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A General Diastereoselective Catalytic Vinylogous Aldol Reaction Among Tetramic Acid-Derived Pyrroles

A Thesis submitted in partial satisfaction of the

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Master of Science in Chemistry

by

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ABSTRACT

A General Diastereoselective Catalytic Vinylogous Aldol Reaction

Among Tetramic Acid-Derived Pyrroles

by

Jonathan Gene David

A catalytic diastereoselective aldol reaction has been developed for N1-arylated/C2-O-silylated/C3-methylated and brominated/C4-O-methylated pyrroles in its reactions with various aldehydes. Syn adducts emerge with regard to the vicinal nitrogen and oxygen heteroatom substituents. The N1-aryl residue undergoes oxidative cleavage, and the C3-bromine atom undergoes palladium-mediated coupling reactions, both without disturbing the newly created stereocenters.

I. Introduction

The tetramic acid ring system has been known since the early twentieth century. It was only around 1960 that its importance was realized when its structural moiety was found in numerous natural products. These compounds that contained the tetramic acid core were shown to exhibit various bioactivity such as antibiotic and antiviral properties along with tumor inhibition.

Tetramic acids are traditionally represented as derivatives of the enolic tautomer, 4-hydroxy-3-pyrrolin-2-one. The three main derivatives of the core are differentiated by the substituent at the C3 position: C3-acyl, C3-hydrido, and C3-methyl (Figure 1).

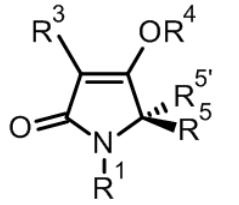


Figure 1. Tetramic acid derivatives

II. A General Diastereoselective Catalytic Vinylogous Aldol Reaction Among Tetramic Acid-Derived Pyrroles

Tetramic acid aldolate adducts are known with both syn and anti stereochemical arrangements. Natural product examples include tetrapetalone B (**1**)[1], cylindramide A (**2**)[2], militarinone B (**3**)[3], paecilosetin (**4**)[4], and cryptocin (**5**)[5] (Figure 2). Given their occurrence, it was surprising for us to learn that a general diastereoselective aldol method leading to the construction of this motif had not been reported. A chief problem appears to have been selection of the protecting group for the nitrogen atom. This residue affects the acidity,

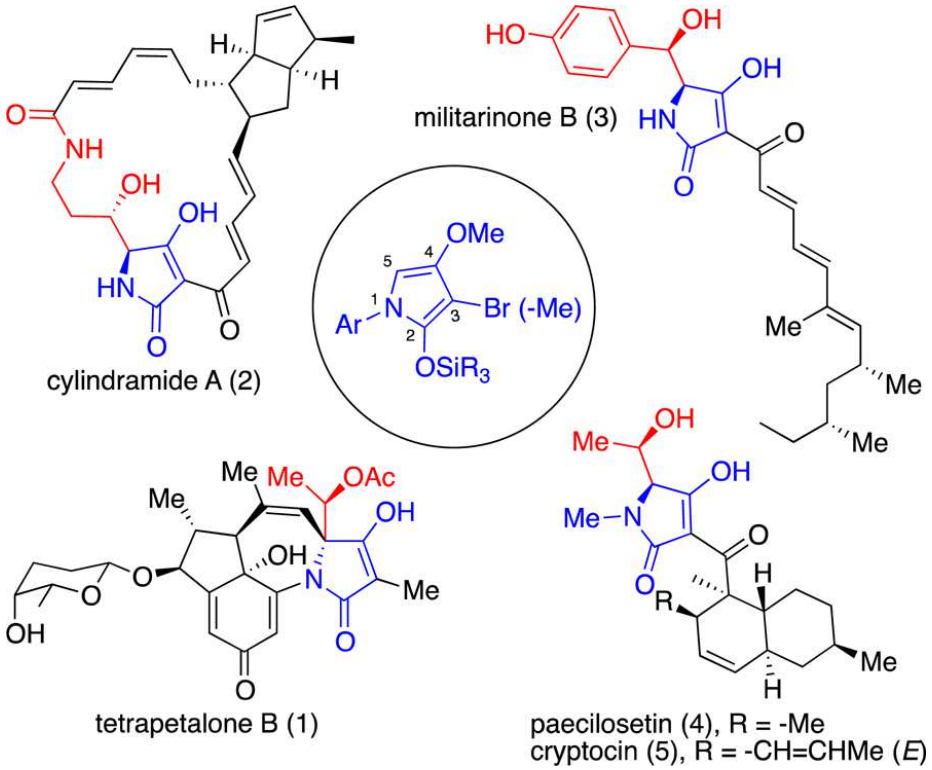


Figure 2. Some natural products containing tetramic acid aldolate motifs

sterics, selectivity, and chemistry surrounding the neighboring C5 atoms far more so than for their corresponding *des*-C4-methoxy counterparts[6]. The chemical literature revealed only two reported examples of aldol reactions involving tetramic acid derivatives. Neither was comprehensively studied nor appeared general. Hunter employed an N1-benzylated/C2-O-silylated/C4-O-methylated pyrrole in combination with a chiral α-alkoxy aldehyde and observed an anti-aldolate[7], whereas Stachel employed an N1-benzylated/C2-O-lithiated/C4-O-methylated pyrrole with an α-alkoxy aldehyde and observed a syn-aldolate[8]. We speculated that an N1-aryl residue might prove sterically smaller than the customary N1-benzyl and -Boc derivatives and lessen the acidity of the C5 proton(s) of the tetramic acid and thereby fortify any emerging stereochemistry by thwarting potential epimerization processes or retroaldol events that are notorious among these systems[9].

A. Construction of Tetramic Acids

The syntheses of the tetramic acids were adapted using the Jones' protocol[10] (Figure 3). The known γ-bromo unsaturated ethyl esters **6a**−**b**[11] were independently coupled with *p*-methoxy aniline in a single pot to afford the corresponding tetramic acid derivatives **7a**−**b** in good yields. The adduct **7b** was then converted to the corresponding C3-bromo derivative **7c** by exposure to bromine.

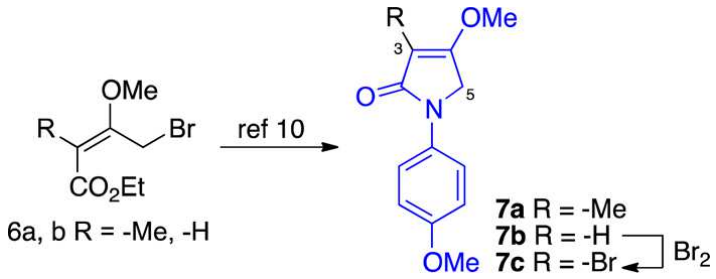
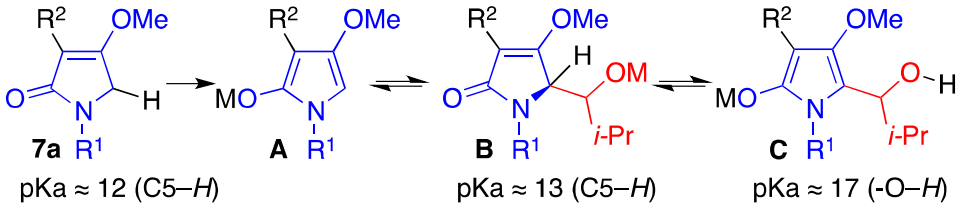


Figure 3. Preparation of tetramic acid derivatives

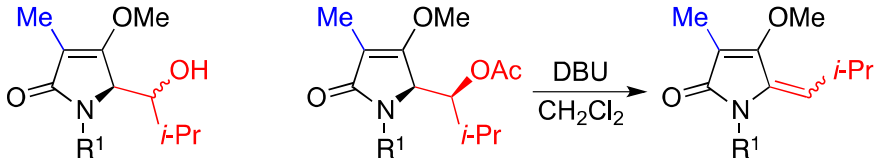
B. Investigation of their Enolate Reactivity

With these in hand, we set out to determine their reactivity as their respective enolate **A**. We found that treatment of the tetramic acid derivative **7a** in dichloromethane (DCM) at 50 °C with triethylamine (Et_3N) and deuterium oxide (D_2O) yielded very little deuterium incorporation at the C5 position. However, treatment with either 1,8-diazabicycloundec-7-ene (DBU) and D_2O, or lithium bis-(trimethylsilyl)amide (LHMDS) and subsequent D_2O workup, led to complete bis- deuteration at the C5 position. From these observations, we estimated the pK_a of the C5 hydrogen in derivative **7a** to be between 12 and 16. Deprotonation of adduct **7a** with DBU followed by addition of isobutyraldehyde at ambient temperature failed to yield appreciable amounts of product (Table 1, entry 1). Similarly, deprotonation at −78 °C with LHMDS followed by the addition of isobutyraldehyde and

Table 1. Enolate outcomes of the N1-Ar tetramic acid derivative **7a**



entry	base	solvent	RCHO added	additive / workup	yield **8a** or **9**	ratio
1	DBU	DCM	25 °C	none / 1M HCl	< 5%	na
2	LHMDS	THF	-78 to 25 °C	none / 1M NH_4Cl	< 5%	na
3	LHMDS	THF	-78 °C	none / 1M NH_4Cl	90%	1:1
4	LHMDS	THF	-78 °C	Ac_2O / NH_4Cl	60%	5:1
5	LHMDS	THF	-78 °C	TMSCl / NH_4Cl	45%	2:1



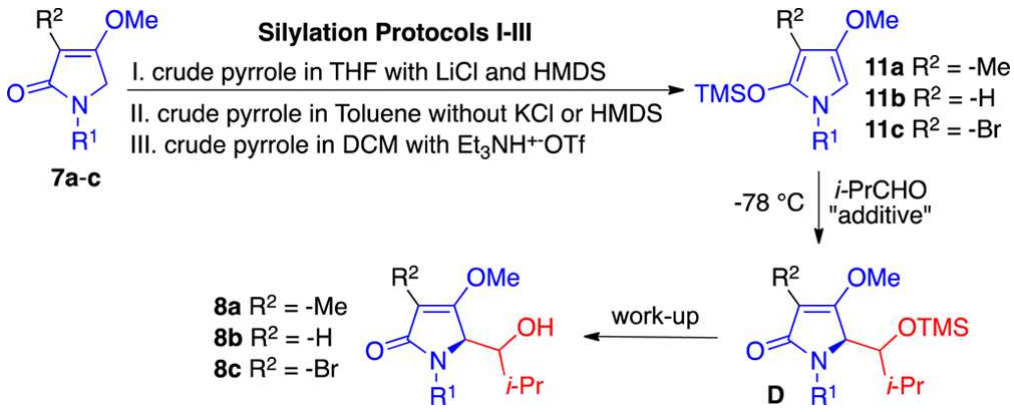
subsequent quenching with 1 M ammonium chloride (NH_4Cl) at ambient temperature also failed to yield product (entry 2). However, upon quenching aldol reactions initiated with LHMDS at −78 °C with 1 M NH_4Cl the desired aldolate **8a** formed (90% yield, 1:1 mixture; entry 3). These observations, when taken together, implied to us that a facile retroaldol had returned the starting material at higher temperatures owing to the stability of the enolate **A** as compared to the alkoxide **B**. This assumption was further supported by the observation that, when the product **8a** was retreated with LHMDS, as in entry 2, the starting material **7a** was returned. However, we attributed the poor diastereoselection to an intramolecular deprotonation and enolization to **C** followed by stereoindiscriminate reprotonation, as this was supported by the observation that, when the alcohol **8a**[12] was treated with DBU at 50 °C, the diastereomeric ratio was nearly fully degraded. We subsequently found that if the

addition of the aldehyde was rapidly followed by the addition of acetic anhydride (Ac_2O), then the selectivity improved to 5:1 (entry 4). None of the elimination product **10** was observed. However, it could be formed upon exposing the acetate **9** to DBU. Application of trimethylsilyl chloride (TMSCl) as the quenching additive failed to provide gains in selectivity (entry 5).

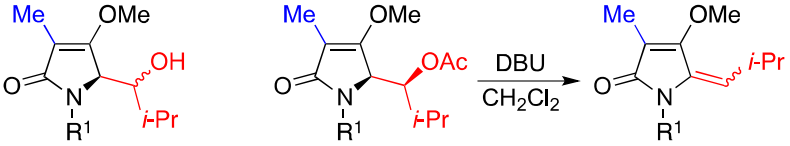
C. Investigation and Optimization of Conditions of the Aldol Reaction

We next investigated the 2-siloxypyrroles **11a**−**c** (Table 2). These materials were formed from three different protocols from the corresponding tetramic acid derivatives **7a**−**c**. In the first, the material was deprotonated with LHMDS followed by the addition of TMSCl and then used in crude form at −78 °C. Thus, the effects of lithium chloride (LiCl), hexamethyldisilazane (HMDS), and tetrahydrofuran (THF) had to be considered. In the second, the starting compound was deprotonated with potassium bis(trimethylsilyl)amide (KHMDS), followed by the addition of TMSCl and then evaporated, whereupon the residue was suspended into toluene and used at −78 °C. Thus, the effects of potassium chloride (KCl), HMDS, and THF were eliminated. In the third, the starting compound was individually subjected in DCM to an admixture of Et_3N and trimethylsilyl trifluoromethanesulfonate (TMSOTf) and then used at −78 °C. Thus, the effects of Et_3NH^+ $^-$OTf had to be contemplated. For example in our hands spectroscopic characterization of the pyrroles **11a**−**c** prepared from protocol-III proved to be fruitless, as they fell apart upon removal of the solvent. However, they could be characterized if obtained from protocol-II. When the pyrrole **11a** (protocol-I) was successively treated with isobutyraldehyde, tin tetrachloride ($SnCl_4$) and aqueous NH_4Cl, compound **8a** emerged in a 4:1 ratio of diastereomers (Table 2, entry 1). On the other hand, when pyrrole **11a** (protocol-II/THF-free)

Table 2. Aldol reactions of pyrroles **11a-c** with isobutyraldehyde



entry	sm	Silylation Protocol	primary solvent	Lewis Acid (equiv)	yield (%)	product, ratio
1	**7a**	I	THF	$SnCl_4$ (2)	90	**8a**, 4:1
2	**7a**	II	toluene	$SnCl_4$ (2)	90[a]	**8a**, 7:1
3	**7a**	II	toluene	$SnCl_4$ (0.2)	88[a]	**8a**, 7:1
4	**7c**	II	toluene	$SnCl_4$ (0.2)	65[a]	**8c**, 9:1
5	**7a**	III	DCM	$SnCl_4$ (2)	90	**8a**, 14:1
6	**7a**	III	DCM	$SnCl_4$ (0.2)	83	**8a**, 14:1
7	**7a**	III	DCM	–	< 5	**8a**, na
8	**7a**	III	DCM	TMSOTf (1)	50	**8a**, 1:1
9	**7a**	III	DCM	BF_3•Et_2O (2)	72	**8a**, 2:1
10	**7a**	III	DCM	$TiCl_4$ (2)	78	**8a**, 3:1
11	**7b**	III	DCM	$SnCl_4$ (2)	90	**8b**, 3:1
12	**7c**	III	DCM	$SnCl_4$ (2)	86	**8c**, >20:1



8a [1:1]
90% yield

9 [5:1]
60% yield

10

[a]isolated yield based on recovered starting material

was treated in an identical fashion, then an improved 7:1 ratio was realized (entry 2). Application of catalytic $SnCl_4$ (0.2 equiv) afforded comparable results albeit with a slightly reduced yield (entry 3). The bromopyrrole **11c** prepared in similar fashion also underwent

reaction mediated by catalytic $SnCl_4$ to afford compound **8c** in a 9:1 ratio (entry 4). Treatment of pyrrole **11a** (protocol-III) with $SnCl_4$ in DCM provided the adduct **8a** with a further improved ratio and yield (entry 5). Use of catalytic $SnCl_4$ afforded comparable selectivity albeit at a slightly reduced yield (entry 6). However, if $SnCl_4$ was not added at all, then the reaction failed (entry 7). Use of TMSOTf resulted in no selectivity for the reaction (entry 8). Boron trifluoride diethyl etherate ($BF_3 \cdot Et_2O$) and titanium tetrachloride ($TiCl_4$) led to some improvement (entry 9−10). The C3 substituent had a profound consequence upon the diastereoselectivity [**8b** < C3-methyl **8a** < C3-bromo **8c**].

D. Scope of the Aldol Reaction

We next explored the substrate scope for our catalytic conditions by combining various aldehydes with the starting pyrroles **11a**−**c**. Our results are summarized in Figure 4. In general, the C3 pyrrole **11b** proved significantly less diastereoselective than its C3-methyl and -bromo counterparts. The exception was its reaction with pivalaldehyde, which afforded outstanding selectivity among adducts **12**−**14** for all three pyrrole cores. Both acyclic and

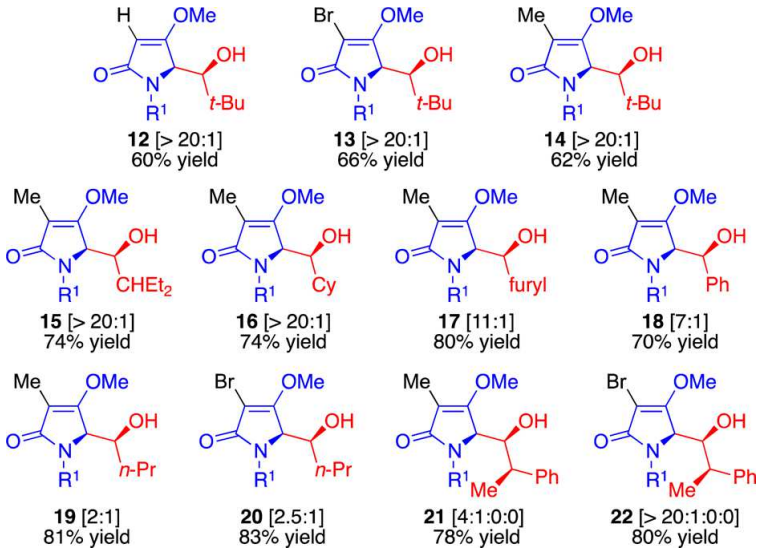


Figure 4. Range and scope for the catalytic aldol reaction

cyclic aliphatic aldehydes afforded excellent yields and selectivity for pyrroles **11a** and **11c**. In general, branched aldehydes expectedly led to higher selectivities as seen for 2-ethylbutyraldehyde and cyclohexanecarboxaldehyde in adducts **15**−**16**. Aryl aldehydes, which are prone toward reversible reactions, provided slightly lower selectivity as seen in compounds **17**−**18**. The linear *n*-butyl aldehyde led to the poor outcome we observed in products **19**−**20**. It should be noted that the reactions with chiral 2-phenylpropionaldehyde, which is well-known to undergo diastereoselective reactions owing to internal allylic strain[13], led to almost a single adduct for both the methyl- and bromo- products **21**−**22**, a further testament to the diastereoselectivity and asymmetric synthetic potential for this new protocol.

E. Determining the Syn Diastereomer through X-ray Crystallography

Since both of the diastereomers gave similar ^{1}H-NMR signals for their respective C5-methine in adducts **8a**−**c** and **12**−**22**, we obtained an X-ray structure of **8a** and learned that the preferred isomer displays a syn relationship between the vicinal nitrogen and oxygen atoms (Figure 5)[14]. We then assumed that further syn and anti assignments could be determined empirically from the ^{1}H-NMR, as the C5 methine signal appears further downfield for the syn diastereomers as compared with the anti diastereomer in adducts arising from aliphatic aldehydes.

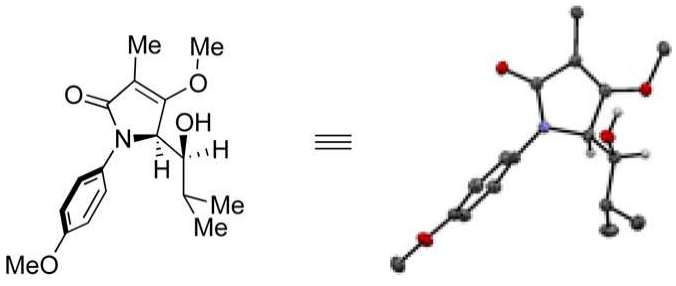


Figure 5. X-ray structure determined for major diastereomer (syn) of compound **8a**

Equipped with this knowledge, we can imagine three transition states, open, closed, or [4 + 2]-exo arrangement, as leading to the syn adduct we have observed (Figure 6). The [4 + 2] exo transition state seems unlikely because an unfavorable steric interaction exists between the Lewis acid and the R^2 substituent. Moreover, chelation of the metal atom with the siloxy oxygen atom (RO) seems unlikely. The closed transition state can be excluded because of an

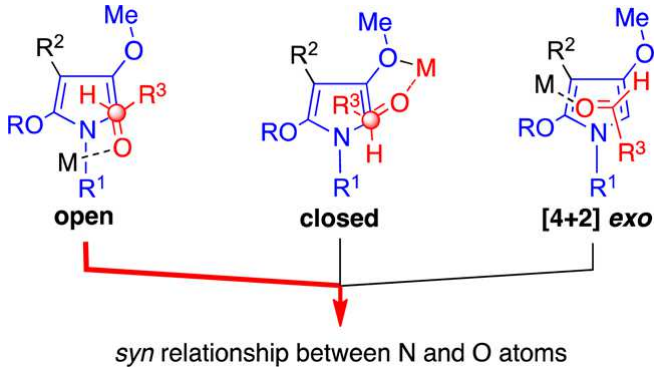


Figure 6. Three transition states leading to syn products

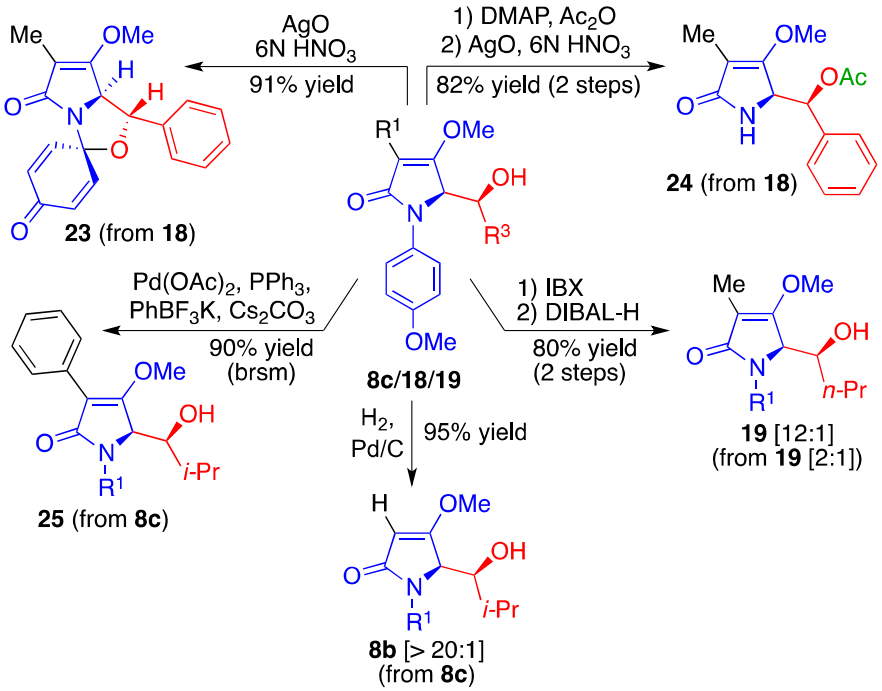
unfavorable interaction between the R^3 aldehyde substituent and the pyrrole R^2 substituents, poor alignment between the lone pairs and the coordinating metal atom, as well as the unlikely circumstance that the metal atom and R^3 substituent would be on the same side of the carbonyl. We therefore attribute the selectivity to an open transition state; as the R^1 substituent (-N1-aryl) is sterically small, it can adopt coplanarity and increase the pyrrole's nucleophilicity and provide room for the coordinated metal atom (M).

F. Reactivities of Aldol Adducts

These novel adducts participate in a number of other notable transformations (Scheme 1). For example, exposure of the compound **18** to argentic oxide[15] afforded the unusual spirocyclic aminal **23** in 91% yield. On the other hand, the alcohol **18**, once protected as its corresponding acetate, when similarly treated smoothly afforded the unprotected tetramic

acid derivative **24** in 82% yield over two steps. Cerium ammonium nitrate could also be used. The brominated compound **8c** underwent palladium-mediated coupling under Molander's conditions to afford the C3-aryl derivative **25**[16]. This outcome suggests potential late-stage stitching strategies for a number of C3-substituted tetramic acid natural products rather than concluding their syntheses with its construction as has been customarily done[2c]. The bromo derivative **8c** can also be converted into the aldolate **8b** by hydrogenolysis, thereby enabling access to these aldol products with better stereocontrol. In addition, aldol products with lower diastereoselectivities from linear aldehydes, such as adduct **19** (2:1) are readily improved to >12:1 by oxidation of the secondary alcohol and subsequent reduction with DIBAL-H.

Scheme 1. Some reactivities of aldol adducts **8c**, **18**, and **19**



III. Conclusion

We have developed the first general diastereoselective method for accessing tetramic acid aldolate derivatives from their corresponding siloxy pyrroles. $SnCl_4$ was found to be an outstanding Lewis acid among those examined, and the reaction proved to be catalytic. The C3-bromo tetramic acid derivative afforded superior results. The reactions with chiral aldehydes, which resulted in compounds **21** and **22** with three contiguous stereocenters, demonstrate that this procedure can be used to access nonracemic substrates in an enantioselective fashion. Lower diastereoselectivities emanating from adducts such as **8b** or linear aldehydes such as **19** can be respectively improved by hydrogenolysis of the corresponding bromo adduct **8c** or by an oxidation−reduction sequence. The bromo derivative **8c** participates in palladium-mediated coupling reactions, indicating access to an even greater range of tetramic acid derivatives. It therefore appears that this new method, which employs tetramic acid-derived pyrroles bearing an N1-aryl residue, may be amenable to catalysis with chiral Lewis acids in future asymmetric regimes.

IV. Experimental Section

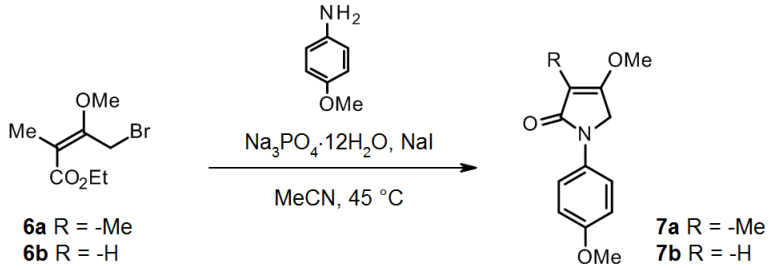
A. General Information

In reactions where water was not present as a solvent, reagent, or byproduct, glassware was flame dried under nitrogen or oven-dried. All reactions were carried out under an inert atmosphere of nitrogen unless otherwise noted; glassware was capped via rubber septa and sealed with parafilm. Reactions were monitored by analytical thin-layer chromatography on EMD silica gel 60 F254 plates cut into 1.5 x 5.0 cm pieces; visualization was effected by ultraviolet light (254 nm). Solvents were removed using a rotary evaporator. If the product was non-volatile, trace solvents were removed at a pressure of approximately 0.01 mmHg.

All purchased chemicals were used without purification unless otherwise stated. All aldehydes were distilled. Dichloromethane was distilled from CaH2. Diethyl ether, tetrahydrofuran, benzene, and toluene were distilled from sodium and benzophenone. Deuterated chloroform was stored over 4Å molecular sieves before use.

1H-NMR spectra were recorded at 400, 500, or 600 MHz instruments with the solvent resonance of CDCl3 (7.26 ppm) or C6D6 (7.16 ppm). 13C-NMR spectra were recorded at 500 or 600 MHz instruments with a solvent resonance of CDCl3 (77.00 ppm). Infrared spectra were recorded on an FTIR-8300 Fourier transform infrared spectrometer with neat sample. Infrared frequencies are reported in reciprocal centimeters (cm-1). High resolution mass spectra (HRMS) were obtained by electrospray ionization/time-of-flight experiments. Melting points were uncorrected.

B. Tetramic Acid Synthesis

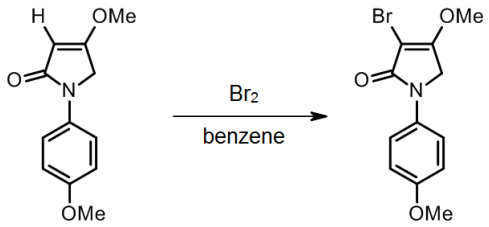


To a flask containing *p*-anisidine (2.081 g, 16.90 mmol, 2 equiv) in MeCN (50 mL, 0.34 M) was added Na_3PO_4•12 H_2O (2.151 g, 5.66 mmol, 0.67 equiv), NaI (72 mg, 0.51 mmol, 0.06 equiv), and γ-bromo unsaturated ethyl ester **6a** (2.003 g, 8.45 mmol, 1.0 equiv). The solution was stirred at rt for 30 min, then refluxed at 45 ºC overnight. The reaction mixture was then taken up in DI H_2O and ethyl acetate, and extracted three times. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, eluent: pure hexanes to 2:1 hexanes/ethyl acetate to 1:1) to afford compound **7a** (1.3 g, 5.57 mmol, 66% yield).

7a: 66% yield. Grey solid. **MP**: 108-111 ºC. **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.56-7.53 (m, 2H), 6.90-6.88 (m, 2H), 4.21 (d, J = 1.3 Hz, 2H), 3.97 (s, 3H), 3.80 (s, 3H), 1.88 (s, 3H). **^{13}C-NMR** (150 MHz; $CDCl_3$): δ 171.7, 164.2, 155.7, 132.8, 120.2, 114.2, 105.4, 57.4, 55.7, 55.5, 48.8. **HRMS** (EI) *m/z* calculated for $C_{13}H_{15}NO_3$ $[M]^+$ 233.1052, found 233.1056. **IR** (DCM) cm^{-1}: 2997, 2947, 2835, 1667, 1512, 1447, 1381, 1342, 1300, 1242. **TLC** R_f = 0.16 (2:1 hexanes/ethyl acetate).

7b: 64% yield. Light brown solid. **MP**: 147-152 ºC. **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.50 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.18 (s, 1H), 4.24 (s, 2H), 3.84 (s, 3H), 3.79 (s, 3H). **^{13}C-NMR** (150 MHz; $CDCl_3$): δ 172.4, 170.5, 155.9, 132.4, 120.7, 114.2, 95.4,

58.2, 55.5, 51.2. **HRMS** (EI) *m/z* calculated for $C_{12}H_{13}NO_3$ $[M]^+$ 219.0895, found 219.0892. **IR** (DCM) cm^{-1}: 3117, 2936, 2835, 1682, 1636, 1454, 1354 1250, 1204, 1146. **TLC** R_f = 0.35 (2:1 ethyl acetate/hexanes).

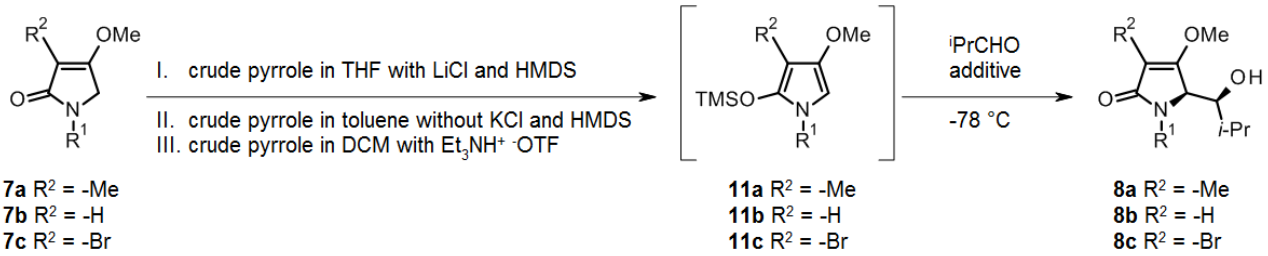


7b **7c**

To a flask containing compound **7b** (234.1 mg, 1.07 mmol, 1.0 equiv) in benzene (12 mL, 0.09 M) was added bromine (61 µL, 1.17 mmol, 1.1 equiv). The flask was capped with a septum and stirred for 3h. The solution was quenched with $Na_2S_2O_3$ and extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, eluent: pure hexanes to 1:1 hexanes/ethyl acetate) to afford compound **7c** (305.6 mg, 1.03 mmol, 96% yield)

7c: 96% yield. Tan solid. **MP**: 148-154 ºC. **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.51 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 4.32 (s, 2H), 4.16 (s, 3H), 3.80 (s, 3H). **^{13}C-NMR** (150 MHz; $CDCl_3$): δ 165.9, 165.2, 156.3, 131.9, 120.7, 114.3, 87.3, 58.4, 55.5, 50.5. **HRMS** (EI) *m/z* calculated for $C_{12}H_{12}BrNO_3$ $[M]^+$ 297.0001, found 297.0010. **IR** (DCM) cm^{-1}: 2997, 2951, 2835, 1686, 1651, 1512, 1443, 1389, 1335, 1246. **TLC** R_f = 0.37 (1:1 hexanes/ethyl acetate).

C. Silylation Protocols



7a R^2 = -Me
7b R^2 = -H
7c R^2 = -Br

11a R^2 = -Me
11b R^2 = -H
11c R^2 = -Br

8a R^2 = -Me
8b R^2 = -H
8c R^2 = -Br

Protocol I:

To a vial containing tetramic acid **7** (1.0 equiv) in THF (0.1M) was added LHMDS (0.7 M in toluene, 1.3 equiv) at -78 °C, and was stirred for 30 min. TMSCl (1.4 equiv) was then added and the solution was stirred for an additional 25 min. Isobutyraldehyde (2.0 equiv) was then added, followed by $SnCl_4$ (2.0 or 0.2 equiv). It was stirred for 30 min at -78 °C and was quenched with 1M NH_4Cl, during which the solution became frozen. The solution was warmed to rt, then extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by column chromatography (pure hexanes to 1:1 hexanes/ethyl acetate) to obtain tetramic acid aldol adduct **8**.

Protocol II:

A 10-mL Schlenk flask was charged with a stir bar and flame-dried under an inert atmosphere. The tetramic acid **7** (1.0 equiv) was added to the flask and diluted in dry THF (0.1 M). The resultant mixture was cooled to -78 °C. After cooling, KHMDS (0.9 M in THF, 1.4 equiv) was added via syringe followed by addition of freshly distilled TMSCl (2.0 equiv). Upon deprotonation, a slight color change was observed and lightened upon addition

of the silyl protecting group. The reaction mixture was stirred at -78 °C for 10 minutes and then concentrated *in vacuo* to obtain the highly reactive diene **11**[1].

The diene contained in the 10-mL Schlenk flask was suspended in toluene (0.1 M) and cooled to -78 °C. Isobutyraldehyde (2.0 equiv) was added to the reaction flask, followed by $SnCl_4$ (2 or 0.2 equiv) and stirred at -78 °C for 30 minutes. After this time, the reaction was quenched with saturated NH_4Cl at -78 °C. The solution was extracted three times with ethyl acetate and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixtures were doped with a standard and crude yields were determined by ^{1}H-NMR integration.

11a: **^{1}H-NMR** (600 MHz, C_6D_6): δ 7.28 (d, J = 9 Hz, 2H), 6.75 (d, J = 9 Hz, 2H), 5.89 (s, 3H), 3.52 (s, 3H), 3.28 (s, 3H), 2.22 (s, 3H), -0.03(s, 9H).

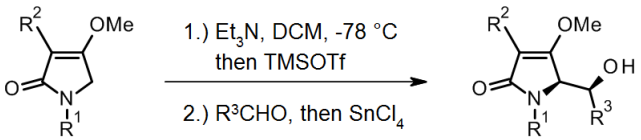
11b: **^{1}H-NMR** (400 MHz, C_6D_6): δ 7.38 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.06 (d, *J* = 2 Hz, 1H), 5.64 (d, *J* = 5.20 Hz, 1H), 3.61 (s, 3H), 3.36 (s, 3H), 0.12 (s, 9H).

11c: **^{1}H-NMR** (500 MHz, C_6D_6): δ 7.11 (d, *J* = 9.0 Hz, 2H), 6.67 (d, *J* = 9.0 Hz, 2H), 5.77 (s, 1H), 3.40 (s, 3H), 3.24 (s, 3H), 0.05 (s, 9H).

Protocol III: See *Diastereoselective Aldol Reaction Scope*.

[1] To obtain diene spectra, residual solvent was removed on a lyophilizer and the resultant reactive intermediate was diluted in d_6-benzene to obtain a ^{1}H NMR spectrum. The spectra often contain residual tetramic acid starting material for the TMS- dienes due to their reactivity. TBS- and TIPS- dienes were also prepared (not included here) which proved to be a bit more stable and produced clean spectra.

D. Diastereoselective Catalytic Aldol Reaction Scope



7a R^2 = -Me
7b R^2 = -H
7c R^2 = -Br

8a-c, **12-22**

To a vial was added tetramic acid **7a** (30 mg, 0.129 mmol, 1.0 equiv) in DCM (1.5 mL, ~1.0 M). The vial was sealed with parafilm, placed under N_2, and cooled to -78 °C. Et_3N (24 µL, 0.17 mmol, 1.3 equiv) was added at -78 ºC and stirred for 10 min. TMSOTf (27 µL, 0.15 mmol, 1.2 equiv) was then added and the reaction solution was stirred for an additional 20 min. Isobutyraldehyde (24 µL, 0.26 mmol, 2.0 equiv) was then added followed by immediate addition of $SnCl_4$ (3 µL, 0.03 mmol, 0.2 equiv). The solution was stirred for 30 min at -78 ºC. After 30 min, the reaction was quenched with 1.5 mL of 1 M NH_4Cl, during which the solution became frozen. The reaction mixture was warmed to rt, then taken up in DI H_2O and DCM. The solution was extracted two times with DCM and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, eluent: pure hexanes to 2:1 ethyl acetate/hexanes to 4:1) to afford compound **8a** as a 14:1 mixture of diastereomers (33 mg, 0.108 mmol, 84% yield).

8a: 84% yield, 14:1 dr. White-yellow solid. **MP**: 129-132 ºC. **^{1}H-NMR** (500 MHz; $CDCl_3$): δ 7.25-7.23 (m, 2H), 6.90-6.88 (m, 2H), 4.61 (d, J = 1.1 Hz, 1H), 4.11 (s, 3H), 3.80 (s, 3H), 3.48 (dd, J = 7.9, 2.4 Hz, 1H), 2.05 (d, J = 4.2 Hz, 3H), 1.42 (dt, J = 14.4, 6.7 Hz, 1H), 0.87 (t, J = 6.8 Hz, 3H), 0.73 (d, J = 6.7 Hz, 3H). **^{13}C-NMR** (150 MHz; $CDCl_3$): δ 172.6, 166.5, 157.4, 130.4, 125.8, 114.3, 103.7, 75.6, 62.5, 58.9, 55.4, 30.3, 19.6, 19.1, 8.6. **HRMS** (EI) *m/z* calculated for $C_{17}H_{23}NO_4$ $[M]^+$ 305.1627, found 305.1624. **IR** (neat) cm^{-1}:

3406, 2955, 2928, 2870, 1659, 1512, 1451, 1384, 1331, 1246. **TLC** R_f = 0.27 (2:1 ethyl acetate/hexanes).

8b: 85% yield, 3:1 dr (inseparable). Yellow oil. **HRMS** (EI) *m/z* calculated for $C_{16}H_{21}NO_4$ $[M]^+$ 291.1471, found 291.1478. **IR** (neat) cm^{-1}: 3306, 2959, 2940, 1670, 1632, 1512, 1443, 1354, 1246, 1150. **TLC** R_f = 0.12 (3:1 ethyl acetate/hexanes).

8c: 91% yield, >20:1 dr. Yellow oil. **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.23 (d, *J* = 8.3 Hz, 2H), 6.90 (d, *J* = 8.2 Hz, 2H), 4.70 (s, 1H), 4.34 (s, 3H), 3.80 (s, 3H), 3.50 (d, *J* = 8.2 Hz, 1H), 1.70 (d, *J* = 9.41 Hz, 1H) 1.40 (dt, *J* = 13.7, 6.8 Hz, 1H), 0.87 (d, *J* = 6.5 Hz, 3H), 0.74 (d, *J* = 6.6 Hz, 3H). **^{13}C-NMR** (150 MHz; $CDCl_3$): δ 167.2, 157.9, 129.8, 126.1, 114.4, 85.6, 75.8, 64.4, 59.7, 55.4, 30.3, 19.5, 19.2. **HRMS** (EI) *m/z* calculated for $C_{16}H_{20}BrNO_4$ $[M]^+$ 369.0576, found 369.0575. **IR** (neat) cm^{-1}: 3402, 2955, 2870, 1686, 1636, 1512, 1443, 1397, 1300, 1246. **TLC** R_f = 0.19 (1:1 hexanes/ethyl acetate).

12: 60% yield, >20:1 dr. Yellow oil. **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 5.24 (s, 1H), 4.87 (d, *J* = 2.7 Hz, 1H), 3.87 (s, 3H), 3.80 (s, 3H), 3.68 (d, *J* = 2.7 Hz, 1H), 0.80 (s, 9H). **^{13}C-NMR** (150 MHz; $CDCl_3$): δ 175.8, 170.8, 157.0, 130.2, 125.0, 114.2, 94.9, 76.7, 63.8, 58.3, 55.4, 35.9, 26.6. **HRMS** (EI) *m/z* calculated for $C_{17}H_{23}NO_4$ $[M]^+$ 305.1627, found 305.1624. **IR** (neat) cm^{-1}: 3368, 2955, 2916, 2870, 1670, 1624, 1512, 1443, 1362, 1246. **TLC** R_f = 0.15 (3:1 ethyl acetate/hexanes).

13: 66% yield, >20:1 dr. Yellow oil. **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.28 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 4.82 (d, *J* = 2.8 Hz, 1H), 4.35 (s, 3H), 3.80 (s, 3H), 3.66 (d,

J = 2.7 Hz, 1H), 0.80 (s, 9H). **^{13}C-NMR** (150 MHz; $CDCl_3$): δ 167.6, 166.5, 157.2, 129.8, 124.7, 114.3, 85.3, 77.0, 64.3, 59.6, 55.4, 35.9, 26.7. **HRMS** (EI) *m/z* calculated for $C_{17}H_{22}BrNO_4$ $[M]^+$ 383.0732, found 383.0730. **IR** (neat) cm^{-1}: 3449, 2955, 2909, 1686, 1632, 1512, 1397, 1300, 1250, 1049. **TLC** R_f = 0.40 (1:1 hexanes/ethyl acetate).

14: 62% yield, >20:1 dr. Yellow oil. **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.30-7.28 (m, 2H), 6.90-6.89 (m, 2H), 4.71 (dd, *J* = 2.9, 1.1 Hz, 1H), 4.12 (s, 3H), 3.79 (d, *J* = 3.7 Hz, 3H), 3.65 (d, *J* = 3.0 Hz, 1H), 2.05 (d, *J* = 0.8 Hz, 3H), 0.79 (s, 9H). **^{13}C-NMR** (150 MHz; $CDCl_3$): δ 172.1, 167.0, 156.7, 130.5, 124.4, 114.2, 103.1, 76.7, 62.3, 58.8, 55.4, 35.9, 26.7, 8.7. **HRMS** (EI) *m/z* calculated for $C_{18}H_{25}NO_4$ $[M]^+$ 319.1784, found 319.1778. **IR** (neat) cm^{-1}: 3399, 2955, 1659, 1512, 1454, 1385, 1362, 1327, 1300, 1246. **TLC** R_f = 0.31 (2:1 ethyl acetate/hexanes).

15: 74% yield, >20:1 dr. Colorless oil. **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.25 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 4.62 (s, 1H), 4.11 (s, 3H), 3.80 (s, 3H), 3.78 (d, *J* = 2.4 Hz, 1H), 2.05 (s, 3H), 1.42-1.36 (m, 1H), 1.28-1.11 (m, 3H), 1.06-1.01 (m, 1H), 0.77 (t, J = 6.9 Hz, 3H), 0.54 (t, J = 7.4 Hz, 3H). **^{13}C-NMR** (150 MHz; $CDCl_3$): δ 172.6, 166.6, 157.2, 130.4, 125.5, 114.2, 103.8, 72.0, 62.3, 58.9, 55.4, 41.3, 22.0, 20.6, 10.57, 10.43, 8.6. **HRMS** (EI) *m/z* calculated for $C_{19}H_{27}NO_4$ $[M]^+$ 333.1940, found 333.1935. **IR** (neat) cm^{-1}: 3418, 3063, 2959, 2874, 1659, 1512, 1462, 1385, 1331, 1246. **TLC** R_f = 0.25 (2:1 ethyl acetate/hexanes).

16: 74% yield, >20:1 dr. Yellow oil. **^{1}H-NMR** (600 MHz; CDCl3): δ 7.23 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 4.61 (s, 1H), 4.11 (s, 3H), 3.80 (s, 3H), 3.52 (d, *J* = 7.9 Hz,

1H), 2.04 (s, 3H), 1.82 (d, *J* = 12.4 Hz, 1H), 1.65 (d, *J* = 6.5 Hz, 1H), 1.57-1.53 (m, 2H), 1.42 (s, 1H), 1.07-1.00 (m, 3H), 0.92-0.87 (m, 3H). **^{13}C-NMR** (150 MHz; $CDCl_3$): δ 172.7, 166.6, 157.4, 130.4, 125.9, 114.2, 103.7, 74.5, 62.1, 58.9, 55.5, 39.9, 29.7, 29.2, 26.1, 25.77, 25.69, 8.6. **HRMS** (EI) *m/z* calculated for $C_{20}H_{27}NO_4$ $[M]^+$ 345.1940, found 345.1940. **IR** (neat) cm^{-1}: 3391, 2924, 2851, 1659, 1512, 1451, 1385, 1331, 1246, 1103. **TLC** R_f = 0.25 (3:1 ethyl acetate/hexanes).

17: 80% yield, 11:1 dr. Yellow oil. **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.22 (d, *J* = 8.3 Hz, 2H), 6.85 (d, *J* = 8.3 Hz, 2H), 6.20 (s, 1H), 5.95 (d, *J* = 2.2 Hz, 1H), 4.93 (s, 1H), 4.77 (s, 1H), 4.13 (s, 3H), 3.96 (s, 1H), 3.79 (d, *J* = 0.3 Hz, 3H), 1.94 (s, 3H). **^{13}C-NMR** (150 MHz; $CDCl_3$): δ 171.6, 165.4, 156.9, 151.4, 142.0, 129.5, 124.6, 114.2, 110.3, 107.4, 104.1, 67.5, 62.7, 59.1, 55.4, 8.5. **HRMS** (EI) *m/z* calculated for $C_{18}H_{19}NO_5$ $[M]^+$ 329.1263, found 329.1267. **IR** (neat) cm^{-1}: 3364, 2997, 2951, 1659, 1512, 1450, 1385, 1335, 1246, 1103. **TLC** R_f = 0.24 (2:1 ethyl acetate/hexanes).

18: 70% yield, 7:1 dr. Colorless oil. **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.33 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 6.7 Hz, 3H), 7.01 (d, *J* = 6.5 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.01 (d, *J* = 2.0 Hz, 1H), 4.83 (s, 1H), 4.06 (s, 3H), 3.81 (s, 3H), 1.80 (s, 3H). **^{13}C-NMR** (150 MHz; $CDCl_3$): δ 171.2, 164.9, 156.4, 138.3, 130.0, 127.84, 127.75, 125.5, 123.6, 114.3, 104.7, 72.3, 63.6, 59.0, 55.5, 8.2. **HRMS** (EI) *m/z* calculated for $C_{20}H_{21}NO_4$ $[M]^+$ 339.1471, found 339.1476. **IR** (neat) cm^{-1}: 3360, 2920, 2851, 1713, 1659, 1512, 1454, 1389, 1250, 1180. **TLC** R_f = 0.20 (1:1 hexanes/ethyl acetate).

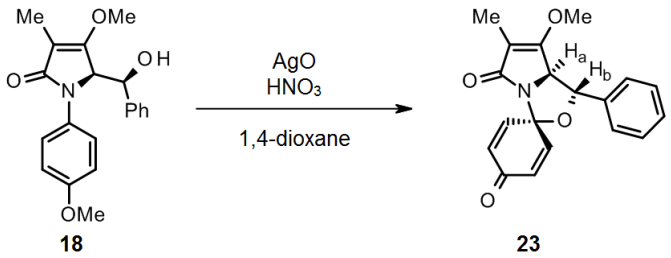
19: 81% yield, 2:1 dr (inseparable). Yellow oil. **HRMS** (EI) *m/z* calculated for $C_{17}H_{23}NO_4$ $[M]^+$ 305.1627, found 305.1619. **IR** (neat) cm^{-1}: 3391, 2932, 2870, 1659, 1613, 1512, 1454, 1335, 1246, 1180. **TLC** R_f = 0.27 (2:1 ethyl acetate/hexanes).

20: 83% yield, 2.5:1 dr (inseparable). Yellow oil. **HRMS** (EI) *m/z* calculated for $C_{16}H_{20}BrNO_4$ $[M]^+$ 369.0576, found 369.0575. **IR** (neat) cm^{-1}: 3444, 3163, 3048, 2955, 1682, 1632, 1512, 1400, 1246, 1161. **TLC** R_f = 0.26 (1:1 hexanes/ethyl acetate).

21: 78% yield, 4:1:0:0 dr (inseparable). White oil. **HRMS** (EI) *m/z* calculated for $C_{22}H_{25}NO_4Na$ $[M + Na]^+$ 390.1676, found 390.1694. **IR** (neat) cm^{-1}: 2997, 2959, 2874, 1659, 1512, 1450, 1385, 1335, 1246, 1107. **TLC** R_f = 0.22 (2:1 ethyl acetate/hexanes).

22: 80% yield, >20:1:0:0 dr. White oil. **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.20 (dq, *J* = 15.3, 7.5 Hz, 3H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 7.2 Hz, 2H), 4.43 (s, 1H), 4.34 (s, 3H), 4.10 (t, *J* = 9.4 Hz, 1H), 3.84 (s, 3H), 2.48 (dd, *J* = 9.6, 7.0 Hz, 1H), 2.01 (d, *J* = 9.6 Hz, 1H), 1.22 (d, *J* = 6.8 Hz, 3H). **^{13}C-NMR** (150 MHz; $CDCl_3$): δ 167.5, 167.0, 158.1, 143.0, 129.9, 128.6, 127.5, 126.85, 126.69, 114.3, 85.8, 74.3, 64.3, 59.7, 55.5, 43.1, 20.4. **HRMS** (EI) *m/z* calculated for $C_{21}H_{22}BrNO_4Na$ $[M + Na]^+$ 454.0624, found 454.0613. **IR** (neat) cm^{-1}: 3406, 3028, 2955, 2932, 1686, 1636, 1512, 1454, 1300, 1246. **TLC** R_f = 0.25 (1:1 hexanes/ethyl acetate).

E. Unexpected Spirocyclicaminal Synthesis[2]



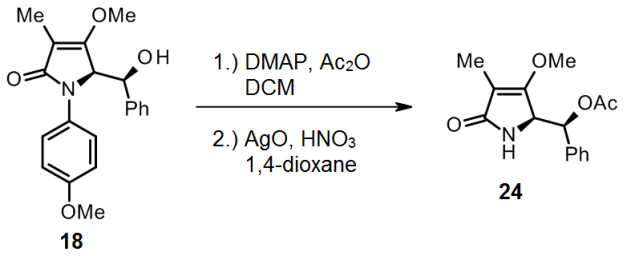
18 **23**

To a flask containing compound **18** (60.5 mg, 0.18 mmol, 1.0 equiv) in 1,4-dioxane (4.4 mL, 0.04 M) was added AgO (132 mg, 1.07 mmol, 6.0 equiv), followed by 6M HNO_3 (0.27 mL, 1.6 mmol, 9.0 equiv). After stirring for 10 min, the solution was quenched with DI H_2O and extracted two times with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, eluent: pure hexanes to 1:1 hexanes/ethyl acetate) to afford compound **23** (51.9 mg, 0.16 mmol, 91% yield).

23: 91% yield. Yellow oil. **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.46 (d, *J* = 7.5 Hz, 2H), 7.43-7.37 (m, 3H), 6.79 (dd, *J* = 10.2, 3.0 Hz, 1H), 6.74 (dd, *J* = 10.0, 3.0 Hz, 1H), 6.36 (dd, *J* = 10.2, 1.9 Hz, 1H), 6.24 (dd, *J* = 10.0, 1.9 Hz, 1H), 4.74 (d, *J* = 8.4 Hz, 1H), 4.41 (d, *J* = 8.4 Hz, 1H), 3.83 (s, 3H), 1.92 (s, 3H). **^{13}C-NMR** (150 MHz; $CDCl_3$): δ 185.0, 174.1, 167.7, 144.4, 142.3, 135.7, 129.7, 129.2, 128.9, 128.2, 126.8, 105.9, 83.8, 81.3, 68.3, 59.0, 8.0. **HRMS** (EI) *m/z* calculated for $C_{19}H_{17}NO_4Na$ $[M]^+$ 346.1050, found 346.1052. **IR** (neat) cm^{-1}: 3055, 2920, 2855, 1701, 1655, 1454, 1389, 1327, 1265, 1196. **TLC** R_f = 0.28 (1:1 hexanes/ethyl acetate).

[2](a) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227. (b) Bai, W.-J.; Green, J. C.; Pettus, T. R. R. *J. Org. Chem.* **2012**, *77*, 379.

F. Tetramic Acid Aldol Adduct Deprotection



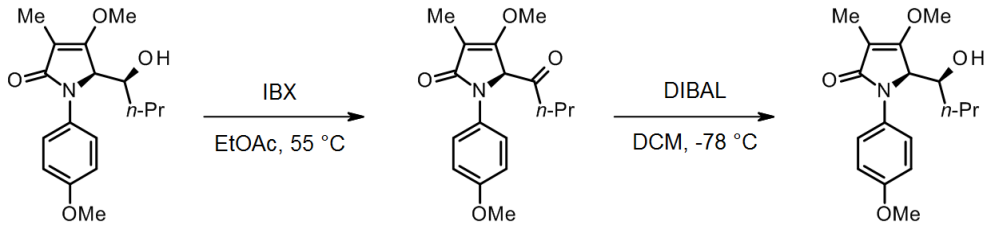
To a flask containing adduct **18** (26.8 mg, 0.08 mmol, 1.0 equiv) in DCM (4 mL, 0.02 M) was added DMAP (29 mg, 0.24 mmol, 3.0 equiv), followed by Ac_2O (22 μL, 0.24 mmol, 3.0 equiv). The reaction mixture was stirred under N_2 for 3h. The solution was quenched with 1 M HCl, and diluted with DI H_2O. The resultant solution was extracted three times with DCM and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography (SiO_2, eluent: pure hexanes to 2:1 hexanes/ethyl acetate) to afford acylated aldol adduct that was used without further purification.

To a flask containing the acylated intermediate (30.1 mg, 0.08 mmol, 1.0 equiv) in 1,4-dioxane (1.95 mL, 0.04 M) was added AgO (58 mg, 0.47 mmol, 6.0 equiv), followed by 6M HNO_3 (0.12 mL, 0.71 mmol, 9.0 equiv). After stirring for 5 min, the reaction mixture was quenched with DI H_2O and extracted two times with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Crude was purified by column chromatography (SiO_2, eluent: pure hexanes to 2:1 ethyl acetate/hexanes to afford compound **24** (18.0 mg, 0.065 mmol, 82% yield over two steps).

24: 82% yield over 2 steps. Pink oil. **^{1}H-NMR** (500 MHz; $CDCl_3$): δ 7.39-7.36 (m, 2H), 7.33-7.30 (m, 3H), 6.03 (d, *J* = 3.1 Hz, 1H), 5.52-5.51 (m, 1H), 4.13 (dd, *J* = 3.1, 0.9 Hz, 1H), 3.99 (s, 3H), 1.96 (d, *J* = 0.7 Hz, 3H). **^{13}C-NMR** (150 MHz; $CDCl_3$): δ 175.4, 169.4,

165.9, 137.2, 128.8, 128.5, 126.0, 104.1, 72.5, 60.7, 58.7, 20.8, 8.0. **HRMS** (EI) *m/z* calculated for $C_{15}H_{17}NO_4Na$ $[M + Na]^+$ 298.1050, found 298.1043. **IR** (neat) cm^{-1}: 3071, 2928, 2859, 1743, 1690, 1663, 1450, 1331, 1234, 1030. **TLC** R_f = 0.25 (2:1 ethyl acetate/hexanes).

G. IBX Oxidation-DIBAL Reduction Sequence

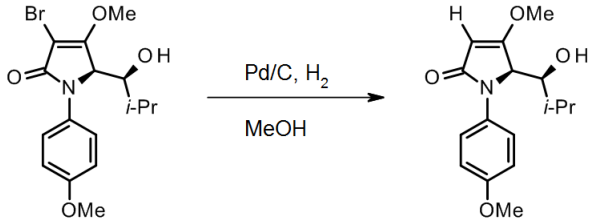


19 (2:1 dr) **19** (12:1 dr)

To a flask containing **19** (2:1 dr) (7.9 mg, 0.026 mmol, 1.0 equiv) in EtOAc (0.2 mL, 0.15 M) was added IBX (22 mg, 0.078 mmol, 3.0 equiv). The reaction mixture was stirred at 55 °C for 5h. The solution was taken up in DI H_2O and extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was used without further purification.

To a vial containing the ketone (7.6 mg, 0.025 mmol, 1.0 equiv) in DCM (0.3 mL, 0.1 M) was added 1M DIBAL (38 μL, 0.038 mmol, 1.5 equiv) at -78 °C under N_2. The reaction mixture was stirred at -78 °C for 1h, then diluted with Et_2O. 1 drop of H_2O was added to the solution, then cooled to 0 °C. A few drops of 1N NaOH were then added, followed by DI H_2O. The resulting solution was warmed to rt over 15 min, then $MgSO_4$ was added and stirred for an additional 10 min. The reaction solution was filtered through celite, and the crude product was purified by preparative TLC (SiO_2, eluent: 2:1 ethyl acetate/hexanes) to afford **19** as a 12:1 mixture of diastereomers (80% yield over 2 steps). **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.28 (d, J = 8.9 Hz, 2H), 6.90 (d, J = 8.9 Hz, 2H), 4.55 (d, J = 1.6 Hz, 1H), 4.14 (s, 3H), 3.80 (s, 3H), 3.76 (d, J = 0.3 Hz, 1H), 1.99 (d, J = 10.6 Hz, 1H), 1.49-1.44 (m, 1H), 1.21-1.17 (m, 1H), 1.11-1.07 (m, 1H), 0.90-0.87 (m, 1H), 0.77 (t, J = 7.2 Hz, 3H). The rest of the characteristic data is same as before.

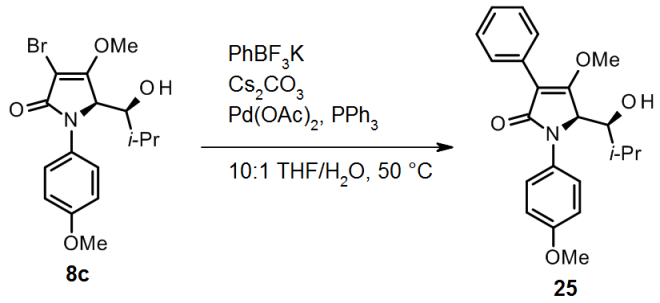
H. Hydrogenolysis of C3-Bromo Tetramic Acid Aldol Adduct



8c (>20:1 dr) **8b** (>20:1 dr)

To a vial containing compound **8c** (>20:1 dr, 5 mg, 0.014 mmol, 1.0 equiv) in EtOH (0.14 mL, 0.1 M) was added 10% Pd/C (1 mg, 0.0014 mmol, 0.1 equiv). The solution was stirred under H_2 (balloon) for 2h. After 2h, the solution was filtered through celite to afford the crude residue. The crude product was purified by preparative TLC (SiO_2, eluent: 1:1 hexanes/ethyl acetate) to afford compound **8b** as a >20:1 mixture of diastereomers (3.7 mg, 0.013 mmol, 95% yield). **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.24 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 5.24 (s, 1H), 4.77 (d, J = 1.9 Hz, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.53-3.50 (m, 1H), 1.78 (d, J = 9.9 Hz, 1H), 1.45 (dd, J = 14.0, 6.8 Hz, 1H), 0.87 (d, J = 6.6 Hz, 3H), 0.76 (d, J = 6.7 Hz, 3H). The rest of the characteristic data is same as before.

I. Palladium-Mediated sp^2-sp^2 Coupling[3]



To a reaction threaded vial was added adduct **8c** (40 mg, 0.11 mmol, 1.0 equiv), $PhBF_3K$ (59 mg, 0.32 mmol, 3.0 equiv), Cs_2CO_3 (101 mg, 0.31 mmol, 2.9 equiv), $Pd(OAc)_2$ (6 mg, 0.027 mmol, 0.25 equiv), and PPh_3 (14 mg, 0.054 mmol, 0.50 equiv). The reaction tube was sealed with a rubber septum, wrapped with parafilm, and purged with N_2. A degassed THF/H_2O (10:1) solution (1.6 mL, 0.07 M) was then added to the reaction mixture. The septum was then replaced with a screw cap, and the reaction solution was stirred for 2 minutes at rt. The reaction mixture was then heated at 50 °C for 3h. After 3h, the solution was taken up in DI H_2O and extracted three times with ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by preparative TLC (SiO_2, eluent: 1:1 hexanes/ethyl acetate) to afford compound **25** (61% yield; 90% brsm).

25: 61% yield; 90% yield (brsm). Yellow oil. **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.44 (d, *J* = 7.1 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.7 Hz, 3H), 6.92 (t, *J* = 6.1 Hz, 2H), 4.83 (d, *J* = 2.4 Hz, 1H), 3.81 (s, 3H), 3.75 (s, 3H), 3.61 (s, 1H), 1.96 (d, *J* = 9.8 Hz, 1H), 1.55 (dd, *J* = 13.9, 6.9 Hz, 1H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H). **^{13}C-NMR** (150 MHz; $CDCl_3$): δ 170.7, 167.5, 157.4, 130.8, 130.5, 130.16, 130.12, 127.87, 127.74, 125.6,

[3]Molander, G. A.; Felix, L. A. *J. Org. Chem.* **2005**, *70*, 3950.

114.3, 75.7, 62.5, 60.5, 55.4, 30.4, 19.7, 19.1. **HRMS** (EI) *m/z* calculated for $C_{22}H_{25}NO_4$ $[M]^+$ 367.1784, found 367.1791. **IR** (neat) cm^{-1}: 3410, 3066, 2951, 2870, 1659, 1512, 1397, 1354, 1246, 1053. **TLC** R_f = 0.19 (2:1 hexanes/ethyl acetate).

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