ORGANIC LETTERS

2006
Vol. 8, No. 15
3351−3354

Enantioselective Nitrone Cycloadditions of α,β-Unsaturated 2-Acyl Imidazoles Catalyzed by Bis(oxazolinyl)pyridine–Cerium(IV) Triflate Complexes

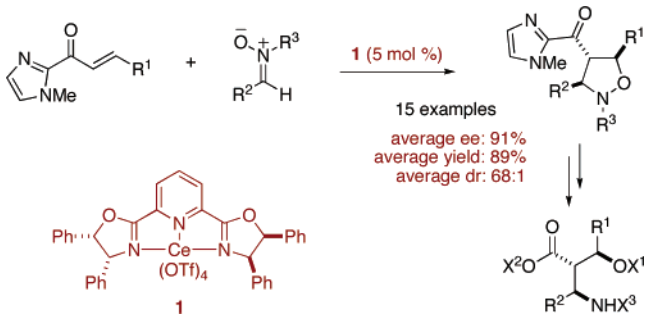
David A. Evans,* Hyun-Ji Song, and Keith R. Fandrick

Department of Chemistry and Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

evans@chemistry.harvard.edu

Received May 18, 2006

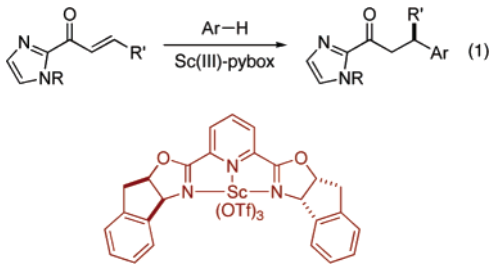
ABSTRACT



Enantioselective nitrone cycloadditions with β-substituted α,β-unsaturated 2-acyl imidazoles catalyzed by bis(oxazolinyl)pyridine–cerium(IV) triflate complexes 1 have been reported. The isoxazolidine products were efficiently transformed into densely functionalized β′-hydroxy-β-amino acid derivatives.

In this study, we report the utility of α,β-unsaturated 2-acyl imidazoles as effective dipolarophiles in the catalyzed enantioselective nitrone cycloaddition with the chiral cerium(IV) complex **1**. The isoxazolidine cycloaddition products are valuable precursors to biologically active β-amino acids, β-lactams, amino sugars, and alkaloids.[1] A range of chiral Lewis acid and organocatalysts have been reported for this useful transformation, and each system has its assets and liabilities.[2] Ideal attributes of this reaction might include high enantio- and diastereoselectivities, a broad reaction scope, and convenient reaction temperatures. The goal in this study has been to attempt to improve on the practicality of these enantioselective processes.

We recently reported the enantioselective Friedel−Crafts alkylation of α,β-unsaturated 2-acyl imidazoles catalyzed by the illustrated chiral Sc(III) complex (eq 1).[3] The preparation



of the requisite α,β-unsaturated 2-acyl imidazoles[3] and the conversion of 2-acyl imidazoles to useful carbonyl derivatives have been previously described.[3,4]

The present study began with a survey of chiral lanthanide−pybox[5,6] complexes in the prototypical cycloaddition

(1) For recent reviews, see: (a) Martin, J. N.; Jones, R. C. F. *Synthetic Application of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley and Sons: Hoboken, NJ, 2003; Chapter 1, p 1. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863−910.

10.1021/ol061223i CCC: $33.50
Published on Web 06/20/2006

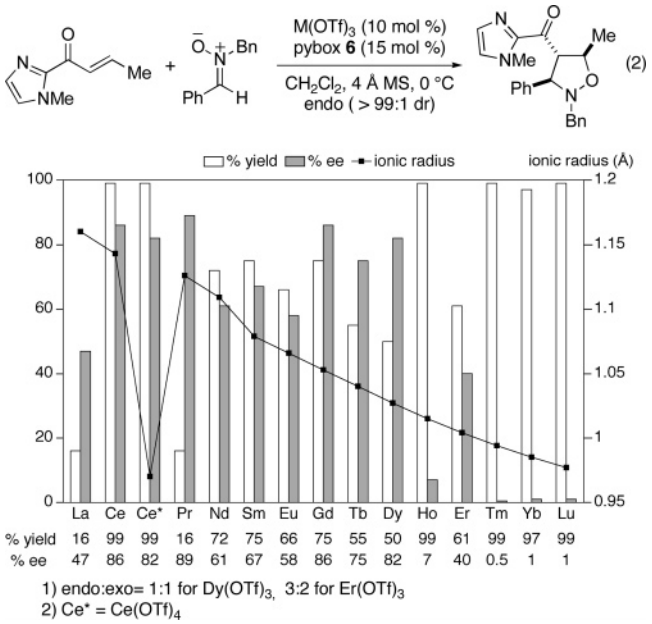


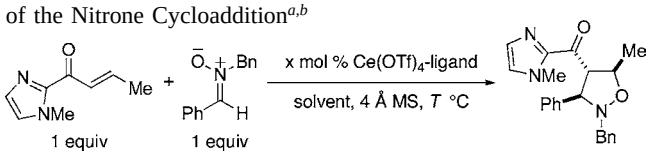
Figure 1. Lanthanide survey for the nitrone cycloaddition reaction with crotyl 2-acyl imidazole.

illustrated in eq 2 (Figure 1). Although the illustrated Sc(III)−pybox complex was an efficient catalyst for the Friedel−Crafts reactions (eq 1),[3] it was found to display poor enantiofacial control for the corresponding nitrone cycloadditions. Other proven Lewis acid catalysts from our group, such as the Cu(II)−pybox, Cu(II)−box,[7] and Ni(II)−box[8] complexes, also performed poorly for the illustrated transformation.[9]

From the lanthanide screen, it was concluded that the early lanthanide−pybox complexes were superior with respect to both overall yields and enantioselectivities as compared to their late lanthanide counterparts.[10,11] Upon further examination, we found that both Ce(III)·**6** triflate and Ce(IV)·**6** triflate (**1**) displayed excellent enantiofacial selectivities and yields for the illustrated reaction with crotyl 2-acyl imidazole. The Ce(IV)·**6** triflate complex (**1**)[12] was found to be a more general catalyst, as Ce(III)·**6** triflate performed sluggishly with more challenging substrates such as cinnamyl 2-acyl imidazole.

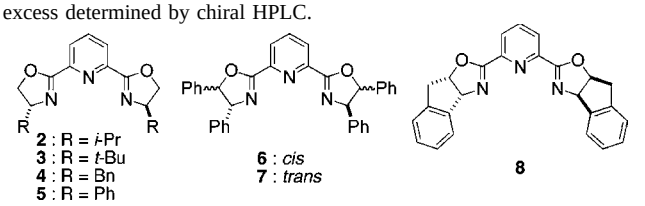
We next turned our attention to the effects of solvent, ligand substitution, and temperature on the cycloaddition (Table 1). It was found that the *cis*- and *trans*-bisphenyl−pybox ligands **6** and **7** afforded the best enantioselectivities and yields of the ligands explored (Table 1, entries 1−7). Ethyl acetate proved to be the solvent of choice (entries 8−14), and the reaction could be performed at ambient temperatures while maintaining excellent enantiofacial selectivities (entries 17 and 18). Trace amounts of moisture were found to be

Table 1. Optimization of the Catalyst and Reaction Parameters of the Nitrone Cycloaddition[a,b]



entry	ligand	solvent	mol %	temp (°C)	*t* (h)	% yield	% ee[c]
1	**2**	CH_2Cl_2	10	0	19	42	96
2	**3**	CH_2Cl_2	10	0	26	18	99
3	**4**	CH_2Cl_2	10	0	100	28	78
4	**5**	CH_2Cl_2	10	0	100	68	78
5	**6**	CH_2Cl_2	10	0	40	82	99
6	**7**	CH_2Cl_2	10	0	40	84	99
7	**8**	CH_2Cl_2	10	0	24	3	96
8	**6**	toluene	10	0	110	86	86
9	**6**	$CF_3C_6H_5$	10	0	17	87	87
10	**6**	EtOAc	10	0	11	96	98
11	**6**	Et_2O	10	0	110	68	91
12	**6**	THF	10	0	17	91	94
13	**6**	CH_3CN	10	0	110	72	64
14	**6**	*i*-PrOH	10	0	110	74	80
15	**6**	EtOAc	5	0	17	97	99
16	**6**	EtOAc	2	0	72	98	97
17	**6**	EtOAc	5	+20	11	90	97
18	**6**	EtOAc	5	+60	8	85	73

[a] All reactions performed at 0.1 M in substrate with 25 mg 4 Å MS/mL of solvent. [b] For all reactions, the endo:exo ratio was >99:1. [c] Enantiomeric excess determined by chiral HPLC.



(2) For Lewis acid catalyst examples, see: (a) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 11926−11927. (b) Suga, H.; Nakajima, T.; Itho, K.; Kakehi, A. *Org. Lett.* **2005**, *7*, 1431−1434. (c) Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355−12356. (d) Palomo, C.; Oiarbide, M.; Arceo, E.; García, J. M.; López, R.; González, A.; Linden, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6187−6190. (e) Sibi, M. P.; Ma, Z.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 718−719. (f) Kobayashi, S.; Kawamura, M. *J. Am. Chem. Soc.* **1998**, *120*, 5840−5841. For organocatalyst examples, see: (g) Jen, W. S.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874−9875. (h) Karlsson, S.; Hogberg, H.-E. *Eur. J. Org. Chem.* **2003**, 2782−2791.

(3) For indole Friedel−Crafts reactions with α,β-unsaturated 2-acyl imidazoles, see: (a) Evans, D. A.; Fandrick, K. R.; Song, H.-J. *J. Am. Chem. Soc.* **2005**, *127*, 8942−8943. For pyrrole Friedel−Crafts reactions, see: (b) Evans, D. A.; Fandrick, K. R. *Org. Lett.* **2006**, *8*, 2249−2252.

(4) For the transformation of 2-acyl-benzimidazoles to esters, amides, β-diketones, and β-ketoesters, see: (a) Miyashita, A.; Suzuki, Y.; Nagasaki, I.; Ishiguro, C.; Iwamoto, K.-I.; Higashino, T. *Chem. Pharm. Bull.* **1997**, *45*, 5, 1254−1258. For the transformation of 2-acyl-imidazoles to ketones, β-diketones, β-ketoesters, and aldehydes, see: (b) Ohta, S.; Hayakawa, S.; Nishimura, K.; Okamoto, M. *Chem. Pharm. Bull.* **1987**, *35*, 1058−1069.

(5) For a good review of metal−pybox complexes as chiral catalysts, see: Desimoni, G.; Faita, G.; Quadrelli, P. *Chem. Rev.* **2003**, *103*, 3119−3154.

(6) For the reviews of asymmetric catalysis by lanthanide complexes, see: (a) Steel, P. G. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2727−2751. (b) Mikami, K.; Terada, M.; Matsuzawa, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3554−3571. (c) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187−2209. (d) Inanaga, J.; Furuno, H.; Hayano, T. *Chem. Rev.* **2002**, *102*, 2211−2225. (e) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227−2302.

(7) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325−335.

(8) Evans, D. A.; Downey, C. W.; Hubbs, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 8706−8707.

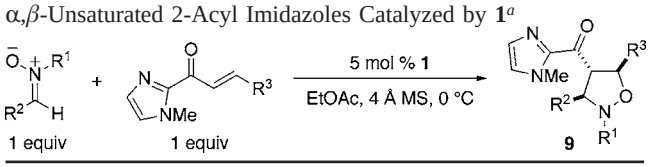
(9) For Sc(III) and Ni(II), excellent endoselectivity (>99:1) with poor enantioselectivity (max 6% ee) was observed. For Cu(II), a high dr (>99:1) with low ee (23%) and a low dr (3.5:1) with moderate ee (46% and 58%) were observed.

(10) For the ionic radii of lanthanide cations, see: Shannon, R. D. *Acta Crystallogr.* **1976**, *A32*, 751−767.

deleterious to the diastereo- and enantioselectivity of the cycloaddition.[13]

The scope of the reaction is provided in Table 2. The

Table 2. Substrate Survey of the Nitrone Cycloaddition with α,β-Unsaturated 2-Acyl Imidazoles Catalyzed by **1**[a]



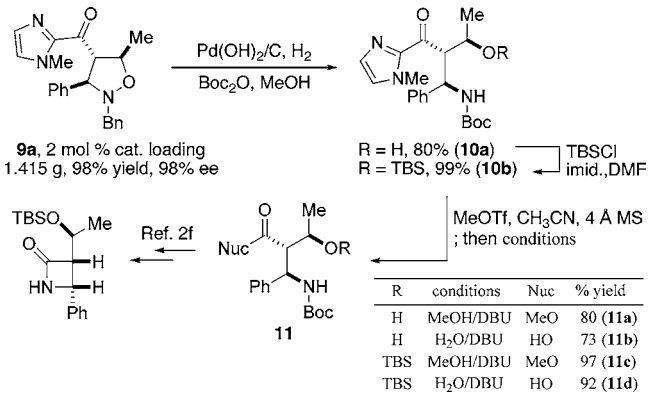
entry	R^1	R^2	R^3	t (h)	endo:exo	% ee[b]	% yield
1	Bn	Ph	Me	17	>99:1	97	99 (**9a**)
2	Me	Ph	Me	48	>99:1	92	92 (**9b**)
3	Ph	Ph	Me	36	6:1	80(90)[c]	98 (**9c**)
4	Bn	4-MeO-C_6H_4	Me	20	>99:1	96	88 (**9d**)
5	Bn	4-Cl-C_6H_5	Me	20	>99:1	95	90 (**9e**)
6	Bn	4-MeO_2C-C_6H_5	Me	36	>99:1	99	95 (**9f**)
7	Bn	1-naphthyl	Me	24	>99:1	90	92 (**9g**)
8	Bn	2-naphthyl	Me	24	>99:1	96	97 (**9h**)
9	Bn	Et	Me	20	2.4:1	87(76)[c]	97 (**9i**)
10	Bn	*c*-Hx	Me	24	1.5:1	85(66)[c]	76 (**9j**)
11	Bn	Ph	Et	36	50:1	92	80 (**9k**)
12[d]	Bn	Ph	*i*-Pr	36	>99:1	91	92 (**9l**)
13[d]	Bn	Ph	*n*-Bu	36	>99:1	87	72 (**9m**)
14[d,e]	Bn	Ph	Ph	120	3:1	95(93)[c]	80 (**9n**)
15[d]	Bn	Ph	CO_2Et	72	60:1	83	80 (**9o**)

[a] All reactions performed at 0.1 M in substrate with 25 mg 4 Å MS/mL of solvent. [b] Enantiomeric excess was determined by chiral HPLC. [c] Numbers in parentheses are for minor diastereomers. [d] 10 mol % of **1** was needed. [e] 3 days at 0 °C, then 2 days at room temperature.

illustrated reaction is well tolerant of *N*-aryl and *N*-alkyl nitrone substitution (entries 1−3). The more versatile *N*-benzyl nitrones provided the best diastereo- and enantioselectivities among the three substituents explored. *C*-Aryl nitrone substitution was also well tolerated in the cycloaddition (entries 4−8). However, reactions with the corresponding *C*-alkyl-substituted nitrones, while maintaining good enantioselectivities (entries 9 and 10), afforded disappointing diastereoselectivities. A range of alkyl, aryl, and carboxyl β-substituents on the α,β-unsaturated 2-acyl imidazole reaction component is well tolerated in the illustrated reaction (entries 11−15).

To elaborate the cycloaddition products, we turned our attention to the conversion of isoxazolidine **9a** to the synthetically useful β′-hydroxy-β-amino acid derivatives **11a**−**d** (Scheme 1).[2f] Hydrogenation of the N−O bond catalyzed by $Pd(OH)_2$/C with concurrent *N*-Boc protection proceeded well (80% yield, Scheme 1). Utilizing our previously reported

Scheme 1. Conversion of Isoxazolidine **9a** to β′-Hydroxy-β-amino Acid Derivatives **11a**−**d**



R	conditions	Nuc	% yield
H	MeOH/DBU	MeO	80 (**11a**)
H	H_2O/DBU	HO	73 (**11b**)
TBS	MeOH/DBU	MeO	97 (**11c**)
TBS	H_2O/DBU	HO	92 (**11d**)

cleavage procedure (MeOTf in CH_3CN),[3b] we could obtain the corresponding methyl ester (80% yield) or carboxylic acid (73% yield) without protecting the base-labile β-hydroxyl group of the 2-acyl imidazole **10a** (Scheme 1). Improved yields of the corresponding ester and carboxylic acid were realized if the sensitive β-hydroxyl group of the 2-acyl imidazole **10a** was protected as the TBS ether. We also found that the addition of 4 Å MS during the methylation of **10a**,**b** was advantageous.

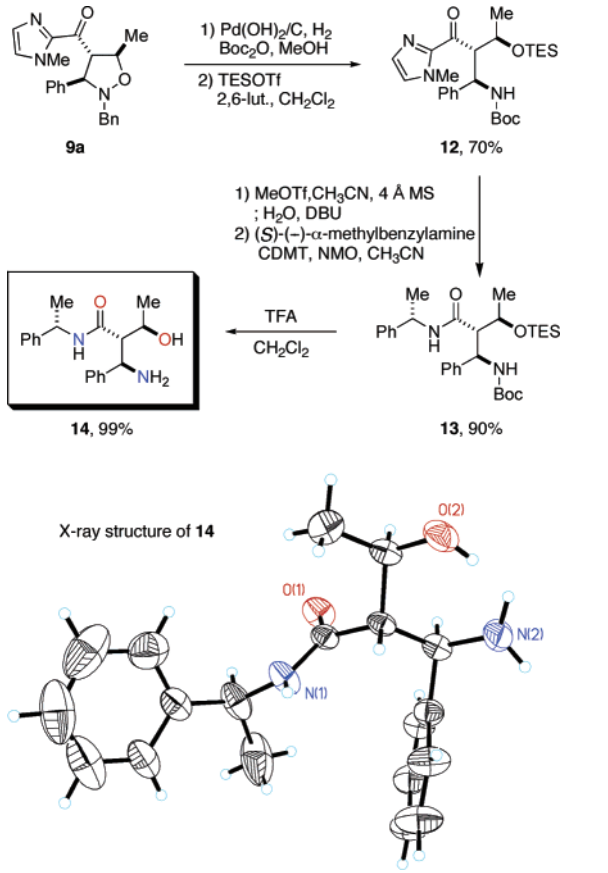


Figure 2. Determination of the absolute stereoconfiguration of **14**.

(11) For the size effect of rare earth metals on ee, see: (a) Evans, D. A.; Nelson, S. G.; Gagne, R.; Muci, A. R. *J. Am. Chem. Soc.* **1993**, *115*, 9800−9801. (b) Sasai, H.; Suzuki, T.; Itoh, N.; Arai, S.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 2657−2660. (c) Kobayashi, S.; Ishitani, H. *J. Am. Chem. Soc.* **1994**, *116*, 4083−4084. (d) Schaus, S. E.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 1001−1004. (e) Kobayashi, S.; Hamada, T.; Nagayama, S.; Manabe, K. *Org. Lett.* **2001**, *3*, 165−167.

(12) Ce(IV) triflate was prepared from CAN and dispensed from a glovebox. For the preparation of Ce(IV) triflate, see: Imamoto, T.; Koide, Y.; Hiyama, S. *Chem. Lett.* **1990**, 1445−1446.

(13) The addition of 4 Å MS to the reaction mixture of catalyst **1**, 2-acyl imidazole, and (*Z*)-*N*-benzylidene(phenyl)methanamine oxide in ethyl acetate (Table 2, entry I) raised the endo:exo diastereoselectivity from 22:1 to >99:1, the enantioselectivity from 71% ee to 98% ee, and the yield from 86% to 97%.

Employing the reaction sequence illustrated in Figure 2 followed by coupling of the carboxylic acid with (*S*)-(−)-α-methylbenzylamine and subsequent Boc and TES deprotections, we were able to obtain the crystalline amide **14** in 62% overall yield. The absolute stereochemistry of **14**, and thus the parent isoxazolidine **9a**, was determined by an X-ray structure of **14**.[14]

Nonlinear effects can act as a probe for the reaction mechanism.[15] The enantiomeric excess of nitrone cycloaddition product **9a** was monitored as a function of enantiomeric composition of the chiral ligand **6** (Figure 3). Significant (+)-nonlinear effects were observed in this analysis, which might suggest the possible formation of a reservoir of nonreactive aggregates.[15] We were able to obtain **9a** with the selectivity of 90% enantiomeric excess while only employing the ligand that had an enantiomeric excess of 60%.

In summary, we have developed a Ce(IV)−*cis*-bis-Phpybox complex (**1**) catalyzed asymmetric endoselective nitrone cycloaddition with an excellent substrate scope under mild reaction conditions employing α,*β*-unsaturated 2-acyl imidazoles. This chemistry was found to be amenable for the efficient asymmetric synthesis of densely functionalized *β*′-hydroxy-*β*-amino acid derivatives.

Acknowledgment. This research was supported by grants from the National Science Foundation, NIH (GM-33328-20), and Merck research laboratories. H.-J.S. gratefully acknowledges a Novartis Graduate Fellowship.

(14) This absolute stereoconfiguration was consolidated via Mosher's ester analysis and optical rotation comparison with a known compound. Details are provided in the Supporting Information. The stereochemistry of all the other isoxazolidines was assigned by analogy.

(15) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922−2959.

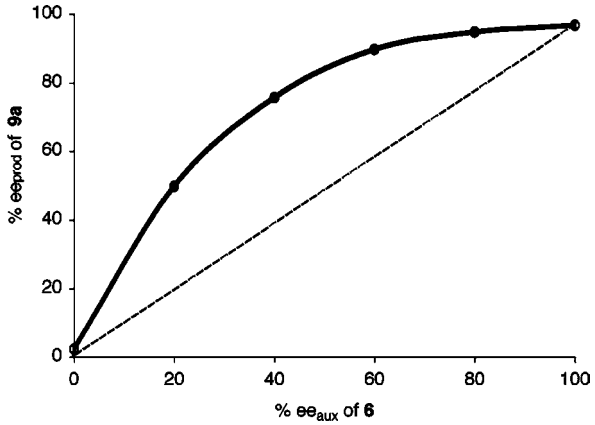


Figure 3. (+)-Nonlinear effects of the nitrone cycloaddition with crotonyl 2-acyl imidazole catalyzed by **1**.

Supporting Information Available: Experimental procedures, proton and carbon NMR spectra for all new compounds, and stereochemical determination with X-ray crystallographic data are available. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061223I