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Reversal of enantioselectivity using tethered bisguanidine catalysts in the aza-Henry reaction

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ABSTRACT

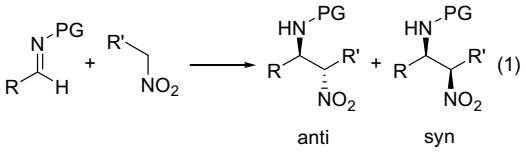
A series of chiral guanidines were synthesized and shown to efficiently catalyze the aza-Henry reaction. Modifications of the catalyst structure revealed important selectivity trends as well as an intriguing reversal in stereoselectivity with bisguanidine variants. These compounds were applied to the aza-Henry reaction between *N*-Boc imines and nitroalkanes generating the β-nitroamines in up to 77% ee and up to 20:1 diastereoselectivity.

In recent years, the use of organic molecules as stereoselective catalysts has gained considerable attention due to their numerous potential advantages, such as lower cost and reduced toxicity.[1] Many examples have been reported including the Diels–Alder reaction, the Mannich reaction, and aldol condensations.[2] One class of catalysts that are especially promising due to their potential generality are those that operate as stereoselective Brønsted bases.[3]

In nature, guanidines are known to interact strongly with anionic moieties and therefore often play a pivotal role in enzymatic substrate recognition or in maintaining protein structure.[4] Additionally, guanidine derivatives have many other useful biological activities including ion channel blocking and hypotensive effects.[5] While guanidines are attractive pharmacological targets, their strong basicity ($pK_a \approx 13.5$)[6] suggests further applications in base-mediated reactions. However, few examples of chiral guanidines in asymmetric synthesis have been reported.[7]

We envisioned that guanidines could potentially control the stereochemistry of base-catalyzed reactions by two mechanisms (Fig. 1). Following nucleophile deprotonation, the resultant guanidinium ion may remain coordinated to the nucleophile to stereoselectively direct the addition step. Alternately, the guanidinium ion may activate the electrophile via hydrogen bonding to provide a chiral environment for the nucleophilic attack. It may also be possible for both mechanisms to operate simultaneously.

To exploit these potential modes of catalysis, we evaluated the reactivity and selectivity of several chiral guanidines in the aza-Henry reaction. The aza-Henry reaction is an important C–C bond forming reaction that generates β-nitroamines (Eq. 1). These compounds can then be transformed into other useful functional groups such as 1,2-diamines and α-amino acids.[8] Several enantioselective versions have appeared in recent literature,[9] but few use base catalysis alone.[10]



(1)

For the initial studies, a variety of guanidines were prepared with differing chiral backbones (Scheme 1). These guanidines were then assayed as catalysts for the reaction between *N*-Boc-benzaldimine **5a** and nitromethane (Table 1).

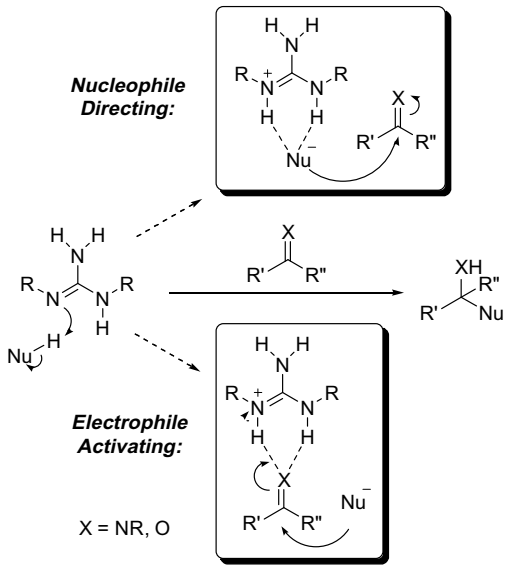


Figure 1. Modes of catalysis using guanidines.

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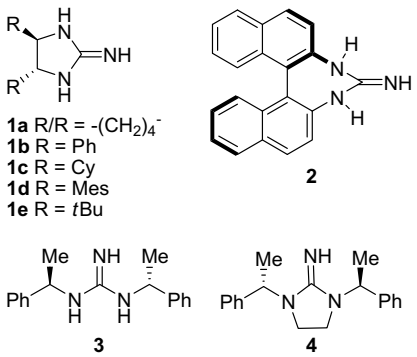
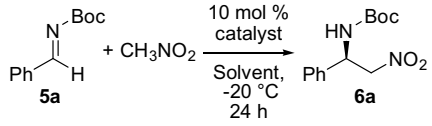


Scheme 1. First chiral guanidines investigated.

Table 1
Guanidine-catalyzed aza-Henry reaction



Entry	Catalyst	Solvent[a]	ee[b] (%) (config)[c]
1	**1a**	CH_3NO_2	0
2	**1b**	Toluene	30 (*R*)
3	**1b**	CH_3NO_2	10 (*R*)
4	**1c**	Toluene	26 (*R*)
5	**1c**	CH_3NO_2	5 (*R*)
6	**1d**	CH_3NO_2	48 (*R*)
7	**1e**	Toluene	62 (*R*)
8	**1e**	CH_3NO_2	50 (*R*)
9	**2**	CH_3NO_2	No product
10	**3**	Toluene	40 (*R*)
11	**3**	CH_3NO_2	0 (N/A)
12	**4**	CH_3NO_2	−31 (*S*)

[a] Two equivalents of CH_3NO_2 when toluene was used.
[b] Determined by chiral HPLC.
[c] Absolute configuration determined by comparison to HPLC retention times in literature.[13]

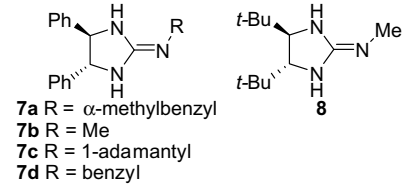
In a preliminary solvent screen, toluene proved to be the optimal solvent for the reaction between **5a** and nitromethane.[11] While the enantioselectivity of the catalysts was nearly always higher in toluene, presumably due to tighter ion pairing, minimal solubility of some of the guanidines (**1a**, **1d**, and **4**) in this solvent decreased their catalytic efficiency. In these cases, the reaction was performed in neat nitromethane (Table 1, entries 1, 6, and 12).

Although the often crucial role of hydrogen bonding or acidic components in the asymmetric aza-Henry reaction is well documented,[9a–e] in our system the catalysts were more effective in the absence of acid additives.[12] The stereoselectivity of the reaction was dramatically improved, as the bulk of the catalyst backbone increased. With cyclohexanediamine-based catalyst **1a**, **6a** was generated in racemic form, yet the more bulky diphenyl-substituted catalyst **1b** produced **6a** in 30% ee. Increasing the size of the backbone substituents from phenyl to cyclohexyl (**1c**) had little effect on the enantioselectivity, but further enlargement to mesityl groups (**1d**) generated nearly a twofold increase in enantioselectivity. The most bulky substituent, *tert*-butyl (**1e**), provided the highest stereoselectivity in this series, providing **6a** in 62% ee. For catalysts **1b**-**1e**, the *R*,*R*-stereoisomer of each catalyst provided the same major enantiomer, (*R*), of **6a**.

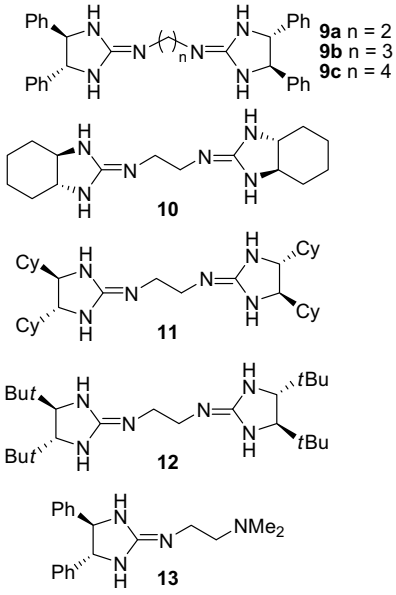
Other guanidine scaffolds revealed additional structure/selectivity relationships. Binaphthyl-derived catalyst **2** was completely unreactive, even in nitromethane, presumably due to its reduced basicity. When the acyclic guanidine **3** was used, modest enantioselectivity (40%) was observed indicating that a cyclic structure is not required for asymmetric induction (entry 10). Finally, substituted guanidine **4** provided **6a** in 31% ee, implying that multiple parallel N–H bonding sites are not essential for stereoselectivity (entry 12).

To improve the stereoinduction of the catalysts, the reactivity of other, related guanidines was assayed (Scheme 2). All of these compounds were applied to the model aza-Henry reaction illustrated in Table 1. Unexpectedly, addition of either bulky or small groups to the apical nitrogen atom (catalysts **7a**–**d**) always reduced the enantioselectivity compared to the unsubstituted version **1b**, all giving <15% ee. This trend was not unique to the diphenylethylene backbone. Substituting guanidine **1e** (which gave 62% ee) with a methylated variant **8** also provided racemic product.

In an attempt to increase the amount of chiral control exerted by the catalysts, a series of bisguanidines were synthesized (Scheme 3). This series revealed some intriguing and unexpected trends. When two **1b**-derived guanidines were tethered together with an ethylene linker (catalyst **9a**), a marked improvement in enantioselectivity from the original monoguanidine **1b** was observed along with a reversal of stereoselectivity (−77% vs 30%, Tables 1 and 2). When the length of the linker was increased to propylene (**9b**), the enantioselectivity remained higher than the monoguanidine **1b**, yet reduced from the initial ethylene linker (Table 2, entry 2). As with catalyst **9a**, bisguanidine **9b** also exhibited reversed stereoselectivity (−50% ee). With a butylene linker (**9c**), the beneficial tethering effect completely disappeared and the enantioselectivity sharply dropped, just as was observed for substituted guanidines **7a–d**.

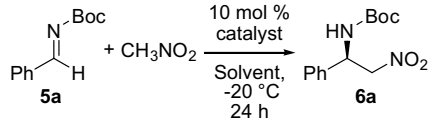


Scheme 2. Nitrogen substituent variation.



Scheme 3. Bisguanidine catalysts.

Table 2
Effectiveness of bisguanidines in the aza-Henry reaction



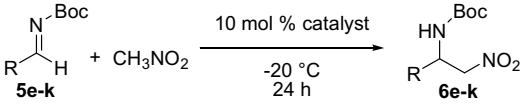
Entry	Catalyst	ee[a] (%) (config)[b]
1	**9a**	−77 (*S*)
2	**9b**	−50 (*S*)
3	**9c**	0 (N/A)
4	**10**	−24 (*S*)
5	**11**	−26 (*S*)
6	**12**	−25 (*S*)
7	**13**	0[c] (N/A)

[a] Determined by chiral HPLC.
[b] Absolute configuration determined by comparison to HPLC retention times in literature.[13]
[c] Performed in neat nitromethane.

The same improved stereoselectivity in the bisguanidine series was observed for catalyst **10**. Unlike its monoguanidine precursor, **10** generated measurable enantiomeric excess in the product (Table 2, entry 4). In contrast, bisguanidines derived from cyclohexyl- (**11**) and *tert*-butyl-substituted (**12**) backbones showed decreased enantioselectivity from their monoguanidine counterparts **1c** and **1e** (entries 5 and 6). Catalyst **13** with a less basic group in the tether failed to provide enantioenriched products. Interestingly, the absolute sense of induction for all bisguanidines was reversed from the original monoguanidines. This factor, as well as the strong dependence of ee on tether length, indicates that the second guanidine plays a key role in the interaction between the catalyst and substrate.

The most successful catalysts **1e** and **9a** were selected for further study against a wider range of substrates. A variety of aryl imines were used in the aza-Henry reaction with nitromethane (Table 3, **5e**–**k**). Electron-rich aryl groups provided the β-nitroamines in good yields (74–85%, entries 1–6). Electron-poor imines were more susceptible to hydrolysis, leading to lower yields of the β-nitroamines (entries 9–10, and 13–14).[14] Unfortunately, minor variations in the structure of the aryl group resulted in a significant drop-off in enantioselectivity, giving the products in 8–60% ee. However, in reactions where both catalysts were stereoselective, the products were obtained in opposite enantioenriched forms (entries 1–2 and 9–10).

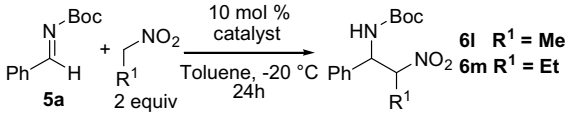
Table 3
Aza-Henry reaction with various *N*-Boc imines



Entry	R (imine)	Catalyst	Adduct	Yield[a] (%)	ee[c] (%)
1	4-MeOC$_6$H$_4$ (**5e**)	**1e**	**6e**	65[b]	26
2	4-MeOC$_6$H$_4$ (**5e**)	**9a**	**6e**	80[b]	−40
3	2-Naphthyl (**5f**)	**1e**	**6f**	88	0
4	2-Naphthyl (**5f**)	**9a**	**6f**	85	−15
5	2-Furyl (**5g**)	**1e**	**6g**	90	0
6	2-Furyl (**5g**)	**9a**	**6g**	74	−12
7	2-ClC$_6$H$_4$ (**5h**)	**1e**	**6h**	60	0
8	2-ClC$_6$H$_4$ (**5h**)	**9a**	**6h**	70	−28
9	2-NO$_2$C$_6$H$_4$ (**5i**)	**1e**	**6i**	39	20
10	2-NO$_2$C$_6$H$_4$ (**5i**)	**9a**	**6i**	42	−60
11	3-ClC$_6$H$_4$ (**5j**)	**1e**	**6j**	60	0
12	3-ClC$_6$H$_4$ (**5j**)	**9a**	**6j**	61	23
13	4-NO$_2$C$_6$H$_4$ (**5k**)	**1e**	**6k**	8	0
14	4-NO$_2$C$_6$H$_4$ (**5k**)	**9a**	**6k**	23	8

[a] Isolated yield after chromatography.
[b] Performed in toluene, with 2 equiv of CH_3NO_2.
[c] Enantiomeric excess was determined by chiral HPLC.

Table 4
Aza-Henry reactions using substituted nitroalkanes



Entry	R^1	Catalyst	Yield[a] (%)	% ee[b] (dr[c])
1	Me	**1e**	86	33/48 (1:4)
2	Me	**9a**	75	−40/33 (1:4)
3	Et	**1e**	30	26[d] (1:20)
4	Et	**9a**	65	−30[d] (1:4)

[a] Isolated yield after chromatography.
[b] Diastereomeric ratio and enantiomeric excess were determined by ^{1}H NMR and chiral HPLC; *syn*/*anti*.
[c] *syn*:*anti*.
[d] Enantiomeric excess of major (*anti*) isomer.

When more substituted nitroalkanes were assayed, the products **6l** and **6m** were isolated in good yields. Both catalysts were selective for the formation of the *anti* diastereomer with moderate ee (Table 4, 26–48%). As with the other β-nitroamines, the *anti* isomer was formed with opposite stereoinduction when **1e** was used in place of **9a**.

Studies to determine the mechanism of stereoselectivity are underway, but a plausible model for the reversal of stereochemistry in the reaction is presented in Figure 2. Because the aza-Henry reaction proceeds in non-polar solvents like toluene, formation of a free carbamate anion intermediate is unlikely. As a result, electrophile activation by the guanidinium salt is expected to play an important role in the stereochemistry determining step. When a monoguanidine catalyst is used, the guanidinium ion may activate and orient the imine via hydrogen bonds to both the imine nitrogen and carbonyl oxygen. The phenyl group on the guanidine catalyst backbone then blocks the bottom face of the imine, forcing the nitronate anion to attack the top face of the imine (Fig. 2a).

With the bisguanidine catalysts, the imine is activated by the guanidinium moiety via the same double hydrogen bonds. However, the additional guanidine group can now deliver the nitronate from the bottom face instead (Fig. 2b), thereby taking advantage of both the electrophile-activating and nucleophile-directing modes

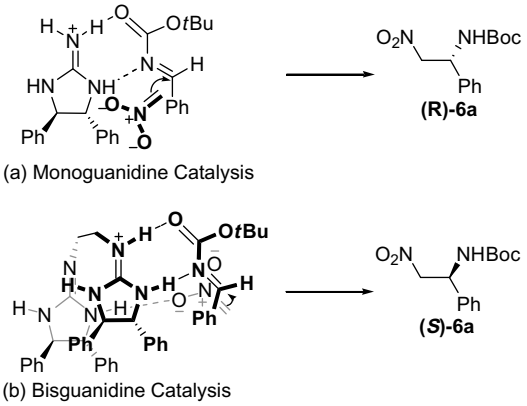


Figure 2. Proposed stereochemical model: monoguanidine and bisguanidine catalysis.

of catalysis. Delivery of the nucleophile by the linked guanidine results in inversion of the stereochemistry.

In summary, we have shown several new chiral guanidine organocatalysts capable of asymmetric induction in the aza-Henry reaction. A variety of structural modifications were examined, revealing a unique enhancement in stereoselectivity for an ethylene-linked bisguanidine. Furthermore, the enantiomeric form of the β-nitroamine products could be selectively reversed when a bisguanidine was used rather than a monoguanidine. Preliminary work shows that these catalysts also provide asymmetric induction in other carbonyl/imine addition reactions.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.058.

References and notes

1. Some recent reviews: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138–5175; (b) Schreiner, P. R. *Chem. Soc. Rev*. **2003**, *32*, 289–296; (c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520–1543.
2. Diels–Alder: (a) Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. *J. Am. Chem. Soc.* **2000**, *122*, 4243–4244; Mannich: (b) Wenzel, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 12964–12965; Aldol: Northrup, A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798–6799. For more examples see Ref. 1..
3. (a) Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542–9543; (b) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157–160.
4. Suhs, T.; König, B. *Chem. Eur. J.* **2006**, *12*, 8150–8157.
5. (a) Schmidtchen, F. P.; Berger, M. *Chem. Rev.* **1997**, *97*, 1609–1646; (b) Maillard, M. C.; Perlman, M. E.; Amitay, O.; Baxter, D.; Berlove, D.; Connaughton, S.; Fischer, J. B.; Guo, J. Q.; Hu, L.-Y.; McBurney, R. N.; Nagy, P. I.; Subbarao, K.; Yost, E. A.; Zhang, L.; Durant, G. J. *J. Med. Chem.* **1998**, *41*, 3048–3061; (c) Carmignani, M.; Volpe, A. R.; Botta, B.; Espinal, R.; de Bonnevaux, S. C.; de Luca, C.; Botta, M.; Corelli, F.; Tafi, A.; Sacco, R.; Monache, G. D. *J. Med. Chem.* **2001**, *44*, 2950–2958.
6. Angyal, S.; Warburton, W. K. *J. Chem. Soc.* **1951**, 2492–2494.
7. (a) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719–724; (b) Ye, W.; Leow, D.; Min Goh, S. L.; Tan, C.-T.; Chian, C.-H.; Tan, C.-H. *Tetrahedron Lett.* **2006**, *47*, 1007–1010; (c) Terada, M.; Ikehara, T.; Ube, H. *J. Am. Chem. Soc.* **2007**, *129*, 14112–14113; (d) Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, *5*, 737–752.
8. Palomo, C.; Oiarbide, M.; Laso, An.; López, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 117–120.
9. (a) Yamada, K.; Harwood, S. J.; Gröger, H.; Shibasaki, M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3504–3506; (b) Trost, B. M.; Lupton, D. W. *Org. Lett.* **2007**, *9*, 2023–2026; (c) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418–3419; (d) Xu, X.; Furukawa, T.; Okino, T.; Miyabe, H.; Takemoto, Y. *Chem. Eur. J.* **2006**, *12*, 466–476; (e) Yoon, T. P.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 466–468.
10. Achiral guanidines: (a) Pahadi, N. K.; Ube, H.; Terada, M. *Tetrahedron Lett.* **2007**, *48*, 8700–8703; Cinchona-based: (b) Bernardi, L.; Fini, F.; Herrera, R. P.; Ricci, A.; Sgarzani, V. *Tetrahedron* **2006**, *62*, 375–380; Cinchona-based: (c) Bode, C. M.; Ting, A.; Schaus, S. E. *Tetrahedron* **2006**, *62*, 11499–11505; Phase-transfer catalysis: (d) Palomo, C.; Oiarbide, M.; Laso, A.; Lopez, R. *J. Am. Chem. Soc.* **2005**, *127*, 17622–17623; Phase-transfer catalysts: (e) Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7975–7978.
11. See Supplementary data.
12. In the presence of preformed guanidinium salts, the β-nitroamines were generated in substantially lower yields and enantiomeric excesses.
13. (a) Wang, C.; Zhou, Z.; Tang, C. *Org. Lett.* **2008**, *10*, 1701–1710; (b) Fini, F.; Sgarzani, V.; Pettersen, D.; Herrera, R. P.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 7975–7978.
14. Common decomposition products include the aldehyde, hemiaminal, and the β-nitroalcohols from the Henry reaction.