

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

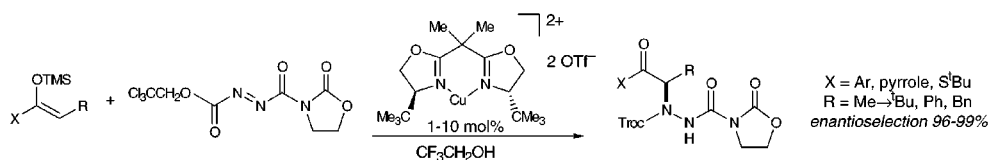
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Received June 1, 1999

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

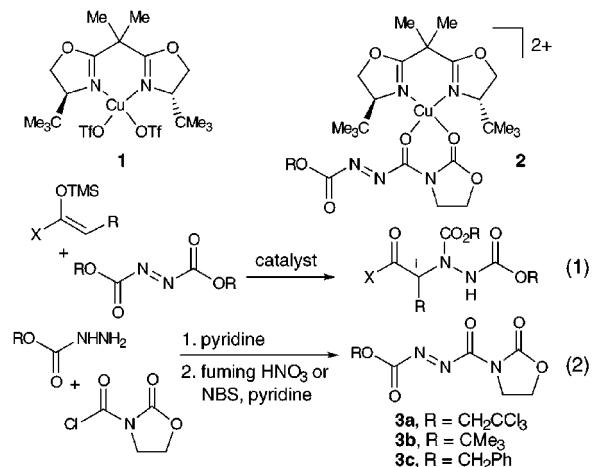
It was envisioned that azo-imides such as **3**,⁶ upon coordination with the chiral Cu(II) complex **1** to give adduct **2**, might participate in enantioselective enol amination

(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.

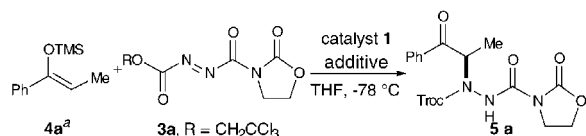
(Scheme 1) in direct analogy to previously reported Diels–Alder reactions.^{1d} While a number of azodicarboxylate derivatives were prepared, **3a** (mp 86 °C) was selected over **3b** (mp 99 °C) and **3c** (mp 105 °C) for the present study on the basis of its favorable solubility properties and reactivity profile. A survey of Cu(II) complexes revealed that [Cu-

Scheme 1



(*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 ₃ CH ₂ OH	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: O₂CCH₂CCl₃.)

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

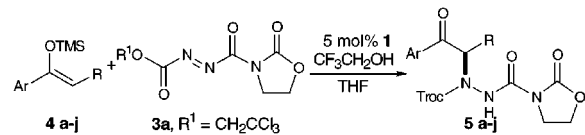
(3) For diastereoselective aminations of enolates with chiral aminating reagents, see: (a) Oppolzer, W.; Tamura, O.; Sundarababu, G.; Signer, M. *J. Am. Chem. Soc.* **1992**, *114*, 5900–5902. (b) Harris, J. M.; McDonald, R.; Vederas, J. C. *J. Chem. Soc., Perkin Trans. 1*, **1996**, 2669–2674.

(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.

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**)



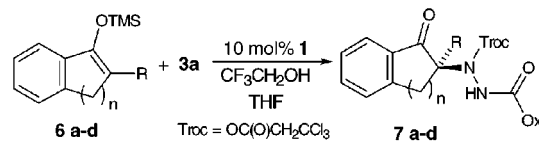
entry	4 ^b	Ar	R	T (°C)	% yield ^f	% ee ^d	time ^e
1	4a	Ph	Me	–20	95	99	2 min
2	4b	4'-MeOPh	Me	–20	96	99	<1 min
3	4c	6'-MeONap ^d	Me	–20	96	99	1 min
4	4d	Ph	Et	–20	93	98	0.5 h
5	4e	Ph	Allyl	–20	92	97	2 h
6	4f	Ph	^t Bu	–20	92	98	2 h
7	4g	Ph	ⁱ Pr	–20	86	99	3 h
8	4h	4'-MeOPh	^t Bu	–20	84 ^f	98	(6 h)
9	4i	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: O₂CCH₂CCl₃.)

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

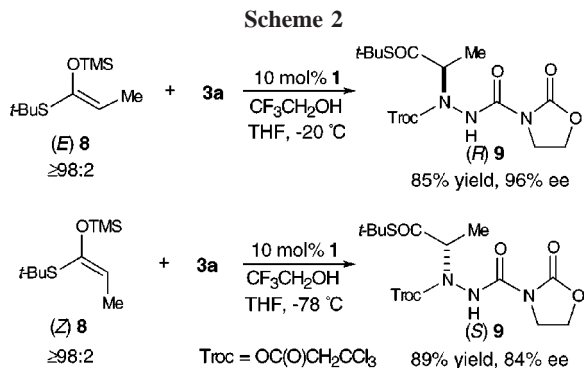
Table 3. Amination of Cyclic Enolsilanes (**6**)



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	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.

(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.



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 ($\geq 98:2$) (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	-

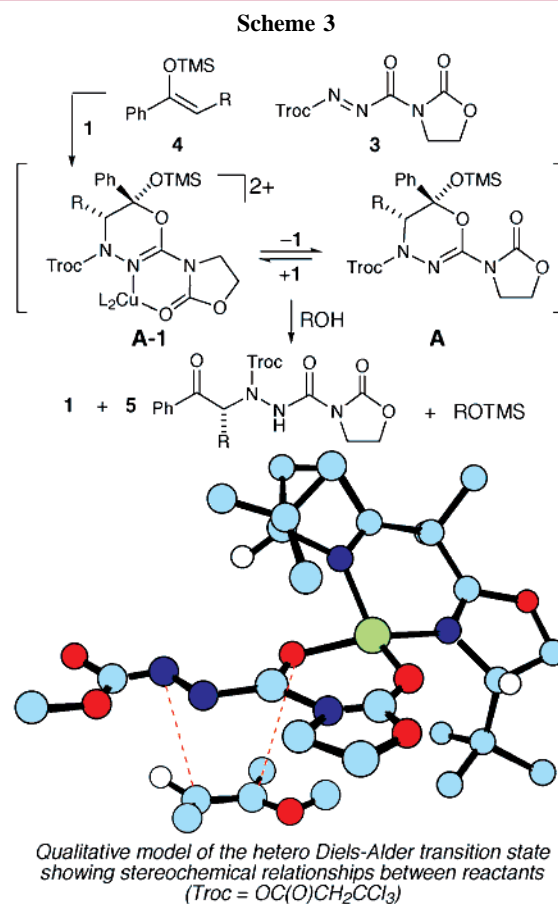
^a *Z*:*E* $\geq 98:2$. ^b The hydrate catalyst of **1** was used. ^c Isolated yields.

^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



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

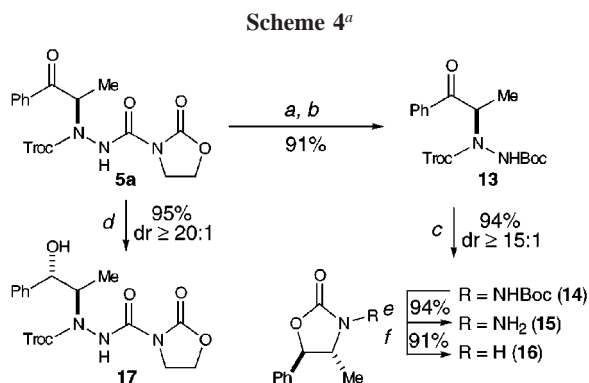
(6) Details on the preparation of the azo compounds **3a–c** and an X-ray crystal structure of **3c** may be found in the Supporting Information.

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(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 LiOH to give orthogonally protected hydrazine **13** (Scheme 4).¹⁹ Alternatively, these adducts may

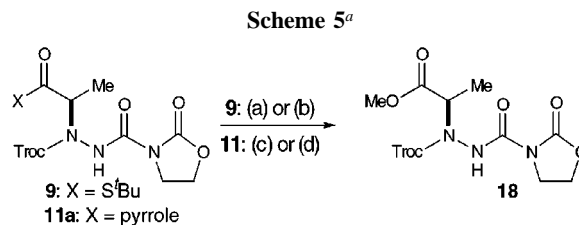


^a Key: (a) Boc₂O, cat. DMAP, THF; (b) LiOH, THF, H₂O, 0 °C; (c) L-Selectride, THF, -78 °C to room temperature; (d) Et₃SiH, TFA, 0 °C; (e) 4 M HCl in dioxane; (f) Zn, HOAc, acetone.

be stereoselectively reduced to provide the derived *syn* or *anti* hydrazino alcohols, respectively.²⁰ For example, the Et₃SiH 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, CHCl₃)) with the literature value²² 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/



^a Key: [X = S^tBu (**9**)] (a) NBS, THF, H₂O; CH₂N₂, 72%; (b) LiOH, THF, H₂O, 0 °C; CH₂N₂, 60%; [X = pyrrole (**11a**)] (c) MeOH, Et₃N, 90%; (d) H₂SO₄, H₂O, dioxane, reflux; CH₂N₂, 74% (yields are unoptimized). (Troc: O₂CCH₂CCl₃.)

H₂O provided the carboxylic acid which was converted to ester **18** with CH₂N₂. Acylpyrrole **11a** could be hydrolyzed to the carboxylic acid (H₂SO₄, H₂O, dioxane) or converted directly to ester **18** (MeOH, Et₃N).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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(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.

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(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 N₂ (see ref 5a). Grehn, L.; Ragnarsson, U. *Synthesis* **1998**, 1817–1821.

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