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Asymmetric Aza-Mannich Addition of Oxazolones to *N*-Tosyl Aldimines: Synthesis of Chiral α-Disubstituted α,β-Diamino Acids

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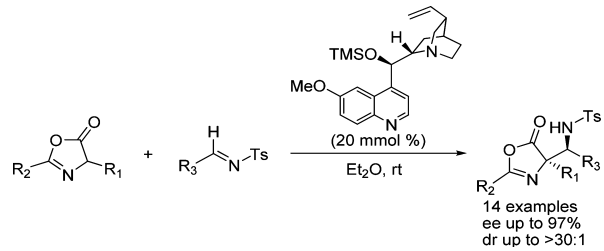
ABSTRACT



An organocatalytic enantioselective addition of oxazolones to *N*-tosyl aldimines has been developed. The process is promoted by a readily prepared cinchona alkaloid ligand and affords a series of valuable α-disubstituted α,β-diamino acid derivatives with excellent enantioselectivities (up to 97% ee) and diastereoselectivities (up to >30:1 dr). The adducts can be transformed into the corresponding protected chiral α-disubstituted α,β-diamino acids by a one-pot hydrolyzed reaction smoothly.

Chiral α-disubstituted α,β-diamino acids are known as the key structural components in many biological active compounds.[1] Such molecules can, for instance, serve as building blocks for the synthesis of chiral auxiliaries and pharmaceuticals.[2] Moreover, they can also be incorporated into the peptides to impart conformational stability and display antibiotic activity.[3] Therefore, the synthesis of α-disubstituted α,β-diamino acids in an optically pure form has gained considerable interest and has become a significant and challenging work for organic chemists. In 2008, on the basis of several different catalytic routes for the α,β-diamino acid synthesis,[4] a metal catalytic approach for the preparation of α-disubstituted α,β-diamino acids was developed by the Shibasaki group.[5] Since then, a handful of protocols have been described in the literature by several groups.[6] In the past decade, due to its operational and economic advantages, asymmetric organocatalysis has been proven to be a powerful tool for the synthesis of optically pure compounds.[7] Therefore, it is significant to develop organocatalytic approaches for the synthesis of α-disubstituted α,β-diamino acids.

Because of the easy availability and the well-documented power, the cinchona alkaloids and their derivatives have become efficient bifunctional organocatalysts in various asymmetric reactions.[8] Recently, in our own work, a sodium demethylquinine salt derived from the cinchona alkaloid has been successfully applied to the Michael reaction between

(1) Viso, A.; Fernández de la Pradilla, R.; García, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167.

(2) (a) Lucet, D.; LeGall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580. (b) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517.

(3) (a) Kan, T.; Kawamoto, Y.; Asakawa, T.; Furuta, T.; Fukuyama, T. *Org. Lett.* **2008**, *10*, 168. (b) Takahashi, A.; Naganawa, H.; Ikeda, D.; Okami, Y. *Tetrahedron.* **1991**, *47*, 3621.

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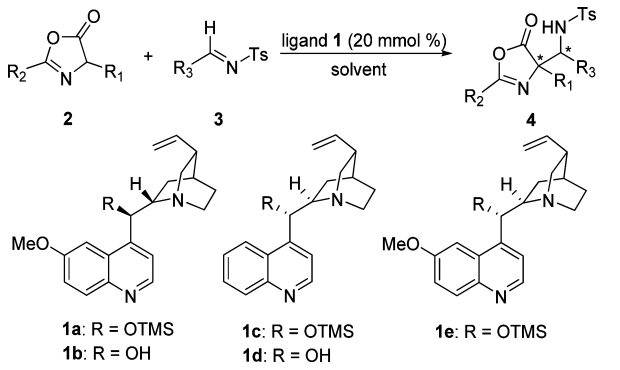
the trisubstituted carbanion and the nitroalkenes.[9] We decided to investigate this initial observation further and to apply

Scheme 1. Cinchona Alkaloid Derived Ligands Explored for the Synthesis of Optically Active α-Disubstituted α,β-Diamino Acids



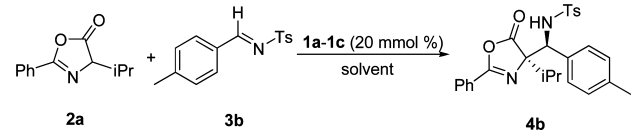
the cinchona alkaloid ligands **1a**−**d** to the Mannich addition of racemic oxazolones to *N*-tosyl aldimines (Scheme 1).

An additional impetus for this work was that, although the oxazolones were important masked amino acid fragments[10] and have been employed to synthesize α-substituted α,β-diamino acids by Jørgensen and Ooi successively,[11] the use of these aza species for the synthesis of amino acid derivatives was still scarce. To the best of our knowledge, using *N*-tosyl aldimines as electrophile reagents in this field has not been thoroughly explored.

In our exploratory study, we decided to choose *N*-tosyl imine **3b** and oxazolone **2a** as substrates for the proposed aza-Mannich reaction in the presence of a chiral cinchona alkaloid ligand **1a** (20 mmol %) in toluene at room temperature. We found that the reaction proceeded efficiently to afford the adduct **4b** in a good diastereomeric ratio of 11:1 but with the moderate enantioselectivity (Table 1, entry 1). Switching solvents to tetrahydrofuran or acetonitrile (entries 2 and 3) had a negative influence on the enantioselectivities, whereas the use of benzene or tetrachloromethane (entries 4 and 5) gave better results. Gratifyingly, when the ethyl ether was used as the solvent, the adduct was smoothly obtained with an excellent ee value of 96% and a further improved 17:1 diastereomeric ratio (entry 6). Under the same conditions, the impact of ligand frameworks was examined.

The disadvantage of the free OH group in the catalyst structure was verified by the lower enantioselectivity of the reaction catalyzed by **1b** (entry 7). Less efficiency was also observed in terms of enantioselectivities for the analogues **1c** and **1d** (entries 8 and 9). Furthermore, the similar diastereomeric ratio and enantioselectivity were obtained with the low reaction temperature of 10 °C (entry 10).

Table 1. Representative Screening Results for the Reaction of Oxazolone **2a** and *N*-Tosyl Imine **3b**[a]



entry	cat. (20 mmol %)	temp.	solvent	dr[b]	ee [%][c]
1	**1a**	rt	Tol	11:1	71
2	**1a**	rt	THF	10:1	52
3	**1a**	rt	MeCN	7:1	65
4	**1a**	rt	C_6H_6	11:1	86
5	**1a**	rt	CCl_4	14:1	92
6	**1a**	rt	Et_2O	17:1	96
7	**1b**	rt	Et_2O	19:1	91
8	**1c**	rt	Et_2O	20:1	80
9	**1d**	rt	Et_2O	17:1	52
10[d]	**1a**	−10 °C	Et_2O	17:1	91

[a] Experimental conditions unless otherwise stated: a mixture of **2a** (0.2 mmol), **2b** (0.1 mmol), and catalyst (20 mmol %) in the corresponding solvent (1 mL) was stirred at room temperature for 8−12 h, and full conversion was observed in all the cases. [b] Determined by ^{1}H NMR spectroscopic analysis. [c] The enantiomeric excess was determined by HPLC analysis on a Chiralcel column. [d] Reaction time: 16 h.

With the optimized conditions established, the scope of *N*-tosyl aldimines and oxazolones in the presence of 20 mmol % catalyst **1a** was explored (Table 2). Overall, all of the reactions proceeded smoothly to furnish the corresponding α-disubstituted α,β-diamino acid derivatives **4** in good yields and excellent diastereo- and enantioselectivities. For the reactions with the oxazolone **2a**, a wide range of substituents could be present at the aryl position on the *N*-tosyl imine **2**. All of the aryl-substituted substrates with either electron-rich or electron-deficient at different sites had limited effect on the results of the diastereo- and enantioselectivity of the

(4) (a) Cutting, G. A.; Stainforth, N. E.; John, M. P.; Kociok-Köhn, G.; Willis, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 10632. (b) Singh, A.; Yoder, R. A.; Shen, B.; Johnston, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 3466. (c) Kiss, L.; Mangelinckx, S.; Sillanpää, R.; Fülöp, F.; De Kimpe, N. *J. Org. Chem.* **2007**, *72*, 7199. (d) Shibuguchi, T.; Mihara, H.; Kuramochi, A.; Ohshima, T.; Shibasaki, M. *Chem. Asian J.* **2007**, *2*, 794. (e) Tranchant, M.-J.; Dalla, V. *Tetrahedron* **2006**, *62*, 10255. (f) Rinaudo, G.; Narizuka, S.; Askari, N.; Crousse, B.; Bonnet-Delpon, D. *Tetrahedron Lett.* **2006**, *47*, 2065. (g) Salter, M. M.; Kobayashi, J.; Shimizu, Y.; Kobayashi, S. *Org. Lett.* **2006**, *8*, 3533. (h) Chowdari, N. S.; Ahmad, M.; Albertshofer, K.; Tanaka, F.; Barbas, C. F., III *Org. Lett.* **2006**, *8*, 2839. (i) Couturier, C.; Blanchet, J.; Schlama, T.; Zhu, J. *Org. Lett.* **2006**, *8*, 2183. (j) Shimizu, M.; Inayoshi, K.; Sahara, T. *Org. Biomol. Chem.* **2005**, *3*, 2237. (k) Davis, F. A.; Deng, J. *Org. Lett.* **2004**, *6*, 2789. (l) Ooi, T.; Kameda, M.; Fujii, J.-i.; Maruoka, K. *Org. Lett.* **2004**, *6*, 2397. (m) Bernardi, L.; Gothelf, A. S.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 2583. (n) Knudsen, K. R.; Risgaard, T.; Nishiwaki, N.; Gothelf, K. V.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 5843. (o) Nishiwaki, N.; Knudsen, K. R.; Gothelf, K. V.; Jørgensen, K. A. *Angew. Chem, Int. Ed.* **2001**, *40*, 2992.

(5) Chen, Z.; Morimoto, H.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2008**, *130*, 2170.

(6) (a) Arrayás, R. G.; Carretero, J. C. *Chem. Soc. Rev.* **2009**, *38*, 1940. (b) Hernández-Toribio, J.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2008**, *130*, 16150. (c) Singh, A.; Johnston, J. N. *J. Am. Chem. Soc.* **2008**, *130*, 5866. (d) Han, B.; Liu, Q.-P.; Li, R.; Tian, X.; Xiong, X.-F.; Deng, J.-G.; Chen, Y.-C. *Chem.—Eur. J.* **2008**, *14*, 8094.

(7) For some selected general reviews on asymmetric organocatalysis, see: (a) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138. (b) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. (c) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560. (d) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 463. (e) Xu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037. (f) Pellissier, H. *Tetrahedron* **2007**, *63*, 9267. (g) List, B.; Yang, J. W. *Science* **2006**, *313*, 1584. (h) List, B. *Chem. Commun.* **2006**, 819. (i) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719. (j) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138.

reaction. A series of aza-Mannich adducts were obtained in excellent diastereomeric ratios and ee values (entries 1, 2, and 4−9). Good results were also gained by using an *N*-tosyl imine with a bulky naphthyl substituent group as a substrate (entry 10). In addition, different substituents on the C=N bond of the oxazolone were also tested. The outstanding diastereo- and enantioselectivity were observed for the oxazolone with the *para*-chlorophenyl group at this position (entry 12). Other oxazolones with a different alkyl substituent at the R_1 position could also be smoothly applied as substrates in this reaction (entries 13−15). For example, an ee value of as high as 97% with an excellent diastereomeric ratio of 20:1 was attained when the imine **3d** and oxazolone **2d** were used in entry 13.[12]

Under the optimized conditions, the opposite enantiomer of product **4b** could also be favorably obtained by carrying out the reaction with the opposite configuration quinidine derivative **1e** in excellent diastereoselectivity and good enantioselectivity (entry 3).

The constitution and absolute configuration of the product **4g** were determined by using X-ray crystallography (Figure 1) as well as by NMR spectroscopic studies.[13]

The synthetic versatility of the aza-Mannich adducts in this reaction was illustrated by a further transformation. Optically active α-disubstituted α,β-diamino acids **5** were

(8) For reviews on chiral cinchona alkaloid catalysts, see: (a) Connon, S. J. *Chem. Commun.* **2008**, 2499. (b) Marcelli, T.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 7496. (c) Tian, S.-K.; Chen, Y. G.; Hang, J. F.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621. (d) Chen, Y. G.; McDaid, P.; Deng, L. *Chem. Rev* **2003**, *103*, 2965. For selected examples of chiral cinchona alkaloid catalysis, see: (e) Liu, Y.; Sun, B. F.; Wang, B. M.; Wakem, M.; Deng, L. *J. Am. Chem. Soc.* **2009**, *131*, 41. (f) Dodda, R.; Goldman, J. J.; Mandal, T.; Zhao, C.-G.; Broker, G. A.; Tiekink, E. R. T. *Adv. Synth. Catal* **2008**, *350*, 537. (g) Singh, R. P.; Bartelson, K.; Wang, Y.; Su, H.; Liu, X. J.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 2422. (h) Liu, T.-Y.; Cui, H.-L.; Chai, Q.; Long, J.; Li, B. J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Chem. Commun.* **2007**, 2228. (i) Comer, E.; Rohan, E.; Deng, L., Jr.; Porco, J. A. *Org. Lett.* **2007**, *9*, 2123. (j) Wang, Y.; Li, H. M.; Wang, Y.-Q.; Liu, Y.; Foxman, B. M.; Deng, L *J. Am. Chem. Soc.* **2007**, *129*, 6364. (k) Wang, B. M.; Wu, F. H.; Wang, Y.; Liu, X. F.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 768. (l) Wang, J.; Li, H.; Zu, L.; Jiang, W.; Xie, H.; Duan, W.; Wang, W. *J. Am. Chem. Soc.* **2006**, *128*, 12652. (m) Li, H. M.; Wang, Y.-Q.; Deng, L. *Org. Lett.* **2006**, *8*, 4063. (n) Wu, F. H.; Hong, R.; Khan, J. H.; Liu, X. F.; Deng, L. *Angew. Chem., Int. Ed* **2006**, *45*, 4301. (o) Wang, Y.; Liu, X. F.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 3928. (p) Li, H. M.; Wang, B. M.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 732. (q) Liu, X. F.; Li, H. M.; Deng, L. *Org. Lett.* **2005**, *7*, 167. (r) 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. (s) Saaby, S.; Bella, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 8120. (t) Li, H. M.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906. (u) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691.

(9) (a) Chen, F.; Shao, C.; Liu, Q.; Gong, P.; Liu, C.; Wang, R. *Chirality* **2009**, *21*, 600. (b) Chen, F.; Shao, C.; Wang, Y.; Gong, P.; Zhang, D. Y.; Zhang, B. Z.; Wang, R. *Tetrahedron Lett.* **2007**, *48*, 8456.

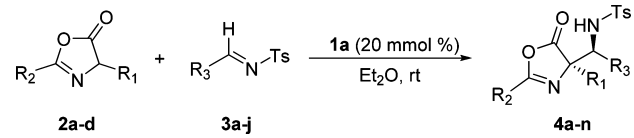
(10) (a) Fisk, J. S.; Mosey, R. A.; Tepe, J. J. *Chem. Soc. Rev.* **2007**, *36*, 1432. (b) Trost, B. M.; Jakel, C.; Plietker, B. *J. Am. Chem. Soc.* **2003**, *125*, 4438. (c) Trost, B. M.; Dogra, K. *J. Am. Chem. Soc.* **2002**, *124*, 7256. (d) Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727. (e) Ruble, J. C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 11532.

(11) (a) Uraguchi, D.; Koshimoto, K; Ooi, T. *Chem. Commun.* **2010**, *46*, 300. (b) Alemán, J.; Milelli, A.; Cabrera, S.; Reyes, E.; Jørgensen, K. A. *Chem.—Eur. J.* **2008**, *14*, 10958. (c) Uraguchi, D.; Ueki, Y.; Ooi, T. *J. Am. Chem. Soc.* **2008**, *130*, 14088. (d) Cabrera, S.; Reyes, E.; Alemán, J.; Milelli, A.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 12031.

(12) Under the optimized conditions, the alkyl-substituted isobutyl *N*-tosyl imine showed no reactivity toward oxazolone **2a**.

(13) CCDC 755504 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table 2. Asymmetric Synthesis of α-Disubstituted α,β-Diamino Acid Derivatives[a]



entry	R_1/R_2, **2**	R_3, **3**	yield [%][b]	dr[c]	ee [%][d]
1	iPr/Ph	Ph	92	15:1	94
	2a	**3a**	**4a**		
2	iPr/Ph	*p*-Me-Ph	80	17:1	96
	2a	**3b**	**4b**		
3	iPr/Ph	*p*-Me-Ph	85	23:1	−80[e]
	2a	**3b**	**4b**		
4	iPr/Ph	*o*-MeO-Ph	80	30:1	93
	2a	**3c**	**4c**		
5	iPr/Ph	*o*-F-Ph	93	26:1	92
	2a	**3d**	**4d**		
6	iPr/Ph	*o*-Cl-Ph	89	30:1	95
	2a	**3e**	**4e**		
7	iPr/Ph	*p*-Cl-Ph	75	19:1	93
	2a	**3f**	**4f**		
8	iPr/Ph	*p*-Br-Ph	70	17:1	92[f]
	2a	**3g**	**4g**		
9	iPr/Ph	*p*-NO_2-Ph	49	24:1	84
	2a	**3h**	**4h**		
10[g]	iPr/Ph	2-naphth	84	9:1	93
	2a	**3i**	**4i**		
11	iPr/o-F-Ph	*p*-Me-Ph	94	3:1	86
	2b	**3b**	**4j**		
12	iPr/p-Cl-Ph	*o*-Cl-Ph	82	>30:1	93
	2c	**3e**	**4k**		
13	iBu/Ph	*o*-F-Ph	78	20:1	97
	2d	**3d**	**4l**		
14	iBu/Ph	*o*-Cl-Ph	90	25:1	90
	2d	**3e**	**4m**		
15	iBu/Ph	*o*-Br-Ph	76	22:1	93
	2d	**3j**	**4n**		

[a] Experimental conditions unless otherwise stated: a mixture of **2a** (0.2 mmol), **2b** (0.1 mmol), and **1a** (20 mmol %) in the ethyl ether (1 mL) was stirred at room temperature for 8−12 h, and full conversion was observed in all the cases. [b] Yield of diastereoisomeric mixture isolated by silica-gel column chromatography. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] The enantiomeric excess was determined by HPLC analysis on a Chiralcel column. [e] The quinidine derived catalyst **1e** was used. [f] The absolute configuration of **4g** was determined by X-ray crystal-structure analysis. The absolute configurations of the other products were assigned by analogy. [g] The reaction was carried out with 20 mmol % **1b** under 0 °C for 16 h.

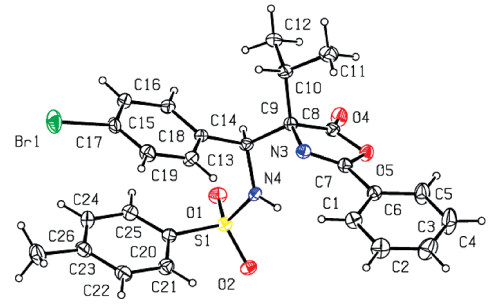
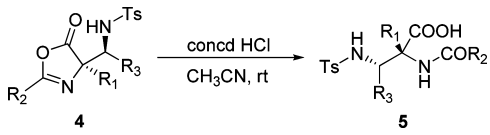


Figure 1. X-ray structure of compound **4g**.

Table 3. Hydrolyzed to the Corresponding Protected α-Disubstituted α,β-Diamino Acids[a]



4 5

entry	substrates	R_1/R_2	R_3	yield [%]
1	**4a**[b]	iPr/Ph	Ph	92 (**5a**)[c]
2	**4g**[b]	iPr/Ph	*p*-Br-Ph	95 (**5b**)[c]

[a] The reaction was carried out with **4** (0.3 mmol) and concd HCl (0.6 mmol) in 1.0 mL of MeCN as solvent. [b] The major diastereoisomer of **4** was isolated and used in this reaction. [c] A single diastereoisomer was obtained.

obtained by using the protocol developed by Trost et al (Table 3).[14] Both of the adducts **4a** and aryl-substituted **4g** could react efficiently to afford the corresponding protected amino acids with excellent yields (entries 1 and 2). When the R_2 was a phenyl substituent group, the Ts- and Bz-diprotected α-disubstituted α,β-diamino acids were obtained.

In summary, a simple cinchona alkaloid catalyzed aza-Mannich addition of *N*-tosyl aldimines with oxazolones has been accomplished. It was proven that this was an efficient way to synthesize α-disubstituted α,β-diamino acid derivates with good yields and excellent diastereo- (up to >30:1) and enantioselectivities (up to 97%). The high enantiopure α-disubstituted α,β-diamino acids can be gained from the adducts just by a one-pot hydrolyzed reaction.

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Supporting Information Available: Experimental details, characterization data for the products, and crystal structure data of adduct **4g** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) (a) Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727. (b) Trost, B. M.; Dogra, K. *J. Am. Chem. Soc.* **2002**, *124*, 7256. (c) Trost, B. M.; Jakel, C.; Plietker, B. *J. Am. Chem. Soc.* **2003**, *125*, 4438.