7a

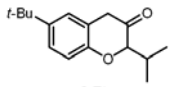
Parameter	Value
1 Data File Name	C:/ Users/ Yanzhao Wang/ Desktop/ proj 4/ NMR/ wyz4-253-pro-c13.fid/ fid
2 Title	wyz4-253-pro-c13
3 Solvent	cdcl3
4 Spectrometer Frequency	100.58
5 Nucleus	13C



3-7a

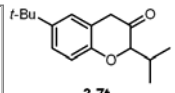


Parameter	Value
1 Data File Name	C:/ Users/ zhang laptop/ Desktop/ NMR/ jkg/ jkg-1-115p-H.fid/ fid
2 Title	jkg-1-115p-H
3 Solvent	CDCl3
4 Acquisition Date	2011-09-26T18:08:51
5 Spectrometer Frequency	499.86



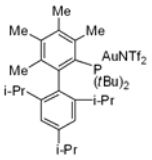
3-7t

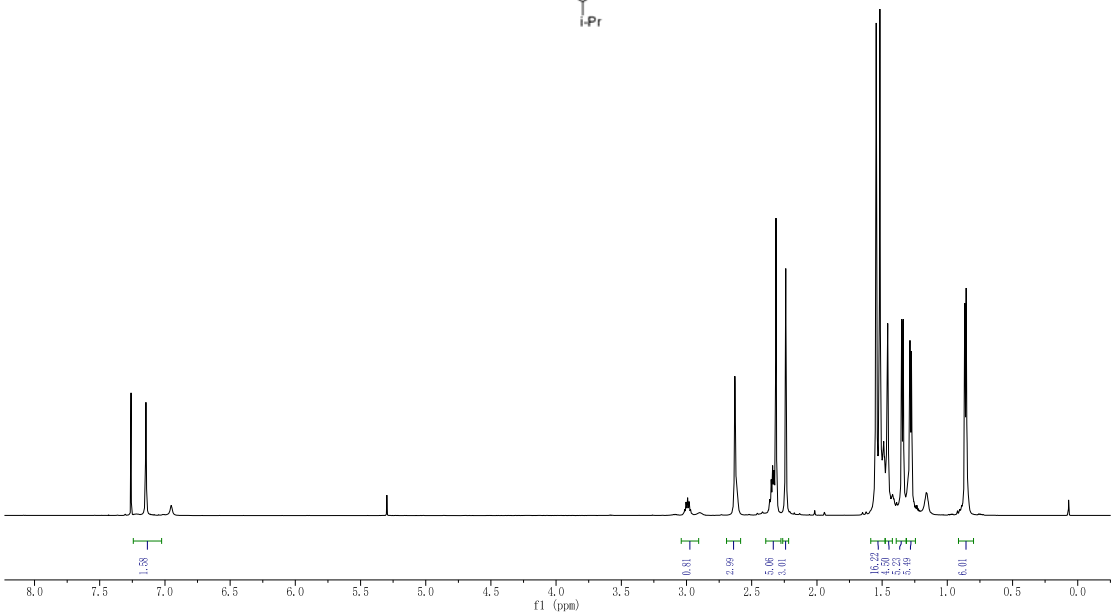
Parameter	Value
1 Data File Name	C:/ Users/ zhang laptop/ Desktop/ NMR/ jkg/ jkg-1-115p-C.fid/ fid
2 Title	jkg-1-115p-C
3 Solvent	CDCl3
4 Acquisition Date	2011-09-26T18:10:44
5 Spectrometer Frequency	125.70



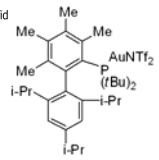
3-7t

Parameter	Value
Data File Name	C:/ Users/ Yanzhao Wang/ Desktop/ proj 4/ NMR/ wyz5-15-pro-h1.fid/ fid
Title	wyz5-15-pro-h1
Solvent	cdcl3
Spectrometer Frequency	599.63
Nucleus	1H

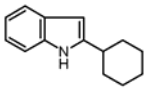




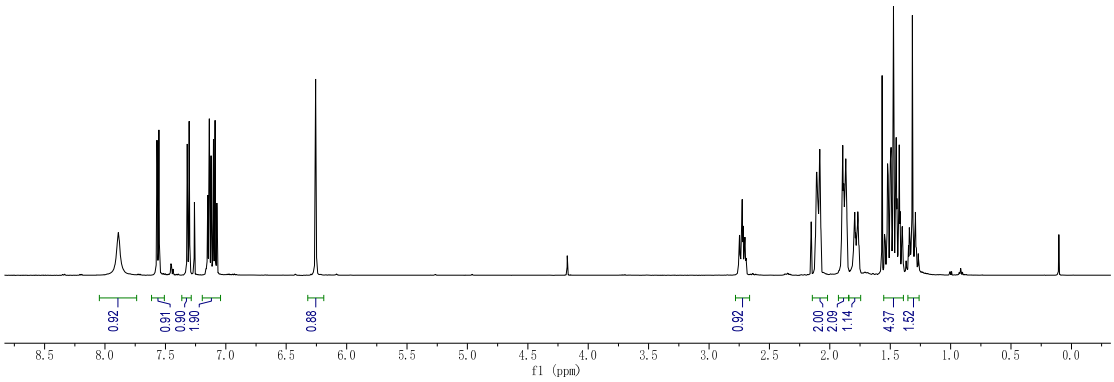
Parameter	Value
Data File Name	C:/ Users/ Yanzhao Wang/ Desktop/ proj 4/ NMR/ wyz5-15-pro-c13-1110.fid/ fid
Title	wyz5-15-pro-c13-1110
Solvent	cdcl3
Spectrometer Frequency	150.79
Nucleus	13C



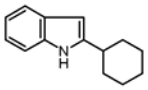
Parameter	Value
Title	ylw-5-17-6ring-15-h
Solvent	"cdcl3"
Relaxation Delay	4.8000
Spectrometer Frequency	499.86



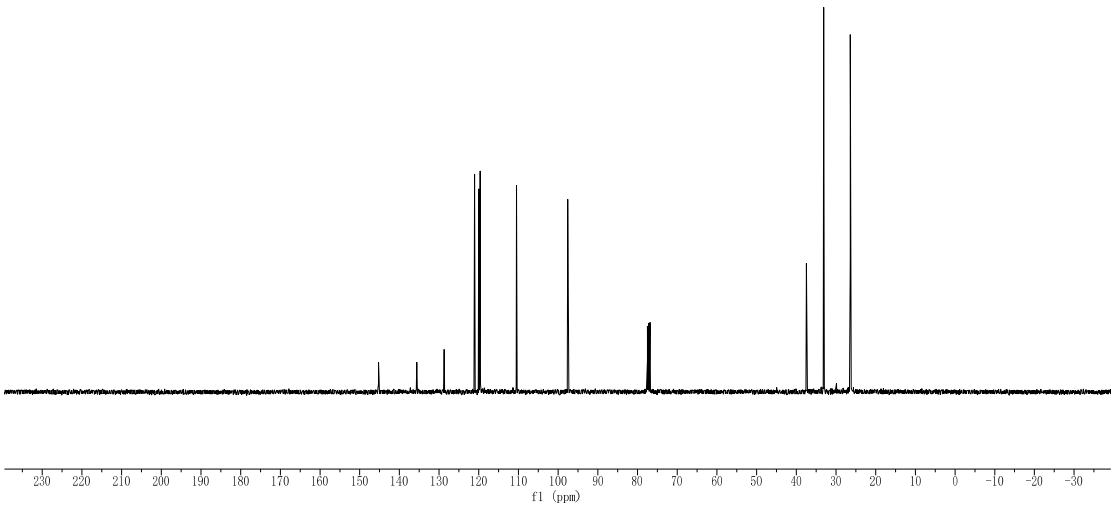
4-2b



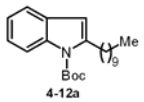
Parameter	Value
Title	ylw-5-17-6ring-cc2
Solvent	"cdcl3"
Relaxation Delay	1.3000
Spectrometer Frequency	100.58



4-2b

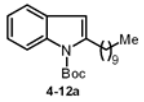


Parameter	Value
Title	wyz3-186-pro-h1
Solvent	"CDCl3"
Relaxation Delay	2.0000
Spectrometer Frequency	499.86

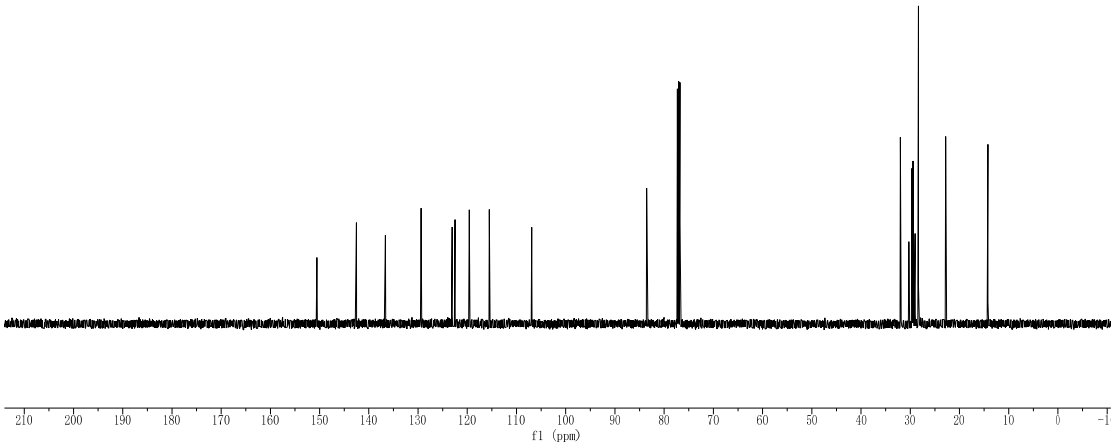


4-12a

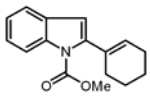
Parameter	Value
Title	wyz3-186-pro-c13
Solvent	"cdcl3"
Relaxation Delay	3.0000
Spectrometer Frequency	125.70



4-12a

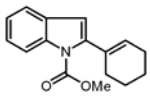


Parameter	Value
Title	wyz3-182-pro-h1
Solvent	"CDCl3"
Relaxation Delay	2.0000
Spectrometer Frequency	499.86

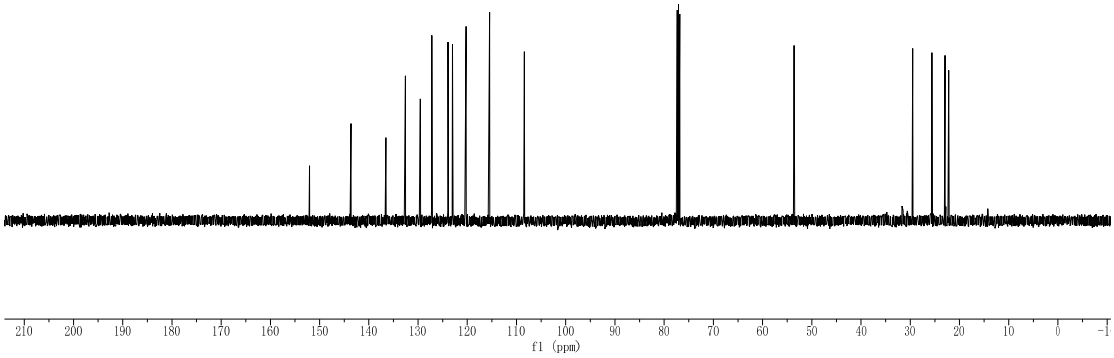


4-13b

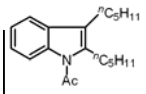
Parameter	Value
Title	wyz3-182-pro-c13-1
Solvent	"cdcl3"
Relaxation Delay	3.0000
Spectrometer Frequency	125.70



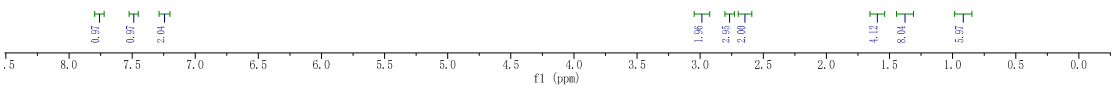
4-13b



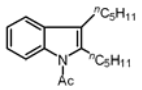
Parameter	Value
Data File Name	F:/ Yanzhao Wang Research/ Proj 2 Protected Indoles/ NMR Internal Indoles/ wyz5-96-pro-h1.fid/ fid
Title	wyz5-96-pro-h1
Solvent	CDCl3
Spectrometer Frequency	499.86
Nucleus	1H



4-14a



Parameter	Value
Data File Name	F:/ Yanzhao Wang Research/ Proj 2 Protected Indoles/ NMR Internal Indoles/ wyz5-96-pro-c13.fid/ fid
Title	wyz5-96-pro-c13
Solvent	CDCl3
Spectrometer Frequency	125.70
Nucleus	13C



4-14a