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Dinuclear Zinc-Catalyzed Enantioselective Aza-Henry Reaction

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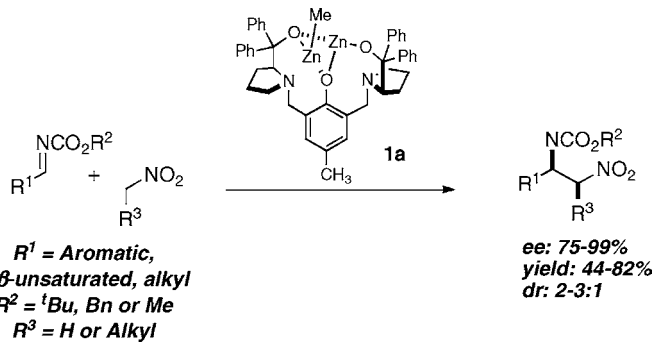
ABSTRACT



The dinuclear zinc catalyst 1a was found to catalyze the addition of nitroalkanes to carbamate-protected imines. This aza-Henry reaction proceeds with high enantioselectivity when various carbamate-protected imines are used. α,β-Unsaturated imines proved to be a particularly useful class of substrate routinely giving the α-nitro amine products in high enantiomeric excess.

The addition of nitroalkanes to imines, the aza-Henry (or nitro-Mannich) reaction, is a powerful and efficient method for the construction of carbon−carbon bonds. β-Nitro amines formed in this way are readily converted into 1,2-diamines under reductive conditions[1] or oxidatively cleaved to afford α-amino acids.[2g] In recent years, efforts have been directed toward the development of efficient enantioselective variants of this reaction.[2] Although advances have been made since the pioneering work of Shibasaki,[2a] methods are often limited regarding the imines that can be employed.

In light of our success developing direct enantioselective aldol,[3a,b,e,f] Henry,[3c] Mannich,[3d,h] and alkynylation[3g] reactions catalyzed by **1a**, we decided to investigate the enantioselective aza-Henry reaction. It was postulated that the dual Lewis acid/Lewis basic functionality within **1a** should facilitate both formation of the nitronate anion and activation of the imine, thus making it a useful catalyst for the aza-Henry reaction (eq 1).[4] In the event, we have been able to develop an enantioselective aza-Henry reaction catalyzed by **1a** that utilizes a range of *tert*-butyloxycarbonyl (Boc), methoxycarbonyl (Moc), and benzyloxycarbonyl (Cbz) protected imines.

Our optimization studies began by investigating imines **2a** and **2b**[5a] as the electrophilic partner in the aza-Henry

(1) For a review, see: Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 1017.

(2) For selected references, see: (a) Yamada, K.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3504. (b) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 2992. (c) Okino, T.; Nakamura, S.; Furukawa, T.; Takemoto, Y. *Org. Lett.* **2004**, *6*, 625. (d) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418. (e) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466. (f) Palomo, C.; Oiarbide, M.; Laso, A.; Lopez, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622. (g) Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7975. (h) Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem.−Eur. J.* **2006**, *12*, 466. (i) Palomo, C.; Oiarbide, M.; Halder, R.; Laso, A.; Lopez, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 117.

(3) See: (a) Trost, B. M.; Ito, H. *J. Am. Chem. Soc.* **2000**, *122*, 12003. (b) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367. (c) Trost, B. M.; Yeh, V. S. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 861. (d) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338. (e) Trost, B. M.; Fettes, A.; Shireman, B. T. *J. Am. Chem. Soc.* **2004**, *126*, 2660. (f) Trost, B. M.; Shin, S.; Sclafini, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 8602. (g) Trost, B. M.; Weiss, A. H.; von Wangelin, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 8. (h) Trost, B. M.; Jaratjaroonphong, J.; Reutrakul, V. *J. Am. Chem. Soc.* **2006**, *128*, 2778. (i) Trost, B. M.; Hisaindee, S. *Org. Lett.* **2006**, *8*, 6003.

(4) For a discussion of dual activation with polynuclear catalysts, see: Shibasaki, M.; Kanai, M.; Matsunaga, S. *Aldrichimica Acta* **2006**, *39*, 21. And concerning the aza-Henry reaction, see: ref 2a.

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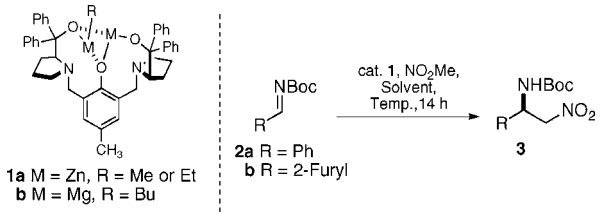
Table 1. Selected Optimization Results for the Aza-Henry Reaction



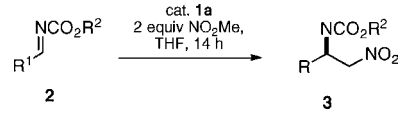
entry	imine	catalyst [mol %]	temp [°C]	solvent	NO_2Me [equiv]	% yield[a]/ % ee[b]
1	**2a**	15	rt	THF	10	57/53
2	**2a**	15[c]	rt	THF	10	55/45
3	**2a**	15	rt	toluene	10	34/4
4	**2a**	15	rt	THF	2	72/74
5	**2b**	15	rt	THF	2	63/77
6	**2b**	15	−20	THF	2	82/92
7	**2b**	10	−20	THF	2	61/85
8	**2b**	5	−20	THF	2	47/75
9	**2a**	30	rt	THF	2	67/91

[a] Isolated yield. [b] HPLC Daicel AD. [c]Catalyst **1b**.

reaction (Table 1). The use of Boc-protected imines as substrates was desirable due to the possibility of multipoint binding[6] and its general utility as a protecting group for nitrogen.[7] To our satisfaction, when imine **2a** was exposed to catalyst **1a** in the presence of nitromethane, the aza-Henry product **3a** was produced in 57% yield and 53% ee (Table 1, entry 1). Both yield and enantioselectivity were decreased when nitromethane was used as solvent. We hypothesized that this may be due to excess nitromethane binding to the catalyst and inhibiting coordination of the imine. Indeed, lowering the nitromethane loading from ten equivalents to two resulted in an increase in ee and yield (Table 1, entry 4). Unfortunately, lowering the temperature to −20 °C stopped the reaction; however, imine **2b** reacted efficiently at this temperature giving carbamate **3b** in good yield and high ee (Table 1, entry 6). Catalyst loading has an effect on the enantioselectivity of the reaction (Table 1, entries 6−9). This result suggests that modification of the catalyst by product occurs over the course of the reaction.[3e] The use of additives that were able to increase catalyst turnover and enantioselectivity in previous work[3a,b] was investigated; however, these did not increase enantioselectivity or yield. Although catalyst loading was high with imine **2a** (Table 1, entry 9), it was acceptable for imine **2b** (Table 1, entry 6) so it was decided to investigate the scope of this reaction, with the hope that the conditions for the later substrate were more typical for this reaction.

The sensitivity of catalyst **1a** to the type of carbamate group of the azomethine was investigated using Cbz- and Moc-protected imines.[5b] Although switching from Boc to Cbz decreased the yield and enantioselectivity (Table 2, entry 2),

Table 2. Aza-Henry Reaction of Aryl and Alkyl Imines



entry	R^1	R^2	catalyst [mol %]	temp [°C]	% yield[a]	% ee[b]
1	Ph	^{t}Bu	30	rt	67	91
2	Ph	Bn	30	rt	52	76
3	Ph	Me	30	rt	65	91
4	*p*-MeC_6H_4	Me	30	rt	65	96
5	*p*-$MeOC_6H_4$	^{t}Bu	30	−20	65	75
6	2-furan	^{t}Bu	15	−20	82	92
7[c]	2-thiophene	^{t}Bu	30	−20	48	82
8	$(CH_3)_3C-$	Me	15	rt	58	89
9[d]	$TBSOCH_2(CH_3)_2C-$	Me	30	rt	66	91

[a] Isolated yield. [b]HPLC Daicel OD-H, OJ-H, AD. [c]Reacted for 38 h. [d]Reacted for 72 h.

the Moc-protected imine gave results similar to those obtained with Boc imine **2a** (Table 2, entry 3). The reaction showed sensitivity to electronics with *p*-tolualdehyde-derived imine reacting with high enantioselectivity (Table 2, entry 4), while the more electron-rich *p*-anisaldehyde derivative gave a significant decrease in the enantioselectivity (Table 2, entry 5). As previously noted, heteroaromatic imines are useful substrates for the aza-Henry reaction (Table 2, entry 6). When the 2-thiophene-derived Boc imine was reacted with 15 mol % of **1a**, only a modest yield of the expected product was obtained. Increasing the catalyst loading allowed the formation of the expected product in an acceptable yield and ee (Table 1, entry 7).

As noted, methyl carbamate protection of the imine does not decrease the enantioselectivity or yield of the aza-Henry reaction. This proved significant when the reactivity of imines bearing α-tertiary centers was investigated. These molecules, although difficult to prepare with Boc protection, could be prepared as the Moc analogues[8] and, when subjected to the aza-Henry reaction conditions, provided the expected products with good enantioselectivity (Table 2, entries 8 and 9). Unfortunately, when imines derived from enolizable aldehydes were used, significant isomerization to the enamine occurred. This result, and the presence of an elegant route to aza-Henry products derived from enolizable aldehydes,[2f] indicated that an exploration of this class of substrate would not be worthwhile. Indeed, our subsequent studies demonstrated that the utility of our reaction lay with substrates that had until this stage been unexplored.

Imines derived from α,β-unsaturated aldehydes[9] have received little attention in the field of asymmetric catalysis

(5) For Boc imines, see: (a) Kanazawa, A. M.; Denis, J.-N.; Greene, A. E. *J. Org. Chem.* **1994**, *59*, 1238. For Moc imines, see: (b) Vidal, J.; Damestoy, S.; Guy, L.; Hannachi, J.; Aubry, A.; Collet, A. *Chem.−Eur. J.* **1997**, *3*, 1691.

(6) For an example of two-point binding with catalyst **1a**, see: ref 3b.

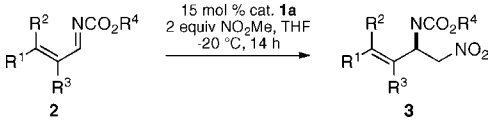
(7) For a review on nitrogen protection, see: Theodoridis, G. *Tetrahedron* **2000**, *56*, 2339.

(8) Trost, B. M.; Jonasson, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 2063.

(9) For other applications of α,β-unsaturated carbamate-protected imines, see: (a) Ting, A.; Lou, S.; Schaus, S. E. *Org. Lett.* **2006**, *8*, 2003. (b) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777.

and are yet to be used as substrates in the aza-Henry reaction. The potential of these substrates to provide interesting materials for organic synthesis, along with the excellent results observed with the alkynylation of α,β-unsaturated aldehydes catalyzed by the bisprolinol ligand,[3g] made these substrates worthy of investigation. Gratifyingly, when exposed to 15 mol % of catalyst **1a**, each α,β-unsaturated imine gave the expected aza-Henry product in good yield and excellent enantioselectivity (Table 3).[10] As was noted previously (Table 2, entry 2), the use of Cbz-protected imines gave lower enantioselectivity (Table 3, entry 2). In the case of Table 3, entries 3−5, the yields observed are, in part, due to the instability of the starting materials that decompose readily under non-inert conditions.

Table 3. Aza-Henry Reaction of α,β-Unsaturated Imines

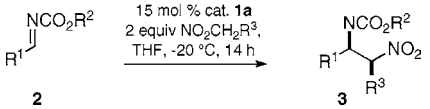


entry	R^1	R^2	R^3	R^4	% yield[a]	% ee[b]
1	Ph	H	H	Me	60	93
2	Ph	H	H	Bn	65	81
3	*p*-$MeOC_6H_4$	H	H	Me	44	97
4[c]	2-furan	H	H	Me	58	93
5	Ph	Ph	H	Me	56	94
6[c,d]	Ph	H	CH_3	Me	69	82

[a] Isolated yield. [b]HPLC Diacel OD-H or AD. [c]Room temperature. [d]30 mol % of **1a**.

Higher-order nitroalkanes can serve as nitronate anion sources in the aza-Henry reaction. When nitroethane was reacted with either the furfural-derived Boc imine **2b** or the cinnamaldehyde-derived Moc imine, the diastereomeric products formed with excellent ee and modest dr (Table 4, entries 1 and 2).[11] Unfortunately, when 2-nitropropane was used the reaction did not proceed. The use of nitroethanol gave an isolable aminal product,[3h,12] while TBS-protected nitroethanol provided the expected product with high enantioselectivity (Table 4, entry 3).

Table 4. Aza-Henry Reaction Using Alternate Nitroalkanes

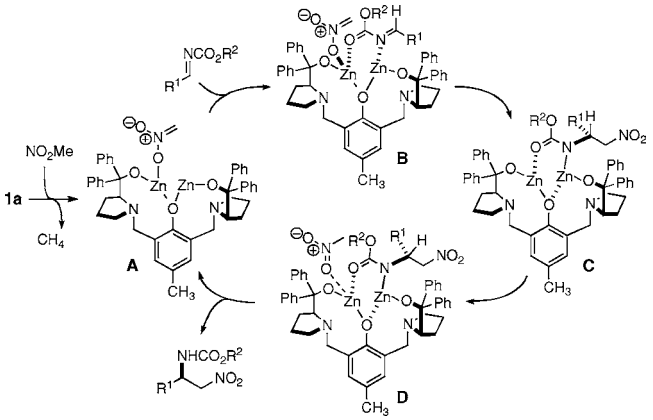


entry	R^1	R^2	R^3	dr[a]	% yield[b]	% ee[c]
1	2-furan	^{t}Bu	Me	3:1	65	98/92
2[d]	PhCH=CH	Me	Me	3:1	52	99/99
3[e]	PhCH=CH	Me	CH_2OTBS	2:1	61	94/92

[a] Ratio determined by ^{1}H NMR. [b]Isolated yield. [c]HPLC Daicel OD-H or AD. [d]Room temperature. [e]96 h reaction time.

Although attempts to detail the reaction mechanism have not been undertaken, a useful cycle that explains the absolute stereochemistry of the products can be proposed (Scheme 1). The initial step of this cycle involves deprotonation of nitromethane by catalyst **1a**[13] to give the zinc nitronate intermediate **A**. Binding of the imine in the orientation indicated then gives structure **B** that can be attacked by the nitronate to give intermediate **C**. Although this scenario is consistent with the absolute stereochemistry of the product, an alternate scenario in which the nitronate adds directly to the unbound imine to give intermediate **C** is also plausible. Association of nitromethane followed by proton transfer then returns intermediate **A**, via a structure such as **D**.

Scheme 1. Possible Mechanism for the Aza-Henry Reaction



In conclusion, we have been able to develop an enantioselective aza-Henry reaction catalyzed by **1a** that performs well over a range of substrates. Aromatic substrates gave high enantioselectivity; however, the use of 30 mol % of catalyst in some cases detracts from this method. Gratifyingly, the hitherto unreported aza-Henry reaction of α,β-unsaturated imines with nitromethane in the presence of 15 mol % of **1a** gave the expected products in consistently high enantiomeric excess. These materials have great potential in organic synthesis as the olefinic group can undergo either reduction or oxidation to give a range of new materials.

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(10) Absolute stereochemistries of these new products were not determined by derivatization; however, by analogy to other aza-Henry products obtained using this methodology, we have assigned the stereochemistry as shown.

(11) Absolute stereochemistry determined by $[\alpha]_D$ correlation to known compounds. For diastereoselectivity by ^{1}H NMR correlation, see Supporting Information.

(12) Trost, B. M.; Chung, C. K. *J. Am. Chem. Soc.* **2006**, *128*, 10358.

(13) For the X-ray crystallographic structure of a derivative of catalyst **1a**, see: Xiao, Y.; Wang, Z.; Ding, K. *Chem.−Eur. J.* **2005**, *11*, 3668.

the Mass Spectrometry Regional Center of the University of California—San Francisco, supported by the NIH division of research resources, and by the University of Illinois at Urbana−Champaign Mass Spectrometry laboratories. We thank Aldrich for a generous supply of the chiral ligand.

Supporting Information Available: Characterization data, NMR spectra, and detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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