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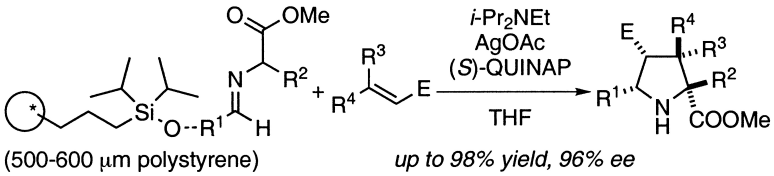
J. Am. Chem. Soc., **2003**, 125 (34), 10174-10175• DOI: 10.1021/ja036558z • Publication Date (Web): 05 August 2003



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Catalytic Asymmetric [3+2] Cycloaddition of Azomethine Ylides. Development of a Versatile Stepwise, Three-Component Reaction for Diversity-Oriented Synthesis

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We report a procedure that should enhance the use of enantioselective 1,3-dipolar cycloadditions of azomethine ylides[1] with electronic-deficient olefins in the divergent pathways of diversity-oriented synthesis (DOS).[2] The underlying reaction is of considerable interest in DOS because its stereospecificity enables stereochemical diversification of up to four tetrahedral centers on pyrrolidine rings.

The biological importance of pyrrolidines has inspired the development of diastereoselective [3+2] azomethine ylide cycloadditions using chiral auxiliaries[3] and, recently by Zhang and co-workers[4] and Jørgensen and co-workers,[5] of enantioselective variants using chiral catalysts.[6] Both Zhang's silver(I)/xylyl-FAP and Jørgensen's zinc(II)/*t*-BuBOX systems give moderate to excellent levels of stereoselectivity with imines derived from methyl glycinate.[7] We describe a new catalyst system that extends the scope and selectivity of the azomethine ylide cycloaddition and is compatible with reagents used in a one-bead/one-stock solution technology platform for DOS.[8]

Focusing on the silver(I)-catalyzed enantioselective cycloaddition developed by Zhang and co-workers, we aimed to identify a commercially available and general catalyst system capable of maximizing the number and directionality of pyrrolidine appendages. Six different chiral phosphines, each available in both enantiomeric forms, were examined in combination with silver(I) acetate (Figure 1). The reaction was initially explored by reacting methyl *N*-benzylideneglycinate (**7**), derived from benzaldehyde and methyl glycinate, with 1.5 equiv of *tert*-butyl acrylate (**8**) with 3 mol % catalyst loading. While the Trost ligands (**1** and **2**) gave low conversion at 4 °C, the other four ligands (**3**−**6**) showed excellent reactivity. With the exception of ligand **3**, the diastereoselectivity was in general high. Strikingly, the P,N-ligand QUINAP (**4**) showed excellent levels of both diastereo- and enantioselectivity, comparable to that reported by Zhang and co-workers.[4,9] The catalyst loading can be reduced to 1 mol % without deleterious effect. Pyrrolidine **9**, in this case the enantiomer of that available by the Zhang catalyst, was obtained in 84% yield and 91% ee after reacting at −45 °C for 40 h (Figure 2).

To explore the scope of the silver(I) acetate/QUINAP-catalyzed [3+2] azomethine ylide cycloaddition, we investigated α-iminoesters (**10**−**14**) derived from aromatic aldehydes with a variety of steric and electronic properties (Table 1). Under these conditions, the reaction showed excellent levels of diastereoselectivity (>20:1) and enantioselectivity (94−96% ee) regardless of the electronic property of the aromatic ring (entry 1−4), although the sterically hindered iminoester **14** resulted in slightly lower enantioselectivity (89% ee, entry 5).

We next examined the silver(I) acetate/QUINAP catalyst system with different dipolarophiles (Table 2). Dimethyl maleate (**20**) reacted with iminoester **7** even at −60 °C. However, pyrrolidine

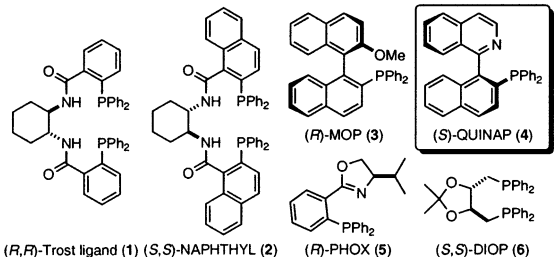


Figure 1. Chiral phosphine ligands screened for the azomethine ylide cycloadditions.

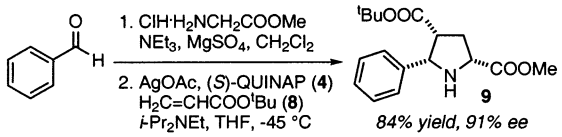
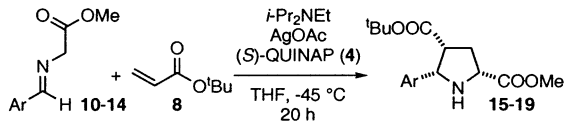


Figure 2. Silver(I)/(*S*)-QUINAP-catalyzed azomethine ylide cycloaddition.

Table 1. Exploration of the Reactivity of the Aromatic Moiety[a]



entry	Ar	pyrrolidine	yield[b]	ee[c]
1	4-methoxyphenyl (**10**)	**15**	93%	95%
2	4-bromophenyl (**11**)	**16**	89%	95%
3	4-cyanophenyl (**12**)	**17**	92%	96%
4	2-naphthyl (**13**)	**18**	89%	94%
5	2-tolyl (**14**)	**19**	95%	89%

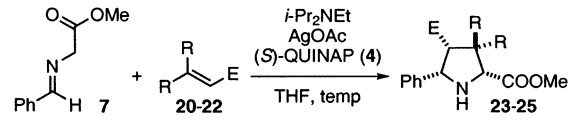
[a] Catalyst loading: 3 mol %. [b] Isolated yield. [c] Determined by HPLC.

23 was obtained only in 60% ee (entry 1).[10] In this case, reactions proceeding in toluene provided higher enantioselectivity than those in THF. In contrast, *tert*-butyl crotonate (**21**) showed lower reactivity, and pyrrolidine **24** was obtained in 97% yield with 84% ee after reacting at −20 °C for 85 h with 10 mol % catalyst loading (entry 2). This represents the first example of incorporating an alkyl group at the 3-position of pyrrolidine using catalytic asymmetric azomethine ylide cycloadditions. On the other hand, *tert*-butyl cinnamate (**22**) showed poor diastereoselectivity (2:1), and the major endo product pyrrolidine **25a** was obtained in 81% ee while the minor exo product **25b** was obtained in 50% ee with a combined yield of 62% (entry 3).

We also probed the silver(I) acetate/QUINAP-catalyzed [3+2] azomethine cycloaddition with iminoesters derived from amino esters other than glycinate. The tested substrates generate pyrrolidines with a quaternary center at the 2-position (Table 3). Pyrrolidine **30** was isolated in 98% yield and 80% ee after reacting

10.1021/ja036558z CCC: $25.00

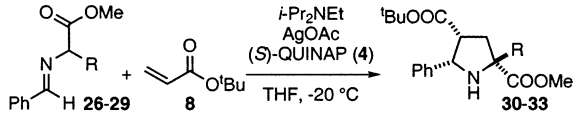
Table 2. Exploration of the Reactivity of Dipolarophiles



entry	dipolarophile	temp	time	yield[c]	endo:exo[d]	ee[e]
1[a]	dimethyl maleate (**20**)	−60 °C	48 h	88%	(**23**) >20:1	60%
2[b]	*tert*-butyl crotonate (**21**)	−20 °C	85 h	97%[f]	(**24**) >20:1	84%
3[b]	*tert*-butyl cinnamate (**22**)	−20 °C	85 h	62%[g]	(**25a**, **25b**) 2:1	81%, 50%[h]

[a] Catalyst loading: 3 mol %, solvent: toluene. [b] Catalyst loading: 10 mol %. [c] Isolated yield. [d] Determined by crude ^{1}H NMR spectra. [e] Determined by HPLC. [f] ca. 95% purity. [g] Combined yield of endo and exo products. [h] Enantioselectivity of the exo product **25b**.

Table 3. Extending the Scope of the Silver(I)/QUINAP-Catalyzed [3+2] Azomethine Ylide Cycloaddition[a]



entry	R	time	yield[b]	pyrrolidine	ee[c]
1	methyl (**26**)	24 h	98%	**30**	80%
2	*iso*-butyl (**27**)	48 h	77%[d]	**31**	80%
3	benzyl (**28**)	48 h	93%	**32**	77%
4	3-indolylmethyl (**29**)	96 h	47%[e]	**33**	81%

[a] Catalyst loading: 10 mol %. [b] Isolated yield. [c] Determined by HPLC. [d] 85% conversion. [e] 50% conversion.

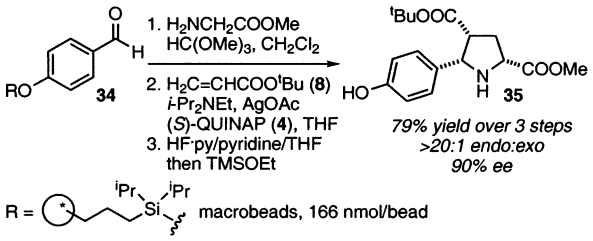


Figure 3. Silver(I)-catalyzed azomethine cycloaddition on macrobeads.

iminoester **26**[11] derived from benzaldehyde and alanine at −20 °C for 24 h with 10 mol % catalyst loading (entry 1). We also examined the iminoesters derived from leucine (**27**, entry 2), phenylalanine (**28**, entry 3), and tryptophan (**29**, entry 4). Good enantioselectivity (77−81%) was observed in all cases, although iminoesters **27** and **29** reacted sluggishly. To the best of our knowledge, this is the first general catalytic asymmetric [3+2] cycloaddition reaction to generate quaternary centers at the 2-position of pyrrolidines.[12]

To show the applicability of this reaction on 500−600 μm polystyrene "macrobeads",[8] we loaded 4-hydroxybenzaldehyde onto alkylsilyl-derivatized macrobeads and condensed the resulting phenolic ether **34** with methyl glycinate. Reacting the macrobead-bound iminoester with *tert*-butyl acrylate (**8**) using 10 mol % silver(I) acetate/(*S*)-QUINAP at −45 °C for 40 h, followed by cleavage with HF-py and TMSOEt quench, provided the pyrrolidine **35** in 79% yield and 90% ee over three steps (Figure 3).

Both enantiomers of the new catalyst system are easily prepared from commercially available reagents. They enable the enantio- and diastereoselective introduction of up to four consecutive stereogenic centers in the [3+2] azomethine ylide cycloaddition, including a previously unreported quaternary center on the pyrrolidine ring with good to excellent levels of selectivity. Its application in a divergent DOS pathway leading to stereochemically diverse alkaloids is underway.

Acknowledgment. We thank the NIGMS for support of this research. Harvard ICCB is supported by Merck & Co., Merck KGaA, the Keck Foundation, and NCI. C.C. is a postdoctoral fellow, and S.L.S is an Investigator with the Howard Hughes Medical Institute at the Department of Chemistry and Chemical Biology, Harvard University. We thank Dr. Michael M.-C. Lo for helpful discussions.

Supporting Information Available: General experimental procedures, characterization data, and X-ray crystallographic file (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews, see: (a) Kanemasa, S. *Synlett* **2002**, 1371−1387. (b) Grigg, R. *Chem. Soc. Rev.* **1987**, *16*, 89−121. (c) *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Padwa, A., Pearson, W., Eds; Wiley-VCH: Weinheim, 2002; pp 169−252.
(2) Schreiber, S. L. *Science* **2000**, *287*, 1964−1969.
(3) Only azomethine ylides derived from aldehydes and α-aminoesters are reviewed here. (a) Kanemasa, S.; Yamamoto, H.; Wada, E.; Sakurai, T. Urushido, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2857−2865. (b) Kanemasa, S.; Hayashi, T.; Tanaka, J.; Yamamoto, H.; Sakurai, T. *J. Org. Chem.* **1991**, *56*, 4473−4481. (c) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L.; Pilati, T. *Tetrahedron: Asymmetry* **1991**, *2*, 1329−1342. (d) Grigg, R.; Montgomery, J.; Somasunderam, A. *Tetrahedron* **1992**, *48*, 10431−10442. (e) Waldmann, H.; Blaeser, E.; Jansen, M.; Letschert, H.-P. *Chem.-Eur. J.* **1995**, *1*, 150−154. (f) Pyne, S. G.; Safaei-G., J.; Koller, F. *Tetrahedron Lett.* **1995**, *36*, 2511−2514. (g) Barr, D. A.; Dorrity, M. J.; Grigg, R.; Hargreaves, S.; Malone, J. F.; Montgomery, J.; Redpath, J.; Stevenson, P.; Thornton-Pett, M. *Tetrahedron* **1995**, *51*, 273−294. (h) Cooper, D. M.; Grigg, R.; Hargreaves, S.; Kennewell, P.; Redpath, J. *Tetrahedron* **1995**, *51*, 7791−7808. (i) Galley, G.; Liebscher, J.; Pätzel, M. *J. Org. Chem.* **1995**, *60*, 5005−5010. (j) Schnell, B.; Bernardinelli, G.; Kündig, E. P. *Synlett* **1999**, 348−350. (k) Roussi, F.; Chauveau, A.; Bonin, M.; Micouin, L.; Husson, H.-P. *Synthesis* **2000**, 1170−1179. (l) Garner, P.; Dogan, O.; Youngs, W. J.; Kennedy, V. O.; Protasiewicz, J.; Zaniewski, R. *Tetrahedron* **2001**, *57*, 71−85. (m) Dogan, Ö.; Öner, I.; Ülkü, D.; Arici, C. *Tetrahedron: Asymmetry* **2002**, *13*, 2099−2104. (n) See also ref 6b.
(4) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400−13401.
(5) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236−4238.
(6) For the early development of catalytic asymmetric [3+2] azomethine ylide cycloaddition, see: (a) Allway, P.; Grigg, R. *Tetrahedron Lett.* **1991**, *32*, 5817−5820. (b) Grigg, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2475−2486.
(7) While the silver(I) system gives better selectivity and has a broader scope than the zinc(II) system, the xylyl-FAP ligand requires an eight-step synthesis. The zinc(II) system resulted in low conversions on the solid phase (500 μm polystyrene beads). The (*R*,*R*)-*t*-BuBOX is not commercially available.
(8) (a) Blackwell, H. E.; Pérez, L.; Stavenger, R. A.; Tallarico, J. A.; Cope Eatough, E.; Foley, M. A.; Schreiber, S. L. *Chem. Biol.* **2001**, *8*, 1167−1182. (b) Clemons, P. A.; Koehler, A. N.; Wagner, B. K.; Sprigings, T. G.; Spring, D. R.; King, R. W.; Schreiber, S. L.; Foley, M. A. *Chem. Biol.* **2001**, *8*, 1183−1195.
(9) In this case, the QUINAP ligand (**4**) showed superior reactivity as it took 48 h at 0 °C for 3 mol % of silver(I) acetate/xylyl-FAP to complete the reaction. For details, see Supporting Information.
(10) The silver(I)/xylyl-FAP catalyst system was reported to give 87% yield and 87% ee after reacting at 0 °C for 7 h (ref 4).
(11) It was reported that condensing aldehydes with α-amino acids or esters provided racemic iminoacids or iminoesters. Grigg, R.; Gunaratne, H. Q. N. *Tetrahedron Lett.* **1983**, *24*, 4457−4460.
(12) Only three scattered examples of catalytic asymmetric [3+2] azomethine cycloaddition reactions using iminoesters derived from amino acid other than glycine were reported. (a) Reference 6b: Iminoester generated from naphthaldehyde and alanine, reacting with methyl vinyl ketone (83% yield, 70% ee) or phenyl vinyl sulfone (64% yield, 70% ee). (b) Longimire, J. M. Ph. D. Dissertation, Penn State University, 2000; iminoester **26** reacting with dimethyl maleate: 70% yield, 65% ee.

JA036558Z