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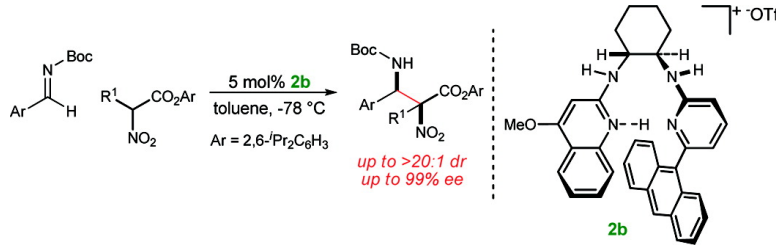


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# A Diastereo- and Enantioselective Synthesis of α-Substituted *syn*-α,*β*-Diamino Acids

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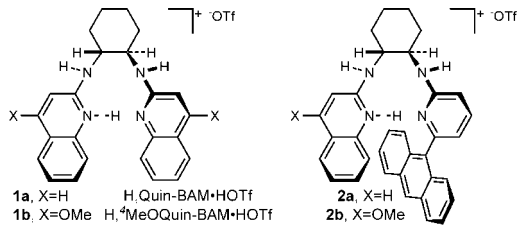
Nonproteinogenic tertiary (α-substituted) α-amino acids have generated broad interest for their use as enzyme-inhibitors,[1] helix-inducing peptide monomers, and robust analogues of natural amino acids.[2] α,*β*-Diamino acids have attracted interest for similar reasons.[3] These attributes have stimulated the development of methods for their synthesis, but few possess the brevity of C−C bond-forming reactions to create the α-substituted amino acid or *vic*-diamine substructures.[4–6] As an approach to α-substituted α,*β*-diamino acids, the use of α-substituted nitro acetates[7–9] is not complicated by postaddition epimerization[10] but demands a catalyst effective in activating this hindered pronucleophile. Additionally, only high levels of kinetically controlled diastereo- and enantioselection can render this approach as practical as it is straightforward. Shibasaki has just reported an *anti*-selective addition of α-substituted nitroacetates catalyzed by a bis(homometallic) chiral catalyst that provides an elegant solution to this problem.[11] We report equally stereoselective and direct access to the complementary *syn*-diastereomers, catalyzed by a (nonmetal) bifunctional chiral proton complex (**2b**).[12]

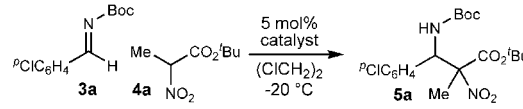
Our earliest attempts to promote addition of α-nitroacetates used *tert*-butyl ester **4a** with catalysts **1a** and **2a**. In contrast to the identical reaction employing the unsubstituted α-nitroacetate, these variations suffered from a low level of reactivity (Table 1, entries 1, 3), requiring days instead of hours to reach a high level of conversion (53% and 84%, respectively). When using methoxy-substituted catalyst **1b**, we noted a significant improvement in rate, reaching 87% conversion under otherwise identical conditions (entry 2). Enantioselection was enhanced slightly (63→73% ee), but diastereoselection was unchanged (2:1 dr). The accelerating effect of methoxy substitution transferred to the unsymmetrical ligand complex **2b**, but interestingly, addition of a single methoxy substituent in this system resulted in sufficient overall reaction rate, providing complete conversion in <48 h (91% isolated yield, entry 4). Some improvement (relative to **2a**) in enantioselection was observed as well (82→97% ee).




Reactivity and enantioselection clearly benefited by use of methoxy-substituted unsymmetrical catalyst **2b**, but throughout these studies, diastereoselection was ≤2:1. This contrasted the high diastereoselection observed in catalyzed additions of *unsubstituted* α-nitroacetates but was not unexpected when anticipating the effect of replacing an H for an alkyl group in the transition state. We hypothesized that this diminished the effective size difference between the alkyl and *tert*-butyl ester groups, leading to *syn*- and *anti*-transition states with similar energies. We therefore evaluated a series of ethyl-substituted α-nitroacetates **6** (Table 2), looking specifically at the potential effect of ester size on diastereo- and enantioselection. Small esters (Et/Ph, entries 1, 3) provided low diastereoselection similar to the *tert*-butyl ester (entry 2), but the latter two provided some enhancement of enantioselection: 73→88 and 97% ee. We investigated the hindered aryl ester **6d** and uncovered an improvement in diastereoselection (10:1, entry 5) while maintaining high enantioselection (94% ee) and reactivity (84% isolated yield). In these studies, we employed 1,2-dichloroethane, as it generally provides the most favorable and general solubility profile. However, dichloromethane provided additional effective temperature range (entries 6, 7) for improved stereoselection, whereas toluene provided slightly higher levels of diastereoselection and enantioselection (entry 8).

These experiments determined conditions for an initial evaluation of scope summarized in Table 3. Using α-nitro butanoate **6d** as a

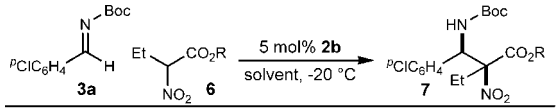
***Table 1.*** Catalyzed Additions of Substituted α-Nitro Esters to Azomethine: Effect of Catalyst Structure on Reactivity[a]




| entry | catalyst | %conversion (48 h) | dr[b] | %ee[b] | yield (%)[c] |
|---|---|---|---|---|---|
| 1 | **1a** | 53 | 2:1 | 63 | 44 |
| 2 | **1b** | 87 | 2:1 | 73 | 81 |
| 3 | **2a** | 84 | 2:1 | 82 | 76 |
| 4 | **2b** | >95 | 2:1 | 97 | 91 |

[a] Conversion approximated by $^1$H NMR. [b] Diastereomer ratios approximated by $^1$H NMR and confirmed by HPLC. Enantiomeric excess determined using HPLC and a chiral stationary phase. [c] Isolated yield.

***Table 2.*** Chiral Proton-Catalyzed Additions of α-Nitrobutanoate Esters to Azomethines: Influence of Ester on Diastereo- and Enantioselection[a]




| entry | R | | solvent | dr[b] | %ee[b] | yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | Et | **a** | $(CH_2Cl)_2$ | 2:1 | 73 | 92 |
| 2 | $^t$Bu | **b** | $(CH_2Cl)_2$ | 2:1 | 97 | 89 |
| 3 | Ph | **c** | $(CH_2Cl)_2$ | 2:1 | 88 | 81 |
| 4 | Ph | **c** | tol | 2:1 | 91 | 87 |
| 5 | 2,6-$^i$Pr$_2$C$_6$H$_3$ | **d** | $(CH_2Cl)_2$ | 10:1 | 94 | 84 |
| 6 | 2,6-$^i$Pr$_2$C$_6$H$_3$ | **d** | $CH_2Cl_2$ | 9:1 | 92 | 85 |
| 7[c] | 2,6-$^i$Pr$_2$C$_6$H$_3$ | **d** | $CH_2Cl_2$ | 11:1 | 93 | 88 |
| 8 | 2,6-$^i$Pr$_2$C$_6$H$_3$ | **d** | tol | 14:1 | 96 | 81 |

[a] All reactions are 0.3 M in imine and use 1.1 equiv of the nitro ester. [b] Diastereomer ratios measured using $^1$H NMR. Assignment of each major diastereomer as syn was made by chemical correlation to the common parent carboxylic acid. Enantiomer ratios measured using HPLC and a chiral stationary phase. [c] Reaction temperature −78 °C.


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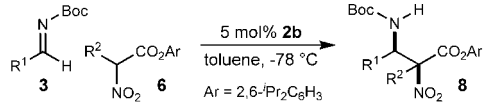
***Table 3.*** Chiral Proton-Catalyzed Additions of α-Alkyl α-Nitroesters to Azomethines: Reaction Scope[a]



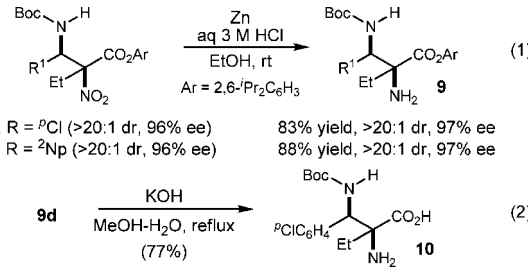

| entry | $R^1$ | $R^2$ | | dr[b] | %ee[b] | yield(%)[b] |
|---|---|---|---|---|---|---|
| 1 | $^{p}ClC_6H_4$ | Et (**6d**) | **7d** | >20:1 | 98 | 83 |
| 2 | $^{2}Np$ | Et | **8a** | >20:1 | 96 | 80 |
| 3 | $^{p}MeSC_6H_4$ | Et | **8b** | 13:1 | 98 | 81 |
| 4 | $^{p}PhSC_6H_4$ | Et | **8c** | 10:1 | 96 | 59 |
| 5[c] | $^{p}PhSC_6H_4$ | Et | **8c** | 8:1 | 96 | 83 |
| 6 | $^{p}MeC_6H_4$ | Et | **8e** | >20:1 | 97 | 61 |
| 7[c] | $^{p}MeC_6H_4$ | Et | **8e** | >20:1 | 96 | 80 |
| 8 | $^{p}MeOC_6H_4$ | Et | **8f** | 12:1 | 95 | 73 |
| 9 | $^{2}Furyl$ | Et | **8g** | 5:1 | 94 | 86 |
| 10 | $^{p}ClC_6H_4$ | Me (**6e**) | **8h** | 12:1 | 99 | 82 |
| 11 | $^{p}ClC_6H_4$ | $^{n}Pr$ (**6f**) | **8i** | 15:1 | 97 | 82 |
| 12[c] | $^{p}ClC_6H_4$ | $^{n}Bu$ (**6g**) | **8j** | 16:1 | 97 | 88 |

[a] All reactions are 1 M in imine and use 1.1 equiv of the nitro ester unless otherwise noted. Conversions of 82% and 71% for entries 1−2, respectively, at 24 h (approximated by $^1$H NMR). [b] Diastereomer ratios measured using $^1$H NMR. Enantiomer ratios measured using HPLC and a chiral stationary phase. Yields are for isolated, analytically pure product. [c] Reaction was 0.3 M in imine and was performed at −20 °C for entries 5, 12; −78 °C, 3.5 days reaction time for entry 7.

representative pronucleophile, a range of aromatic aldimines were used to target β-amino phenyl alanine derivatives **7d/8**. At the higher concentration and lower temperature used in this series, higher diastereoselection (20:1) and excellent enantioselection (98% ee) were observed for **7d** (83% yield, entry 1). This crystalline product was used to assign relative and absolute stereochemistry via single crystal X-ray diffraction. Interestingly, the *syn*-diastereomer is favored in these additions, *opposite* to that normally observed when using these catalysts with simple nitroalkanes[13] or α-nitro *tert*-butyl esters.[10] A survey of additional electronically neutral (entries 2, 6, 7) and rich aromatic aldimines (entries 3−9) revealed generally high diastereoselection (8→20:1) and enantioselection (94−98% ee). In one case, a sluggish reaction at −78 °C (entry 4) could be rectified by raising the reaction temperature to −20 °C, resulting in a slight drop in diastereoselection (10:1→8:1 dr, entry 5). In another case (entry 6), extension of the reaction time provided complete conversion and higher isolated yield (entry 7). The lowest diastereoselection (5:1 dr) was observed for the furyl aldimine, but enantioselection remained high (94% ee, entry 9). The catalyst tolerance to the nature of the α-alkyl group of the nitroester is also good. The behavior of chlorophenyl imine **3d** in the series **6e**, **6d**, **6f**, **6g** (entries 10, 1, 11, 12) led to the derived α,β-diamino esters with generally high diastereoselection (12−20:1 dr), enantioselection (97−99% ee), and isolated yield (>82%). The reaction for hexanoate **6g** was noticeably slower but could be carried out at −20 °C (entry 12) to deliver the desired product (16:1 dr, 97% ee) in good isolated yield (88%). We investigated two *N*-Boc imines derived from aliphatic aldehydes, but these imines decomposed under our standard reaction conditions.

The nitroester products could be easily reduced to the protected *syn*-α,β-diamines by zinc reduction in aq HCl-EtOH at room temperature (eq 1).[7] The diastereo- and enantiomeric excess were unchanged in the diamine products. The aryl ester could also be saponified to provide the free α-amino acid in 77% yield (eq 2).[14]

In summary, a direct synthesis of α-substituted *syn*-α,β-diamino acid derivatives of phenyl alanine has been developed. This required the development of catalyzed additions of substituted α-nitroesters, providing α-nitro-β-amino esters with high diastereo- and enantioselection. Key to this development is the finding that methoxy substitution in the catalyst leads to a more active bifunctional




system, and hindered aryl esters **6d**−**g** work synergistically with the catalyst to provide high diastereoselection; achiral catalysis (Hünig's base) of the same addition proceeds with low diastereoselection (<2:1 dr). The diamine functionality is readily unmasked as in eq 1. Further investigations of reaction scope and the reason for the *syn*-diastereoselection here that is complementary to the Shibasaki bis(nickel) catalyzed *anti*-additions are underway.[15]

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**Supporting Information Available:** Experimental and characterization data. This information is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) (a) Walsh, J. J.; Metzler, D. E.; Powell, D.; Jacobson, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 7136. (b) Schirlin, D.; Gerhart, F.; Hornsperger, J. M.; Hamon, M.; Wagner, J.; Jung, M. J. *J. Med. Chem.* **1988**, *31*, 30.
(2) Reviews on applications: (a) Sagan, S.; Karoyan, P.; Lequin, O.; Chassaing, G.; Lavielle, S *Curr. Med. Chem.* **2004**, *11*, 2799. (b) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580. (c) Kotti, S.; Timmons, C.; Li, G. G. *Chem Biol. Drug Des.* **2006**, *67*, 101. (d) Synthesis: Vogt, H.; Brase, S. *Org. Biomol. Chem.* **2007**, *5*, 406.
(3) Viso, A.; de la Pradilla, R. F.; Garcia, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167.
(4) Olefin diamination does not yet provide a solution: (a) Li, G.; Wei, H.-X.; Kim, S. H.; Carducci, M. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4277. (b) Muniz, K.; Iesato, A.; Nieger, M. *Chem.—Eur. J.* **2003**, *9*, 5581. (c) Muniz, K. *Chem. Soc. Rev.* **2004**, *33*, 166.
(5) Representative approaches to α-substituted α-amino acids: (a) O'Connor, S. J.; Liu, Z. *Synlett* **2003**, 2135. (b) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. *J. Am. Chem. Soc.* **2000**, *122*, 5228. (c) Jew, S. S.; Lee, Y. J.; Lee, J. H.; Myoung, J. K.; Jeong, B. S.; Lee, J. H.; Yoo, M. S.; Kim, M. J.; Choi, S. H.; Ku, J. M.; Park, H. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 2382. (d) Ma, B.; Parkinson, J. L.; Castle, S. L *Tetrahedron Lett.* **2007**, *48*, 2083.
(6) Representative syntheses of α,β-diamino acids: (a) Fondekar, K. P. P.; Volk, F. J.; Khaliq-uz-Zaman, S. M.; Bisel, P.; Frahm, A. W. *Tetrahedron: Asymmetry* **2002**, *13*, 2241. (b) Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jorgensen, K. A. *J. Org. Chem.* **2003**, *68*, 2583. (c) Davis, F. A.; Zhang, Y. F.; Qiu, H. *Org. Lett.* **2007**, *9*, 833.
(7) Moreau, B.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 18014.
(8) Li, H. M.; Wang, Y.; Tang, L.; Wu, F. H.; Liu, X. F.; Guo, C. Y.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105.
(9) Knudsen, K. R.; Jorgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 1362.
(10) Singh, A.; Yoder, R. A.; Shen, B.; Johnston, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 3466.
(11) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170.
(12) Selected reviews of chiral Brønsted acid catalysis and metal-free catalysis: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (c) Palomo, C.; Oiarbide, M.; Mielgo, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5442. (d) Petrini, M.; Torregiani, E. *Synthesis* **2007**, 159. (e) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (f) Gaunt, M. J.; Johansson, C. C. C.; McNally, A.; Vo, N. T. *Drug Discovery Today* **2007**, *12*, 8. (g) List, B.; Yang, J. W. *Science* **2006**, *313*, 1584. (h) Connon, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 3909.
(13) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418.
(14) Miyano, S.; Koike, N.; Hayashizaka, N.; Suzuki, T.; Hattori, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3034.
(15) Opposite, but complementary diastereoselection is observed for nitroalkane additions. For *anti*, ref 13; for *syn*: Handa, S.; Gnanadesikan, V.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 4900.

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