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

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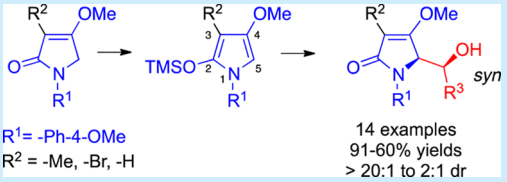
Supporting Information

**ABSTRACT:** A catalytic diastereoselective aldol reaction has been developed for *N*1-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 *N*1-aryl residue undergoes oxidative cleavage, and the C3-bromine atom undergoes palladium-mediated coupling reactions, both without disturbing the newly created stereocenters.




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 1).

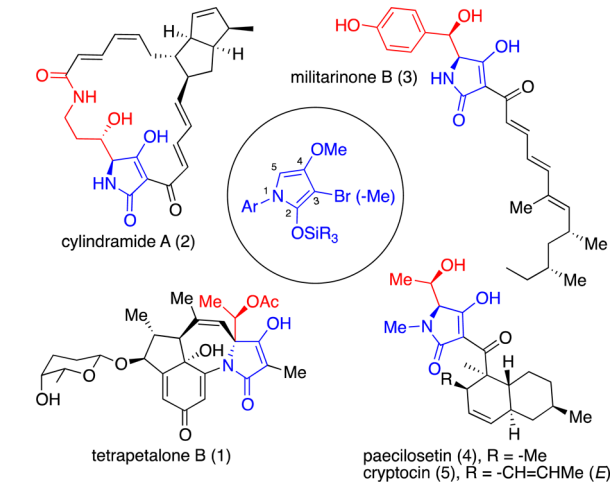



**Figure 1.** Some natural products containing tetramic acid aldolate motifs; varying tautomeric forms including those depicted.

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, sterics, selectivity, and chemistry surrounding the neighboring C5 atoms far more so than for their corresponding *des*-C4-methoxy counterparts.[6] Our analysis of 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 *N*1-benzylated/C2-*O*-silylated/C4-*O*-methylated pyrrole in combination with a chiral $\alpha$-alkoxy aldehyde and observed an *anti*-aldolate,[7] whereas Stachel employed an *N*1-benzylated/C2-*O*-lithiated/C4-*O*-methylated pyrrole with an $\alpha$-alkoxy aldehyde and observed a *syn*-aldolate.[8] We speculated that an *N*1-aryl residue might prove sterically smaller than the customary *N*1-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]

We prepared the desired starting compounds by employing the Jones' protocol (Figure 2).[10] The known $\gamma$-bromo

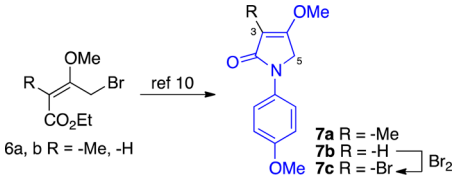



**Figure 2.** Jones' 1986 procedure for preparation of tetramic acid derivatives adapted to prepare **7a**–**c**.

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.

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

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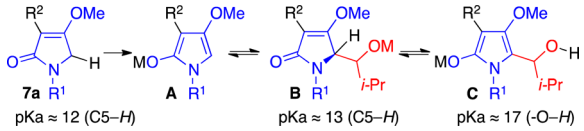
estimated the p$K_a$ of the C5 hydrogen in derivative **7a** to be between 12 and 16. Deprotonation of adduct **7a** with DBU followed by addition of isobutyraldehyde at ambient temperature failed to yield appreciable amounts of product (Table 1, entry 1). Similarly, deprotonation at −78 °C with LHMDS (1.3 equiv, 0.7 M in toluene) followed by the addition of isobutyraldehyde and 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).

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) 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 $SnCl_4$ (0.2 equiv) 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 ($BF_3$·

**Table 1. Enolate Outcomes of the *N*1-Ar Tetramic Acid Derivative 7a**




| entry | base | solvent | RCHO added | additive / workup | yield 8a or 9 | dr |
|---|---|---|---|---|---|---|
| 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 |

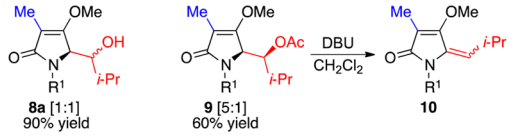
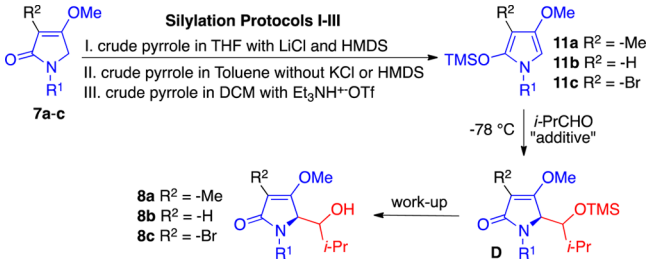
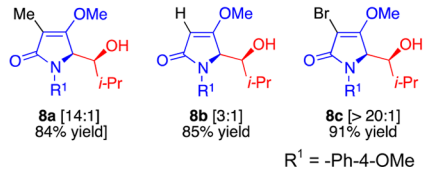



**Table 2. Aldol Reactions of Pyrroles 11a–c with Isobutyraldehyde**




| entry | sm | silylation protocol | primary solvent | Lewis acid (equiv) | yield (%) | product, dr |
|---|---|---|---|---|---|---|
| 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) | 84 | **8a**, 14:1 |
| 7 | **7a** | III | DCM | – | < 5 | **8a**, N/A |
| 8 | **7a** | III | DCM | TMSOTf (1) | 50 | **8a**, 1:1 |
| 9 | **7a** | III | DCM | $BF_3oEt_2O$ (2) | 72 | **8a**, 2:1 |
| 10 | **7a** | III | DCM | $TiCl_4$ (2) | 78 | **8a**, 3:1 |
| 11 | **7b** | III | DCM | $SnCl_4$ (0.2) | 85 | **8b**, 3:1 |
| 12 | **7c** | III | DCM | $SnCl_4$ (0.2) | 91 | **8c**, >20:1 |




[a]Isolated yield based on recovered starting material.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$Et_2O$) 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**].

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 3. In

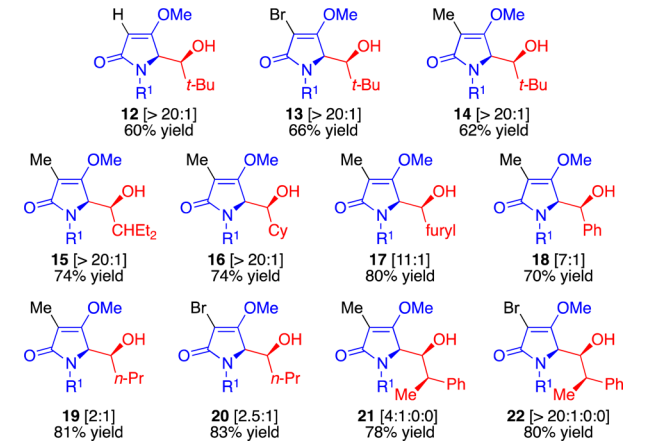



**Figure 3.** Range and scope examined for the reaction via protocol-III.

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 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.

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 4).[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

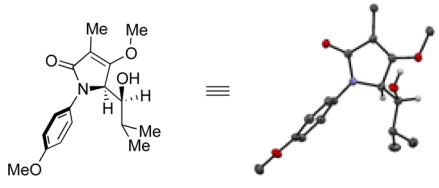


**Figure 4.** X-ray structure determined for major diastereomer of compound **8a** and found to be syn.

compared with the anti diastereomer in adducts arising from aliphatic aldehydes.

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 5). The *exo*

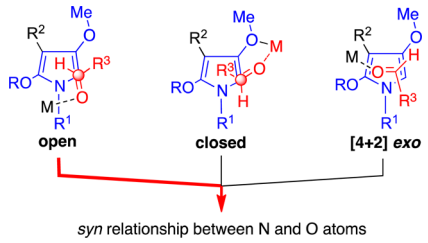
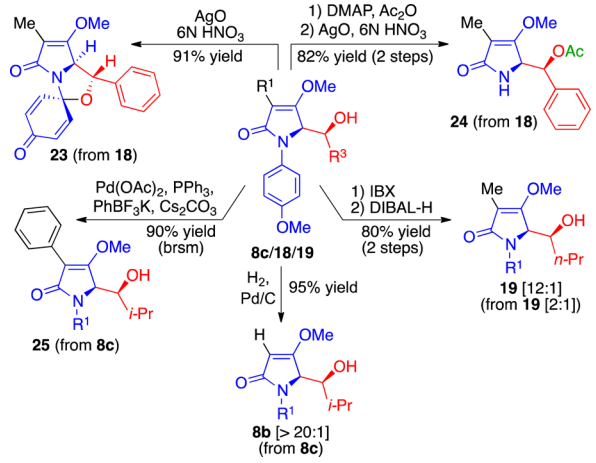



**Figure 5.** Three transition states leading to syn products.

[4 + 2] 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 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 (-*N*1-aryl) is sterically small, it can adopt coplanarity and increase the pyrrole's nucleophilicity and provide room for the coordinated metal atom (M).

These novel adducts participate in a number of other notable transformations (Scheme 1). For example, exposure of the

**Scheme 1. Some Reactivities of Aldol Adducts 8c, 18, and 19**




compound **18** to argentic oxide[15] (6 equiv 6 N $HNO_3$) 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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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.

In summary, 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−Br-substituted 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 *N*1-aryl residue, may be amenable to catalysis with chiral Lewis acids in future asymmetric regimes.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION


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### Notes

The authors declare no competing financial interest.

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