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Asymmetric Aza-Michael Reactions Catalyzed by Cinchona Alkaloids

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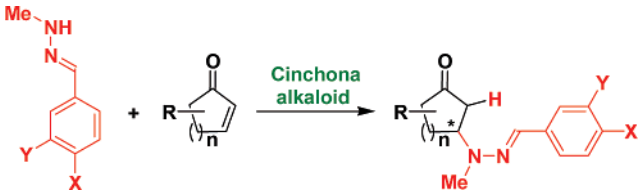

The organocatalysed asymmetric aza-Michael addition of hydrazones to cyclic enones has been achieved in good yield and stereoselection using cheap and commercially available cinchona alkaloids as catalysts. A systematic study of the influence of the structure of the enone on the stereoselectivity was carried out, leading to optically active products with up to 77% ee. The products can be recrystallized to give nearly enantiopure products, and furthermore it was shown that the products could be reduced to the corresponding 1,3-benzylidenehydrazino alcohol derivatives with high diastereoselectivity.

In the past decade stereoselective organocatalysis[1] has developed remarkably, and new reactions have been added to the methodologies that chemists can use in asymmetric synthesis of valuable chiral compounds. Enantioselective organocatalytic transformations, such as aldol reactions, Michael, and thia-Michael additions have been known for a long time and have recently been developed intensively by applying new catalysts or non-conventional reaction solvents or performing multicomponent and tandem reactions.[1h] On the other hand, catalyzed enantioselective aza-Michael reactions[2] have remained elusive, and only few examples have been reported using, e.g., organocatalysis.[3] The aza-Michael reaction is important for C−N bond construction and has frequently been used as the key step in the syntheses of biologically active natural compounds.[4] In the past few years new methods for the non-enantioselective version of the aza-Michael reaction have been reported,[5] while the development of the catalyzed asymmetric version is still considered a challenging research topic.[2a]

In organocatalysis, the majority of reactions are amine catalyst-based and can proceed via enamine or iminium intermediates, or the amine can act as a chiral base. One of the difficulties in developing organocatalyzed enantioselective aza-Michael reactions is the possible competition between the catalyst and the nucleophile, both amino derivatives, to react with the carbonyl functionality in the substrate. This explains the previous choice of nucleophiles with limited reactivity, such as aromatic heterocycles,[3c] *N*-carbamates derivative of hydroxylamine,[3a,b] or azide,[3e] which are unable to form either the iminium or the enamine intermediate.

Hydrazine derivatives are interesting candidates as nucleophiles in enantioselective conjugate aminations considering that they are key intermediates in the synthesis of heterocycles, pharmaceuticals, agrochemicals, polymers, dyestuffs, and photography products,[6] and they can be suitable substrates for further modifications. Moreover, the hydrazine functionality shows a strong α-effect[7] that might ensure an enhanced nucleophilicity. On the other hand, they could also be competitors to amine-based catalysts because they are basic and react quickly with carbonyl groups,[7] and several hydrazine derivatives

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(3) (a) Ibrahem, I.; Rios, R.; Vesely, J.; Zhao, G.-L.; Córdova A. *Chem. Commun.* **2007**, *849*. (b) Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328. (c) Wang, J.; Li, H.; Zu, L.; Wang, W. *Org. Lett.* **2006**, *8*, 1391. (d) Takasu, K.; Maiti, S.; Ihara, M. *Heterocycles* **2003**, *59*, 51. (e) Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134.

(4) For recent examples, see: (a) Chandrasekhar, S.; Reddy, N. R.; Rao, Y. S *Tetrahedron* **2006**, *62*, 12098. (b) Dorbec, M.; Florent, J.-C.; Monneret, C.; Rager, M.-N.; Bertounesque, E. *Tetrahedron* **2006**, *62*, 11766. (c) Prakesch, M.; Srivastava, S.; Leek, D. M.; Arya, P. *J. Comb. Chem.* **2006**, *8*, 762. (d) Nguyen, S.; Xu, J.; Forsyth, C. J. *Tetrahedron* **2006**, *62*, 5338. (e) Dorbec, M.; Florent, J.-C.; Monneret, C.; Rager, M.-N.; Bertounesque, E. *Synlett* **2006**, 591. (f) Ihara, M. *Chem. Pharm. Bull.* **2006**, *54*, 765.

(5) For recent examples, see: (a) Yang, L.; Xu, L.-W.; Zhou, W.; Li, L.; Xia., C.-G. *Tetrahedron Lett.* **2006**, *47*, 7723. (b) Reddy, K. R.; Kumar, N. S. *Synlett* **2006**, 2246. (c) Varala, R.; Sreelatha, N.; Adapa, S. R. *Synlett* **2006**, 1549. (d) Patil, N. T.; Huo, Z.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 6991. (e) Alfonsi, M.; Arcadi, A.; Bianchi, G.; Marinelli, F.; Nardini, A. *Eur. J. Org. Chem.* **2006**, 2393. (f) Rulev, A. Y.; Yenil, N.; Pesquet, A.; Oulyadi, H.; Maddaluno, J. *Tetrahedron* **2006**, *62*, 5411. (g) Surendra, K.; Krishnaveni, N. S.; Sridhar, R.; Rao, K. R. *Tetrahedron Lett.* **2006**, *47*, 2125. (i) Fetterly, B. M.; Jana, N. K.; Verkade, J. G. *Tetrahedron* **2006**, *62*, 440.

(6) (a) Hydrazine and Its Derivatives. In *Kirk-Othmer Encyclopedia Chemical Technology*, 4th ed.; Wiley: New York, 1995; Vol. 13. (b) Schmidt E. W. *Hydrazine and Its Derivatives: Preparation, Properties, Applications*; Wiley: New York, 1984.

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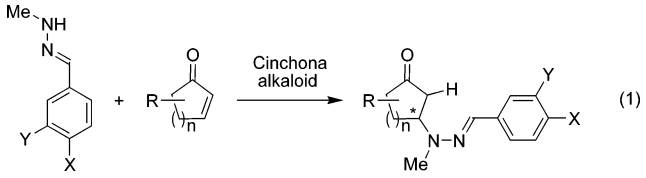
are powerful organocatalysts that easily form iminium ions.[8] We envisioned that hydrazones could be a tuneable replacement for hydrazines in order to modulate the strong reactivity of the latter. Herein, we report the first enantioselective organocatalytic aza-Michael addition of hydrazones with cyclic enones using cinchona alkaloids as catalysts (eq 1).

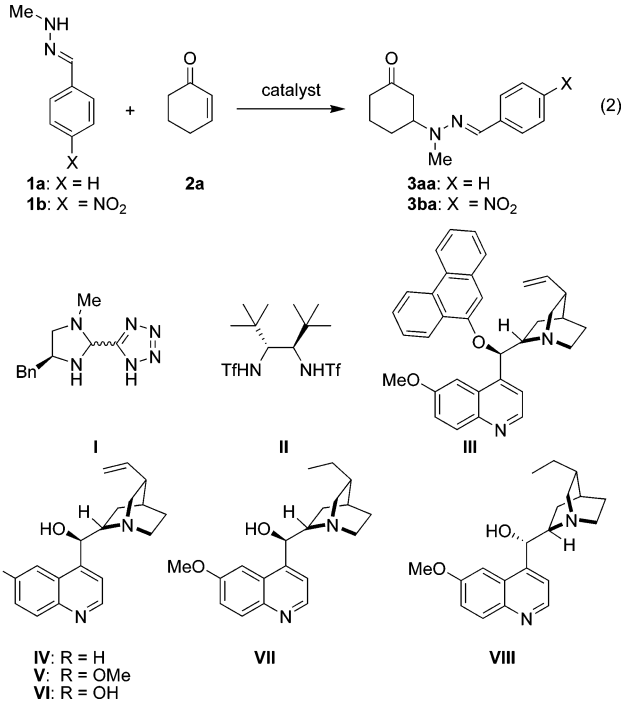


For the screening process we considered two hydrazones, **1a** and **1b**, having different electron density at the external nitrogen atom, and their reaction with cyclohexenone **2a** as a model reaction (eq 2, Table 1). In order to obtain information on the reaction, some achiral catalysts were tested and showed that hydrazone **1a** reacts slowly without a catalyst (Table 1, entry 1), whereas it reacts quickly with pyrrolidine catalysis (entry 2) (via iminium activation of enone) and more slowly with Et_3N (entry 3) (probably via hydrazone activation). It was also observed that hydrazone **1b** reacts faster under acid catalysis (entry 4) (via enone activation), establishing a multiform reactivity with different feasible reaction paths. Attempts to exploit iminium activation with catalyst **I** (entry 5) or acid activation with catalyst **II** (entry 6) failed to provide optically active products, although good conversion was obtained. Base catalysis was more promising, and several cinchona alkaloid derivatives were tested in order to elucidate the structure−activity relation of the catalysts. Quinine (**V**) is an effective catalyst for the aza-Michael reaction, and the product (**3aa**) is formed with good conversion and 56% ee (entry 10), while removal of the methyl group or the methoxy group, as in catalysts **IV** and **VI** (entries 8, 9), led to a decrease of the enantioselectivity. Similarly to the thia-Michael addition,[9] the lack of the free hydroxyl group gave a significant drop of the enantioselectivity, in agreement with the proposed schematic model of the reaction intermediate where the hydroxyl group establishes a hydrogen bond with the carbonyl and the quinuclide group is linked to the hydrazone, forming a tight transition state (Figure 1). The reduction of the ethylenic group in the catalyst **V**, giving catalyst **VII,** provided a minor improvement of the enantioselectivity, and performing the reaction in toluene and under more diluted conditions gave **3aa** in 94% yield and 71% ee (entry 12). It should also be noted that changes of both the temperature or the catalyst loading did not improve the enantioselectivity. With the quasi-enantiomer of the catalyst (**VIII**), we obtained the opposite enantiomer **3aa** with similar yield and little erosion of the enantioselectivity (entry 13).

With this optimized procedure, we tested several hydrazones having electron-withdrawing groups at the aryl unit (Table 2) and performed a systematic analysis of the influence of the structure of the enone on the enantioselectivity testing enones having different ring size, as well as the steric and electronic effects of substituents in the ring (Table 3).

The less nucleophilic hydrazone **1b** required a longer reaction time and higher concentration to obtain a good yield and enantioselectivity comparable to that of **1a** (Table 2, entry 1). Moreover, the more polarized NH-bond of the *p*-nitro derivative (**1b**) led to interaction between the hydrazone **1b** and the catalyst **VII** as observed by NMR in C_6D_6 (see Supporting Information),

TABLE 1. Initial Screening of Catalysts for the Reaction of Hydrazones 1a,b with Enone 2a in the Presence of Various Achiral and Chiral Bases and Acids as the Catalysts



entry	hydrazone	catalyst (20%)	time (d)	conv (%)	ee[a] (%)
1	**1a**	none	3	40	
2	**1a**	pyrrolidine	1	100	
3	**1a**	Et_3N	3	75	
4	**1b**[b]	$PhCO_2H$	1	100	
5	**1b**[b]	**I**	2	96[d]	0
6	**1b**[b]	**II**	2	100	0
7	**1a**	**III**	2	85	−2
8	**1a**	**IV**	2	74	−27
9	**1a**	**VI**	2	100	−31
10	**1a**	**V**	2	91	−56
11	**1a**	**VII**	2	100	−60
12	**1a**[c]	**VII**	2	94[d]	−71
13	**1a**[c]	**VIII**	2	92[d]	+64

[a] Reaction performed on a 0.5 mmol (1 M) scale (**1a**,**b**) with 2 equiv of **2** and 20 mol % of the catalyst in Et_2O; ee determined by CSP-HPLC analysis. [b] In CH_2Cl_2. [c] In toluene (0.5 M). [d] Yield of the isolated product.

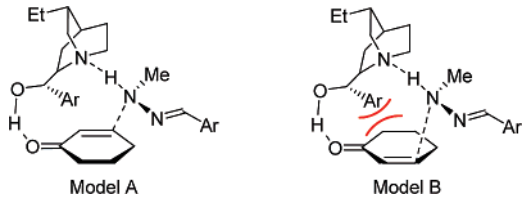


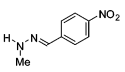
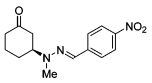
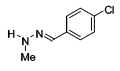
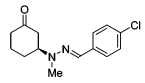
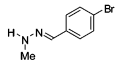
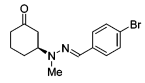
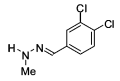
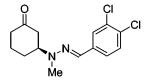
FIGURE 1. Schematic model of the reaction transition state.

(7) (a) Smith, P. A. S. *Derivatives of Hydrazine and Other Hydronitrogens Having N−N Bonds*; The Benjamin Cummings Publishing Company: Massachusetts, 1983. (b) Patai, S. *The Chemistry of Functional Groups. The Chemistry of the Hydrazo, Azo and Azoxy Groups*; Wiley: New York, 1975.

(8) (a) Cavill, J. L.; Elliott, R. L.; Evans, G.; Jones, I. L.; Platts, J. A.; Ruda, A. M.; Tomkinson, N. C. O. *Tetrahedron* **2006**, *62*, 410. (b) Lemay, M.; Ogilvie, W. W. *Org. Lett.* **2005**, *7*, 4141. (c) Cavill, J. L.; Peters, J.-U.; Tomkinson, N. C. O. *Chem. Commun.* **2003**, 728.

(9) Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417.

TABLE 2. Reaction Scope of the Aza-Michael Reaction of Cyclohexenone 2a with Respect to Hydrazones 1b−e

entry	hydrazone	time (d)	yield (%)	ee[a] (%)
1[b]	 **1b**	5	 **3ba** – 75	74
2	 **1c**	3	 **3ca** – 89	75 (84)[c]
3	 **1d**	3	 **3da** – 82	74 (81)[c]
4	 **1e**	3	 **3ea** – 86	68

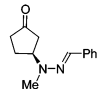
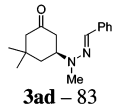
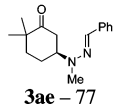
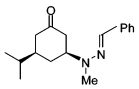
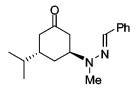
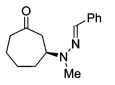
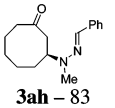
[a] Reaction performed on a 0.5 mmol of hydrazone (0.5 M) scale with 2 equiv of enone and 20 mol % of catalyst **VII** in toluene; ee determined by CSP-HPLC analysis. [b] Hydrazone was 1 M. [c] After crystallization from Et_2O.

in agreement with the model in Figure 1. On the other hand, the chloro and bromo derivatives **1c**−**e** showed similar reactivity and enantioselectivity as the parent hydrazone **1a** (entries 2−4).

The enantioselectivity of **3ca** and **3da** could be improved by a single crystallization in Et_2O (entries 2, 3). The absolute configuration of the products was determined by X-ray diffraction of a single crystal of **3ca**, and the stereogenic center formed was assigned as (*S*) (see Supporting Information). The absolute configuration is in agreement with the model proposed in Figure 1 Model A, where the cinchona alkaloid catalyst establishes two hydrogen bonds and activates both the hydrazone and the enone, while steric repulsion between the aromatic part in the catalyst and the enone as outlined in Model B is disfavored. A similar transition state model has been proposed for the thia-Michael addition.[9]

In Table 3 we present the results for the reaction of different enones with hydrazone **1a**. It appears from these results that the enantioselectivity is very dependent on the ring size and substitution pattern of the ring. For cyclopentenone **2b**, the reaction proceeds well with 87% yield of **3ab**; however, the enantiomeric excess of the product was only 31% ee (entry 1). For the six-membered ring systems, we found that the reaction is very sensitive to the steric hindering in position 4, and enone **2c** shows very low reactivity (entry 2) even without solvent or using a stoichiometric amount of, e.g., Et_3N. Moving the two methyl groups to position 5 (enone **2d**), the reactivity is reestablished and the enantioselectivity is improved to 76% ee (entry 3), whereas for 6,6-dimethyl-2-cyclohexenone **2e** a slight drop in enantioselectivity was found (entry 4). The long reaction time (4 days) in this case is in agreement with the difficulty of the catalyst to coordinate efficiently the carbonyl group as depicted in the schematic model of the transition state (Figure 1). The racemic enone **2f** gave a mixture of diastereoisomers where the *cis*-isomer maintained the enantiomeric excess of 5,5-dimethyl-2-cyclohexenone **2d** (entry 5). It is notable that

TABLE 3. Reaction Scope of the Aza-Michael Reaction of Hydrazone 1a with Respect to Enones

entry	enone	time (d)	yield (%)	ee[a] (%)
1[b]	 **2b**	3	 **3ab** – 87	31
2	 **2c**	5	nr[c]	-
3	 **2d**	3	 **3ad** – 83	76
4	 **2e**	4	 **3ae** – 77	60
5	 **2f**	3	 **3af *cis*** –36  **3af *trans*** – 63	76 (*cis*) 62 (*trans*)
6	 **2g**	3	 **3ag** – 81	72
7	 **2h**	3	 **3ah** – 83	77

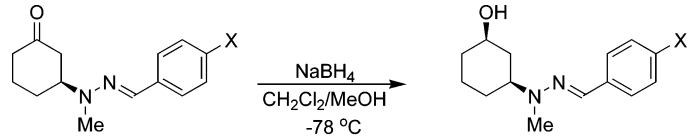
[a] Reaction performed on a 0.5 mmol of hydrazone (0.5 M) scale with 2 equiv of enone and 20 mol % of catalyst **VII** in toluene; ee determined by CSP-HPLC analysis. [b] Hydrazone was 0.25 M. [c] Without solvent.

increasing the ring size to seven- and eight-membered rings led to an improvement in the enantioselectivity up to 77% ee (entries 6, 7).[10]

Several synthetic modifications of the aza-Michael adducts can be envisioned due to the rich chemistry of both the carbonyl and the hydrazino group. Considering the important role of chiral 1,3 amino alcohol derivatives in total synthesis and drug design, we studied the reduction of the carbonyl group to the corresponding alcohol and the generation of a new stereocenter. Although the hydrazone group is far away from the reduction site and no steric influence could be expected in order to obtain a stereoselective formation of the alcohol, we were pleased to find a good diastereoselection for the isomer *cis*-**4aa** and *cis*-**4ba** as the main products (Scheme 1), maintaining the enantiomeric excess of the starting ketone. The reason for such high stereoselectivity might be explained by the theory of charge-transfer stabilization of the transition state by electron donors proposed by Cieplak.[11]

(10) For the very reactive enone **2b**, a more diluted solution was necessary.

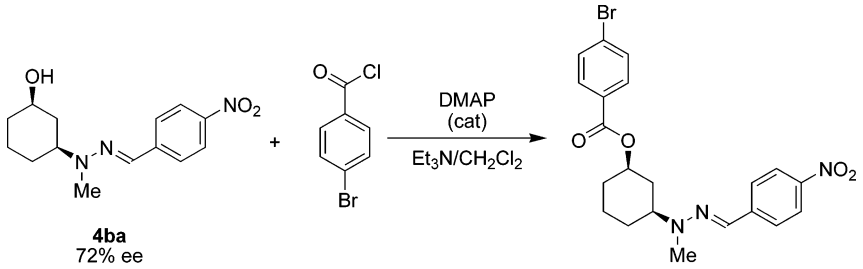
SCHEME 1. Diastereoselective Reduction of Aza-Michael Products 3aa,ba



3aa: X = H 71% ee
3ba: X = NO_2 74% ee

4aa: X = H 99% yield, *cis*:*trans* = 94:6, 70% ee
4ba: X = NO_2 98% yield, *cis*:*trans* = 93:7, 72% ee

SCHEME 2. Benzoylation of Alcohol *cis*-4ba



4ba
72% ee

5ba
96% yield
72% ee, 97% ee (recryst)

Finally, the benzoylation of **4ba** with 4-bromobenzoyl chloride gave in high yield the solid compound **5ba** that, after a single crystallization from Et_2O, led to **5ba** with high enantiomeric excess (Scheme 2).

In conclusion, we have developed the first example of enantioselective aza-Michael addition of hydrazones to cyclic enones catalyzed by cheap and commercially available cinchona alkaloids. Moreover, a systematic study of the steric parameters for the stereoselectivity was conducted, and the possibility of further functionalization of the products toward more complex structures was explored. The interaction between hydrazones and cinchona alkaloids to form a chiral complex might give new possibilities of developing other reactions where the hydrazone unit is involved as nucleophile.

Experimental Section

Representative Procedure for the Enantioselective Addition of Hydrazones 1a to Enone 2a using VII as Catalyst. Hydrazone **1a** (0.5 mmol) and catalyst **VII** (20%) were dissolved in toluene (1 mL) in a glass vial equipped with a magnetic stirring bar. Enone **2a** (1 mmol) was added, and the solution was kept at room temperature for 2 days. The mixture was concentrated at low pressure ,and the crude product was purified by flash chromatography on SiO_2 (eluent Et_2O/pentane 1:1) to give **3aa** as a white solid, yield 94%. ^{1}H NMR ($CDCl_3$): δ 7.60−7.50 (m, 2H), 7.40−7.30 (m, 2H), 7.24 (s, 1H), 7.25−7.15 (m, 1H), 3.65−3.50 (m, 1H), 2.91 (s, 3H), 2.79 (dd, J_{vic} = 9.6 Hz, J_{gem} = 14 Hz, 1H), 2.59 (dd, J_{vic} = 4.8 Hz, J_{gem} = 14 Hz, 1H), 2.40−2.25 (m, 2H), 2.05−1.90 (m, 3H), 1.70−1.50 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 210.5, 137.4, 131.9, 128.7, 127.4, 125.8, 65.4, 46.2, 41.1, 36.7, 28.6, 21.9. HRMS: $C_{14}H_{18}N_2O$ [M + Na]$^+$ calcd 253.1317, found 253.1322. $[\alpha]^{20}_D$ −82.3 (*c* 1.0, $CHCl_3$, 71% ee). The ee was determined by HPLC using a Chiralcel OD column [hexane/*i*PrOH (98:2)]; flow rate 1.0 mL/min; τ_{minor} = 17.2 min, τ_{major} = 18.9 min (71% ee). **Use of Catalyst VIII.** Yield 92%. $[\alpha]^{20}_D$ +77.3 (*c* 1.0, $CHCl_3$, 64% ee). The ee was determined by HPLC using a Chiralcel OD column [hexane/*i*PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 17.2 min, τ_{minor} = 18.9 min (64% ee).

Representative Procedure for the Reduction of Ketone 3aa to Alcohol 4aa with $NaBH_4$. Ketone **3aa** (0.5 mmol) was dissolved with 2 mL of MeOH and 1 mL of CH_2Cl_2 in a glass vial equipped with a magnetic stirring bar; the resulting solution was cooled to −78 °C and $NaBH_4$ was added. After 1 h the reaction was completed. The solvent was removed at low pressure, and the crude product was washed with water and extracted with Et_2O (2 × 25 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The dr was determined on the crude product (*cis*:*trans* = 94:6) by NMR. The pure product **4aa** was obtained by flash chromatography on SiO_2 (eluent: Et_2O:pentane 6:4) to give *cis*-**4aa** (yield 94%) and *trans*-**4aa** (yield 6%) as colorless oils. *trans*-**4aa**: ^{1}H NMR ($CDCl_3$): δ 7.50−7.40 (m, 2H), 7.30−7.20 (m, 2H), 7.20−7.00 (m, 2H), 4.30−4.20 (m, 1H), 3.60−3.45 (m, 1H), 2.80 (s, 3H), 2.00−1.30 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 137.8, 130.7, 128.7, 127.1, 125.6, 67.7, 61.1, 37.1, 36.1, 32.6, 30.0, 19.8. HRMS: $C_{14}H_{20}N_2O$ [M + H]$^+$ calcd 233.1654, found 233.1644. $[\alpha]^{20}_D$ −33.2 (*c* 1.0, $CHCl_3$, 70% ee). The ee was determined by HPLC using a Chiralcel OD column [hexane/*i*PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 20.7 min, τ_{minor} = 24.0 min (70% ee). *cis*-**4aa**: ^{1}H NMR ($CDCl_3$): δ 7.55−7.45 (m, 2H), 7.30−7.20 (m, 2H), 7.20−7.10 (m, 2H), 3.60−3.55 (m, 1H), 3.30−3.15 (m, 1H), 2.79 (s, 3H), 2.20−1.00 (m, 9H). ^{13}C NMR ($CDCl_3$): δ 137.6, 131.3, 128.7, 127.2, 125.7, 70.0, 64.7, 39.6, 35.2, 29.1, 22.0. HRMS: $C_{14}H_{20}N_2O$ [M + H]$^+$ calcd 233.1654, found 233.1640. $[\alpha]^{20}_D$ −28.2 (*c* 1.0, $CHCl_3$, 70% ee). The ee was determined by HPLC using a Chiralcel OD column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 8.9 min, τ_{minor} = 10.8 min (70% ee).

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Supporting Information Available: Experimental procedures and characterization data for all new compounds and X-ray structure of **3ca** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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