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Catalytic Enantioselective Amination of Enolsilanes Using C_2-Symmetric Copper(II) Complexes as Chiral Lewis Acids

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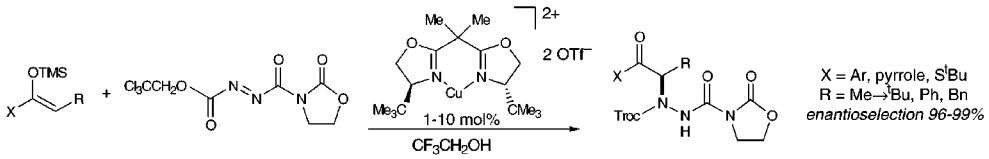
ABSTRACT

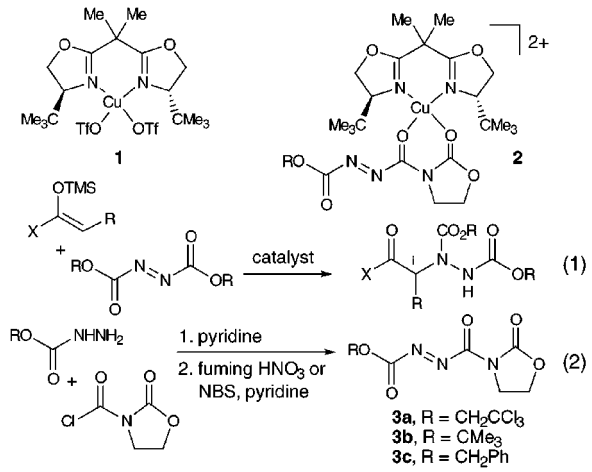


[Cu(*S*,*S*)-*t*-Bu-box](OTf)$_2$ (1) catalyzes the enantioselective amination of enolsilanes with azodicarboxylate derivatives. Isomerically pure enolsilanes of aryl ketones, acylpyrroles, and thioesters added to the azo-imide in greater than 95% ee. The use of an alcohol additive was critical to achieving catalyst turnover.

Recent reports from this laboratory have documented the utility of chiral Cu(II) Lewis acids such as **1** in the enantioselective catalysis of a range of carbon−carbon bond forming reactions, including carbo- and heterocyclic Diels−Alder, aldol, Michael, and ene reactions.[1] Herein, we report the use of these catalysts in the enantioselective amination of enolsilanes with azodicarboxylate derivatives (Scheme 1).[2−4] This methodology provides an enantioselective catalytic route to differentially protected α-hydrazino carbonyl compounds.[5]

It was envisioned that azo-imides such as **3**,[6] upon coordination with the chiral Cu(II) complex **1** to give adduct **2**, might participate in enantioselective enol amination (Scheme 1) in direct analogy to previously reported Diels−Alder reactions.[1d] While a number of azodicarboxylate derivatives were prepared, **3a** (mp 86 °C) was selected over **3b** (mp 99 °C) and **3c** (mp 105 °C) for the present study on the basis of its favorable solubility properties and reactivity profile. A survey of Cu(II) complexes revealed that [Cu-

Scheme 1



(1) (a) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Connell, B. *J. Am. Chem. Soc.* **1999**, *121*, 669−685 and references therein. (b) Evans, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 4895−4896. (c) Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3372−3375. (d) Evans, D. A.; Miller, S. J.; Lectka, T. C. *J. Am. Chem. Soc.* **1993**, *115*, 7027−7030.

(2) For reviews on electrophilic amination, see: (a) Boche, G. In *Stereoselective Synthesis*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 9, pp 5133−5157. (b) Greck, C.; Genet, J. P. *Synlett* **1997**, 741−748. For diastereoselective aminations of chiral enolates or chiral silylketene acetals, see: (c) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 6395−6397. (d) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *Tetrahedron* **1988**, *44*, 5525−5540. (e) Trimble, L. A.; Vederas, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 6397−6399. (f) Gennari, C.; Colombo, L.; Bertolini, G. *J. Am. Chem. Soc.* **1986**, *108*, 6394−6395.

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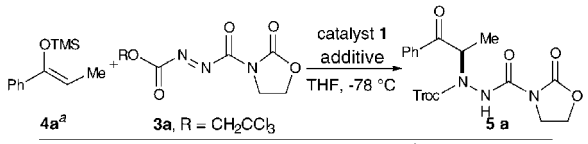
(*S*,*S*)-*t*-Bu-box]$(OTf)_2$ (**1**)[7] was the catalyst of choice for the addition of propiophenone enolsilane (**4a**) to azo-imide **3a**, affording the (*R*) hydrazino adduct **5a** in 99% ee and 96% yield (Table 1).[8] The reaction is completely regioselective

Table 1. Survey of Reaction Conditions for Amination of **4a**



entry	catalyst **1**	additive	% yield[d]	% ee[e]	time
1	25 mol%	none	96	99	24 h
2	10 mol %	none	60	90	24 h
3	10 mol %	$Cu(OTf)_2$[b]	96	99	24 h
4	2 mol %	$Cu(OTf)_2$[c]	95	96	24 h
5	10 mol %	CF_3CH_2OH	95	99	3 h

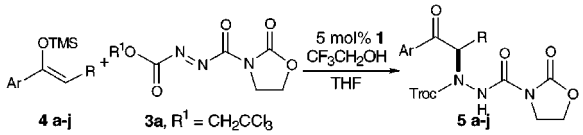
[a] *Z*:*E* ≥ 99:1. [b] 40 mol %. [c] 48 mol %. [d] Isolated yield. [e] Enantiomeric excess determined by HPLC (Chiralcel AD). (Troc: $O_2CCH_2CCl_3$.)

on the azo component, suggesting that **3a** is being activated through the anticipated chelate **2**. Complete conversion was observed when a catalyst loading of 25 mol % was employed; however, reduction of the catalyst loading resulted in lower product yield and enantiomeric excess (entries 1 and 2). Presumably, the adduct was competitively binding to the copper catalyst thus sequestering it from the catalytic cycle. It was found that when the reaction was conducted with excess $Cu(OTf)_2$ (50 mol %) relative to ligand (2−10 mol %), the reaction proceeded to completion without a significant decrease in enantioselectivity (entries 3 and 4), highlighting the importance of ligand acceleration in this reaction.[9] However, more reactive enolsilanes (**4b** and **4c**) were susceptible to $Cu(OTf)_2$-catalyzed additions under these conditions resulting in diminished enantioselectivities (80% and 90% ee, respectively).

The amination of **4a** was complete within 5 min at −78 °C when a stoichiometric amount of **1** was used (versus 12−24 h for entries 1−4), indicating that the initial addition is very fast and catalyst turnover is rate-limiting. Therefore, additives to promote catalyst turnover were evaluated. It was observed that the reaction proceeded to completion in 3 h at −78 °C in the presence of 1 equiv of trifluoroethanol (Table 1, entry 5).[10] Ethanol, 2-propanol, and hexafluoro-2-propanol also worked in a similar manner, but reaction times were slightly longer.

This reaction may also be carried out at higher temperatures (−20 °C)[11] and with lower catalyst loadings (5 mol % **1**) in the presence of alcoholic additives without significant erosion in reaction stereoselection (Table 2). A range of aryl ketone enolsilanes were aminated in excellent enantioselectivity and yield. The reaction of **4a**−**c** provided the adducts **5a**−**c** in 99% ee and 95% yield even at −20 °C (entries 1−3). Reaction times increased as the R group of the enolsilane became larger.

Table 2. Amination of Aryl Ketone Enolsilanes (**4**)



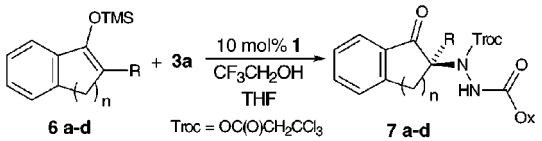
entry	**4**[b]	Ar	R	T (°C)	% yield[c]	% ee[d]	time[e]
1	**4a**	Ph	Me	-20	95	99	2 min
2	**4b**	4′-MeOPh	Me	-20	96	99	<1 min
3	**4c**	6′-MeONap[a]	Me	-20	96	99	1 min
4	**4d**	Ph	Et	-20	93	98	0.5 h
5	**4e**	Ph	Allyl	-20	92	97	2 h
6	**4f**	Ph	*t*Bu	-20	92	98	2 h
7	**4g**	Ph	*i*Pr	-20	86	99	3h
8	**4h**	4′-MeOPh	*t*Bu	-20	84[f]	98	(6 h)
9	**4i**	4′-MeOPh	Bn	-20	88	91	3 min
10	**4i**	4′-MeOPh	Bn	-78	94	99	(12 h)
11	**4j**	4′-MeOPh	Ph	-20	95	91	(2 h)
12	**4j**	4′-MeOPh	Ph	-50	94	97	(13 h)

[a] Enolsilane of 6′-methoxy-2′-propiononaphthone. [b] *Z*:*E* ≥ 99:1. [c] Isolated yield. [d] Enantiomeric excess determined by HPLC (Chiralcel AD). [e] Reaction progress was monitored by in situ IR spectroscopy using a ReactIR 1000 from ASI Applied Systems except entries 8 and 10−12. [f] A total of 1.2 equiv of **3** was used; yield is based on enolsilane. (Troc: $O_2CCH_2CCl_3$.)

Several cyclic enolsilanes were also examined in the amination reaction (Table 3). The enolsilane of indanone (**6a**) was aminated in only 21% ee (entry 1), whereas the 2-methyl-substituted variant **6b** provided the adduct **7b**, containing a tetrasubstituted stereogenic center, in 96% ee (entry 3). In contrast to the low selectivity observed with **6a**, increasing the ring size to the six- and seven-membered homologues **6c** and **6d** resulted in products with high enantioselectivities (entries 4 and 5).

This methodology was extended to thioester silylketene acetals, providing access to α-hydrazino esters and acids

Table 3. Amination of Cyclic Enolsilanes (**6**)



entry	**6**	R	n	T (°C)	% yield[a]	% ee[b]
1	**6a**	H	1	-78	90	21
2	**6b**	Me	1	-20	90	86
3	**6b**	Me	1	-78	88	96
4	**6c**[c]	H	2	-20	51[d]	90
5	**6d**	H	3	-78	94	99

[a] Isolated yields. [b] Enantiomeric excess determined by HPLC (Chiralcel AD or OJ). [c] The corresponding TES enolsilane was aminated in 53% yield and 93% ee (−20 °C, 30 min). [d] The reduced yield is a result of competitive reduction of the azo compound with concomitant production of 1-naphthol.

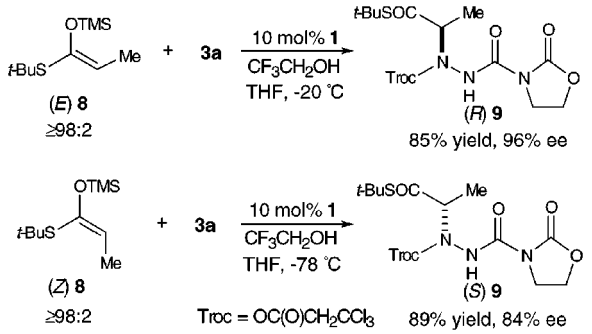
(3) For diastereoselective aminations of enolates with chiral aminating reagents, see: (a) Oppolzer, W.; Tamura, O.; Sundarababu, G.; Signer, M. *J. Am. Chem. Soc.* **1992**, *114*, 5900−5902. (b) Harris, J. M.; McDonald, R.; Vederas, J. C. *J. Chem. Soc., Perkin Trans. 1*, **1996**, 2669−2674.

(4) For a merged enolization enantioselective amination, see: Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, *119*, 6452−6453.

(5) This functionality is present in a number of biologically important natural products: (a) Ciufolini, M. A.; Xi, N. *Chem. Soc. Rev.* **1998**, *27*, 437−445. (b) Schmidt, U.; Braun, C.; Sutoris, H. *Synthesis* **1996**, 223−229. For a ribosome-mediated incorporation of hydrazinophenylalanine into a protein, see: (c) Killian, J. A.; Van Cleve, M. D.; Shayo, Y. F.; Hecht, S. M. *J. Am. Chem. Soc.* **1998**, *120*, 3032−3042.

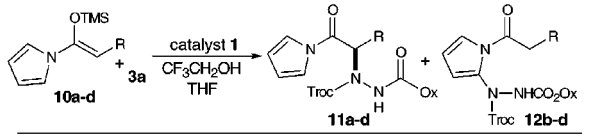
(Scheme 2). Addition of (*E*)-**8** to **3a** provided the (*R*) adduct **9** in 96% ee (−20 or −78 °C). However, a 93:7 (*E*)/(*Z*) mixture of **8** afforded (*R*)-**9** in only 83% ee. In fact, the pure (*Z*) isomer afforded the opposite enantiomer (*S*)-**9** in 84% ee at −78 °C (64% ee, −20 °C).[12] Therefore, it is critical to use geometrically pure enolsilanes to achieve high enantioselection in these additions.

Scheme 2



The preceding conclusion led us to investigate silylketene aminals of acylpyrroles,[13] which can more easily be obtained as the (*Z*) isomer in high geometrical purity (≥98:2) (NaHMDS, THF/DMPU, TMSCl, −78 °C). Enolsilane **10a** proved to be a highly effective nucleophile in the amination reaction, affording (*R*) **11a** in 99% ee and 96% yield in less than 30 min at −78 °C (Table 4, entry 1). The reaction was

Table 4. Amination of Acylpyrrole Enolsilanes (**10**)



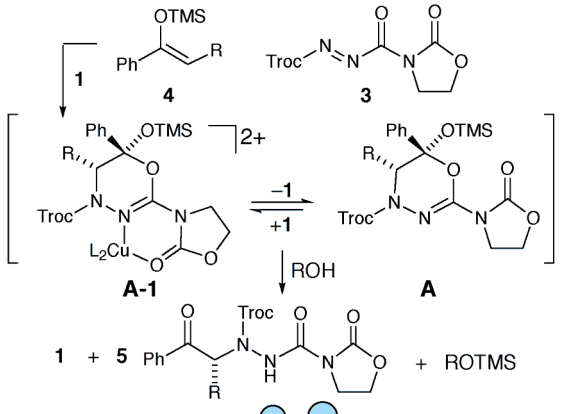
entry	**10**[a]	R	mol% cat	T (°C)	% yield **11**[c]	% yield **12**[d]	% ee[e]
1	**10a**	Me	5	-78	96	-	99
2	**10a**	Me	5	-20	95	-	98
3	**10a**	Me	1	-20	93	-	98
4	**10b**	Allyl	5	-20	73	18	98
5	**10b**	Allyl	5[b]	25	75	15	96
6	**10c**	^{i}Pr	5	-20	65	23	99
7	**10c**	^{i}Pr	5[b]	25	64	20	99
8	**10d**	^{t}Bu	5	-20	-	80	-

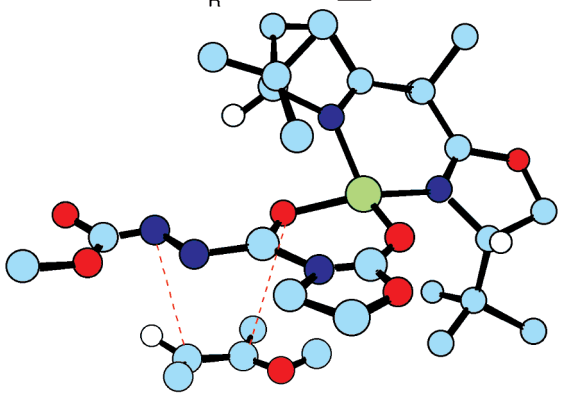
[a] *Z*:*E* ≥ 98:2. [b] The hydrate catalyst of **1** was used. [c] Isolated yields. [d] Isolated yield of **12** after protodesilylation with 10% HCl (see Supporting Information). [e] Enantiomeric excess determined by HPLC (Chiralcel AD).

instantaneous at −20 °C (entry 2). The enhanced nucleophilicity of **10a** allowed the catalyst loading to be lowered to 1 mol %, and the reaction was still complete in less than 5 min (entry 3). Unfortunately, increasing the size of the R group (**10b** and **10c**) slowed the reaction enough to allow for a competing amination of the pyrrole ring (entries 4−7). Nonetheless, the hydrazino adducts **11b** and **11c** are obtained in >96% ee even when the reactions are conducted at 25 °C.[14] The *t*-Bu-substituted enolsilane **10d** proved to be too sterically demanding and amination occurred exclusively on the pyrrole ring to give **12d** (entry 8). Despite their limitation in the present study, acylpyrrole-derived enolsilanes should find widespread use as nucleophiles in Mukaiyama-type addition reactions.

Mechanistic Considerations. The stoichiometric [Cu((*S*,*S*)-*t*-Bu-box)](OTf)$_2$ (**1**)-catalyzed reaction between enolsilane **4** and azo-imide **3** in the absence of trifluoroethanol results in the rapid formation of an intermediate with an IR frequency at 1687 cm^{-1}, characteristic of the C=N stretch in 5,6-dihydrooxadiazenes,[15] as evidenced by in situ IR spectroscopy (Supporting Information). We propose that this intermediate is the formal hetero-Diels-Alder adduct **A** as its derived Cu(II) complex **A-1** (Scheme 3).[16] In the absence

Scheme 3





Qualitative model of the hetero Diels-Alder transition state showing stereochemical relationships between reactants (Troc = OC(O)CH$_2$CCl$_3$)

of the alcohol additive, this intermediate sequesters the chiral catalyst **1** suppressing catalyst turnover. Upon the addition of trifluoroethanol, this intermediate is rapidly transformed into product hydrazide **5** along with silylated alcohol. Alternatively, when the catalytic process (5 mol % **1**, THF, −78 °C) is carried out in the presence of trifluoroethanol, the buildup of this intermediate is not observed. It is

(6) Details on the preparation of the azo compounds **3a**−**c** and an X-ray crystal structure of **3c** may be found in the Supporting Information.

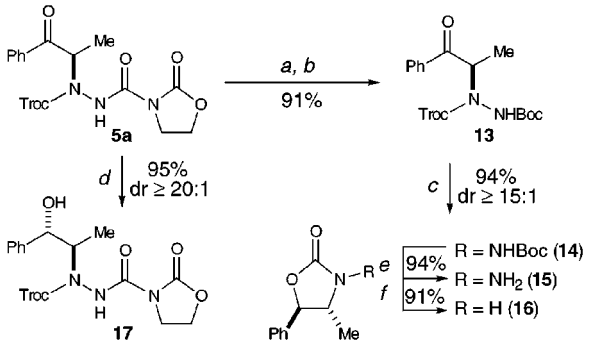
(7) Evans, D. A.; Peterson, G. S.; Johnson, J. S.; Barnes, D. M.; Campos, K. R.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 4541−4544.

(8) The absolute configuration was proven by X-ray crystallography as well as chemical correlation by conversion to the known oxazolidinone **16** (vide infra).

significant that the sense of asymmetric induction in these reactions is coupled to enolsilane geometry (Scheme 2). We propose that the strong *endo* bias for the OR substituent on the electron-rich olefin reaction component,[17] documented for related hetero cycloadditions,[1b,c] provides the organization for the 2π reaction component while face selectivity for the 4π reaction component is controlled by the azo-imide catalyst complex as illustrated in Scheme 3.

Product Modification. The keto hydrazides may be transformed into synthetically useful building blocks. Following Boc protection of adduct **5a**,[18] the imide was hydrolyzed with LiO_2H to give orthogonally protected hydrazine **13** (Scheme 4).[19] Alternatively, these adducts may

Scheme 4[a]



[a] Key: (a) Boc_2O, cat. DMAP, THF; (b) LiOOH, THF, H_2O, 0 °C; (c) L-Selectride, THF, −78 °C to room temperature; (d) Et_3SiH, TFA, 0 °C; (e) 4 M HCl in dioxane; (f) Zn, HOAc, acetone.

be stereoselectively reduced to provide the derived *syn* or *anti* hydrazino alcohols, respectively.[20] For example, the Et_3SiH reduction of **5a** affords the *anti* product **17** with good stereoselectivity. Alternatively, during the related L-Selectride reduction of **13** to the diastereomeric *syn*-hydrazino alcohol, facile cyclization to the derived *N*-amino oxazolidinone **14** is observed. Removal of the Boc group (4 M HCl, dioxane, 25 °C) provided the potentially useful *N*-amino-oxazolidinone **15**. The N−N bond was readily cleaved (Zn, AcOH, acetone) to give oxazolidinone **16**.[21] Comparison of the specific rotation of **16** ($[\alpha]_D = -17.9$ (*c* 1.15, $CHCl_3$)) with the literature value[22] confirmed the absolute stereochemistry of **5a** to be the (*R*) configuration.

The acylpyrrole and thioester hydrazino adducts were converted to the corresponding esters or carboxylic acids (Scheme 5).[23] Treatment of the thioester **9** with NBS in THF/

Scheme 5[a]

[a] Key: [X = S*t*Bu (**9**)] (a) NBS, THF, H_2O; CH_2N_2, 72%; (b) LiOOH, THF, H_2O, 0 °C; CH_2N_2, 60%; [X = pyrrole (**11a**)] (c) MeOH, Et_3N, 90%; (d) H_2SO_4, H_2O, dioxane, reflux; CH_2N_2, 74% (yields are unoptimized). (Troc: $O_2CCH_2CCl_3$.)

H_2O provided the carboxylic acid which was converted to ester **18** with CH_2N_2. Acylpyrrole **11a** could be hydrolyzed to the carboxylic acid (H_2SO_4, H_2O, dioxane) or converted directly to ester **18** (MeOH, Et_3N).[24]

Acknowledgment. Financial support was provided by the NIH (GM33328). A postdoctoral fellowship (D.S.J.) from the NIH (GM18595-02) is gratefully acknowledged. Jason Tedrow is acknowledged for the solution of X-ray structures.

Supporting Information Available: Experimental procedures and characterization of compounds and figure detailing in situ IR experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) The complex between **1** and **3** is cationic because at least one of the triflates is displaced upon binding of the imide moiety. However, $Cu(OTf)_2$ has two open coordination sites so its complex with **3** remains neutral. For a review on ligand accelerated catalysis, see: Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059−1070.

(10) This observation aided the development of two Mukaiyama−Michael reactions: Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994−1995.

(11) The azo compound decomposes in the presence of catalyst **1** at temperatures above −10 °C.

(12) Compound (*S*)-**9** was recrystallized (96% ee) and its absolute configuration was proven by X-ray crystallography.

(13) *N*-Acylpyrroles have been used as acylating agents and, as such, can be regarded as activated carboxylic acid equivalents: (a) Brandange, S.; Rodriguez, B. *Acta Chem. Scand.* **1987**, *B41*, 740−744. (b) Brandange, S.; Holmgren, E.; Leijonmarck, H.; Rodriguez, B. *Acta Chem. Scand.* **1995**, *49*, 922−928. (c) Lee, S. D.; Brook, M. A.; Chan, T. H. *Tetrahedron Lett.* **1983**, *24*, 1569−1572. To the best of our knowledge only the silylketene aminal of acetylpyrrole has been previously described: (d) Frick, U.; Simchen, G. *Liebigs Ann. Chem.* **1987**, 839−845.

(14) It is best to use the hydrate catalyst of **1** when conducting the reaction at room temperature. Compound **3** appears to be stable in the presence of the hydrate catalyst for about 1 h (THF, 25 °C). Notably, the use of sieves is not required, see: ref 1c.

(15) (a) Hall, J. H.; Wojciechowska, M. *J. Org. Chem.* **1978**, *43*, 3348−3353. (b) Hall, J. H.; Wojciechowska, M. *J. Org. Chem.* **1979**, *44*, 4, 38−41. (c) Leblanc, Y.; Fitzsimmons, B. J.; Springer, J. P.; Rokach, J. *J. Am. Chem. Soc.* **1989**, *111*, 2995−3000.

(16) An intermediate such as **A-1** (L = OTf, THF) was detected by electrospray MS (*m*/*z* = 807 with correct Cu and Cl isotope pattern).

(17) (a) For a summary, see: Boger, D. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 451−512. (b) Liu, J.; Niwayama, S.; You, Y.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 1064−1073.

(18) Burk, M. J.; Allen, J. G. *J. Org. Chem.* **1997**, *62*, 7054−7057.

(19) These unsymmetrical hydrazines could serve as templates for diversity chemistry since each nitrogen can be selectively deprotected and then alkylated or acylated. Selective deprotection is crucial because the free α-hydrazino acid derivatives are sensitive to oxidation and loss of N_2 (see ref 5a). Grehn, L.; Ragnarsson, U. *Synthesis* **1998**, 1817−1821.

(20) (a) Paleo, M. R.; Calaza, M. I.; Sardina, F. J. *J. Org. Chem.* **1997**, *62*, 6862−6869. (b) Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Tetrahedron Lett.* **1987**, *28*, 6331−6334. (c) Fujita, M.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 5415−5421.

(21) (a) Leblanc, Y.; Fitzsimmons, B. J. *Tetrahedron Lett.* **1989**, *30*, 2889−2892. (b) McClure, C. K.; Mishra, P. K.; Grote, C. W. *J. Org. Chem.* **1997**, *62*, 2437−2441.

(22) Jephcote, V. J.; Pratt, A. J.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1*, **1989**, 1529−1535. Compound (4*R*, 5*R*)-**16**: $[\alpha]_D = -15.9$ (*c* 0.38, $CHCl_3$).

(23) (a) Minato, H.; Takeda, K.; Miura, T.; Kobayashi, M. *Chem. Lett.* **1977**, 1095−1098. (b) Arai, E.; Tokuyama, H.; Linsell, M. S.; Fukuyama, T. *Tetrahedron Lett.* **1998**, *39*, 71−74. (c) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656−673.

(24) The methyl ester derived from (*R*)-**9** was identical to the methyl ester prepared from **11a** (HPLC, Chiracel AD) confirming the (*R*) absolute stereochemisty for **11a**.