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Catalytic Asymmetric Formal [4 + 1] Annulation Leading to Optically Active *cis*-Isoxazoline *N*-Oxides

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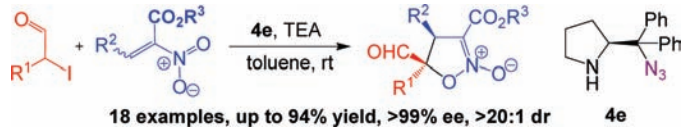
ABSTRACT



The catalytic asymmetric synthesis of densely functionalized *cis*-isoxazoline *N*-oxides was realized with novel use of an organocatalyst, (*S*)-2-(azidodiphenylmethyl)pyrrolidine (4e) (Tan, B.; Zhu, D.; Zhang, L.; Chua, P. J.; Zeng, X.; Zhong, G. *Chem.−Eur. J.* 2010, *16*, 3842; Olivares-Romero, J. L.; Juaristi, E. *Tetrahedron* 2008, *64*, 9992), via an elegant formal [4 + 1] annulation strategy using readily available 2-nitroacrylates and α-iodoaldehydes.

Isoxazoline *N*-oxides are intriguing synthetic targets since they can be readily converted into highly functionalized γ-hydroxy-α-amino acids or γ-amino-α-hydroxy acids.[1] Despite the fact that several synthetic methodologies have been developed,[2] only sporadic examples achieved asymmetric versions by using stoichiometric amounts of chiral reactants.[3] As such, the catalytic asymmetric approach to optically active isoxazoline *N*-oxides is still viewed as a formidable synthetic challenge.[4]

Stereoselective construction of ring systems continues to be considerably important in organic synthesis. In the past few decades, the [4 + 1] annulation has proved to be a powerful strategy in the construction of dihydrofurans, cyclopentenes, cyclopentenones, and pyrrolidines.[5] However, the catalytic asymmetric version of the [4 + 1] annulation was rarely documented, due to the difficulty in controlling relative and absolute stereochemistry.[6,7]

(1) For references of synthetic utilities of isoxazoline *N*-oxides, see: (a) Minter, A. R.; Fuller, A. A.; Mapp, A. K. *J. Am. Chem. Soc.* **2003**, *125*, 6846. (b) Fuller, A. A.; Chen, B.; Minter, A. R.; Mapp, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 5376. (c) Jäger, V.; Schwab, W. *Tetrahedron Lett.* **1978**, *19*, 3129. (d) Jäger, V.; Schwab, W. *Tetrahedron Lett.* **1978**, *19*, 3133. (e) Schreiner, E. P.; Gstach, H. *Synlett* **1996**, 1131. (f) Ashburn, S. P.; Coater, R. M. *J. Org. Chem.* **1984**, *49*, 3127. (g) Manning, J. R.; Davies, H. M. L. *J. Am. Chem. Soc.* **2008**, *130*, 8602. (h) Damkaci, F.; DeShong, P. *J. Am. Chem. Soc.* **2003**, *125*, 4408. (i) Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron* **1986**, *42*, 2129. (j) Righi, P.; Marotta, E.; Landuzzi, A.; Rosini, G. *J. Am. Chem. Soc.* **1996**, *118*, 9446.

(2) For selected synthetic approaches to racemic isoxazoline *N*-oxides, see: (a) Kunetsky, R. A.; Dilman, A. D.; Ioffe, S. L.; Struchkova, M. A.; Strelenko, Y.; Tartakovsky, V. A. *Org. Lett.* **2003**, *5*, 4907. (b) Clagett, M.; Gooch, A.; Graham, P.; Holy, N.; Mains, B.; Strunk, J. *J. Org. Chem.* **1976**, *41*, 4033. (c) Kunetsky, R. A.; Dilman, A. D.; Struchkova, M. I.; Belyakov, P. A.; Tartakovsky, V. A.; Ioffe, S. L. *Synthesis* **2006**, *13*, 2265. (d) Snider, B. B.; Che, Q. *Tetrahedron* **2002**, *58*, 7821. (e) Khan, P. M.; Wu, R.; Bisht, K. S. *Tetrahedron* **2007**, *63*, 1116. (f) Mélot, J. M.; Texier-Boullet, F.; Foucaud, A. *Synthesis* **1988**, 558. (g) Zen, S.; Koyama, M. *Bull. Chem. Soc.* **1971**, *44*, 2882.

(3) For references of asymmetric synthesis of isoxazoline *N*-oxides using chiral reactants, see: (a) Zhu, C.-Y.; Deng, X.-M.; Sun, X.-L.; Zheng, J.-C.; Tang, Y. *Chem. Commun.* **2008**, 738. (b) Zhu, C.-Y.; Sun, X.-L.; Deng, X.-M.; Zheng, J.-C.; Tang, Y. *Tetrahedron* **2008**, *64*, 5583.

(4) Jiang, H.; Elsner, P.; Jensen, K. L.; Falcicchio, A.; Marcos, V.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 6844.

(5) For references of racemic [4 + 1] annulation reactions, see: (a) Padwa, A.; Norman, B. H. *Tetrahedron Lett.* **1988**, *29*, 3041. (b) Dalton, A. M.; Zhang, Y.; Davie, C. P.; Danheiser, R. L. *Org. Lett.* **2002**, *4*, 2465. (c) Loebach, J. L.; Bennett, D. M.; Danheiser, R. L. *J. Am. Chem. Soc.* **1998**, *120*, 9690. (d) Chatani, N.; Oshita, M.; Tobisu, M.; Ishii, Y.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 7812. (e) Rigby, J. H.; Wang, Z. *Org. Lett.* **2002**, *4*, 4289. (f) Rigby, J. H.; Wang, Z. *Org. Lett.* **2003**, *5*, 263. (g) Oshita, M.; Yamshita, K.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2005**, *127*, 761. (h) Giese, M. W.; Moser, W. H. *Org. Lett.* **2008**, *10*, 4215. (i) Danheiser, R. L.; Bronson, K.; Okano, Son, S. *J. Am. Chem. Soc.* **1985**, *107*, 4579. (j) Lu, L.; Li, F.; An, J.; Zhang, J.; An, X.; Hua, Q.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9542.

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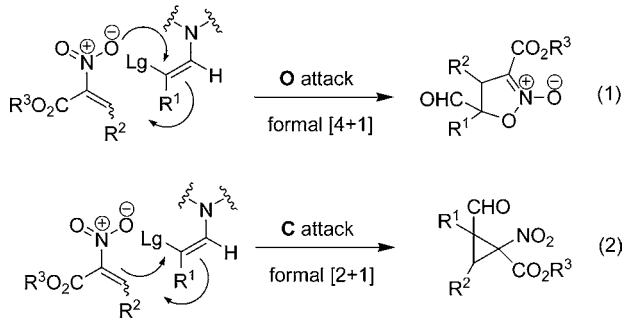
Inspired by organocatalytic enamine chemistry[8] and our previous study of the fluoroaldol reaction,[9] we decided to address these challenges. It was hypothesized that catalytic asymmetric synthesis of isoxazoline *N*-oxides could be achieved through [4 + 1] annulation between 2-nitroacrylates[10] and chiral enamines via elegant control of regio- and chemoselectivity (Scheme 1, eq 1), thereby avoiding the

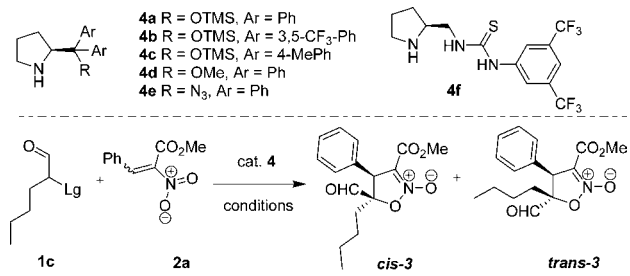
Scheme 1. Regio- and Chemoselectivities of Enamine Cyclization



[2 + 1] pathway which would deliver cyclopropane adducts (eq 2). Herein, we report our preliminary results of this strategy, which gives rise to the formation of *cis*-isoxazoline *N*-oxides. To our knowledge, this is the first example in which *cis*-adducts are achieved.

Initial studies were focused on investigating suitable enamine precursors (Table 1).[11] Readily available α-halogenated hexanals were examined with methyl 2-nitro-3-phenylacrylate (*E*/*Z* = 2:1), in the presence of catalyst **4a**, which possessed high efficiency in enamine chemistry (entries 1−4).[12] The feasibility of our designed catalytic system was first tested with α-chlorohexanal. To our delight, the [4 + 1] annulation product was observed, without any

Table 1. Optimization of Reaction Parameters[a]



entry	4	Lg	solvent	*t* (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**4a**	Cl	TBME	48	50	1:1.4	70
2	**4b**	Cl	TBME	96	18	n.d.	0
3	**4a**	Br	TBME	24	90	1.3:1	99
4	**4a**	I	TBME	5	79	1.8:1	96
5	**4a**	I	toluene	5	77	4.5:1	96
6	**4c**	I	toluene	5	78	2.2:1	95
7	**4d**	I	toluene	3	60	6:1	95
8	**4e**	I	toluene	7	83	9:1	98
9	**4f**	I	toluene	24	20	3:1	n.d.
10[e]	**4e**	I	toluene	8	89	11:1	>99
11[f]	**4e**	I	toluene	14	94	11:1	>99
12[g]	**4e**	I	toluene	23	69	9:1	99

[a] Unless otherwise noted, reactions were performed at rt on a 0.1 mmol scale, in 0.5 mL of solvent, with a molar ratio of α-iodohexanal/2-nitroacyrate/DIPEA/**4** = 4:1:1.1:0.2. [b] The sum of both isomers. [c] dr = *cis*/*trans*, based on analysis of crude ^{1}H NMR. [d] Determined by HPLC for the *cis*-isomer. [e] TEA was employed. [f] Reaction was performed at 0.1 M concentration. [g] 10 mol % **4e** was used. n.d. = not determined. DIPEA = diisopropyl ethyl amine, TEA = triethyl amine, Lg = leaving group.

formation of cyclopropane, although unsatisfactory chemical yield and stereoselectivity were obtained (entry 1). When α-bromohexanal and α-iodohexanal were employed, the yields were significantly increased to 90% and 79%, respectively, and accompanied by excellent enantioselectivities (99% and 96% ee's), with the latter showing promising diastereocontrol and highest reactivity (entries 3 and 4). Replacing the solvent TBME with toluene led to better diastereoselectivity (entry 5). In addition, β-elimination would occur occasionally, hence requiring the use of a slight excess of base as additive.[11]

Further catalyst screening with α-iodohexanal revealed that catalyst **4e** showed the best catalytic performance (entry 8). The superior diastereocontrol achieved by **4e** might have resulted from the predominant formation of the *Z*-enamine and electrostatic interaction between the azido moiety and nitro group in 2-nitroacrylate. Subsequent screening of additives indicated that use of triethyl amine provided the best results (entry 10). Also, lower concentration led to higher yield of the desired product (entry 11). It was found that the catalyst loading could be decreased to 10 mol %, to achieve acceptable chemical yield, as well as slightly lower diastereoselectivity, while maintaining enantioselectivity (entry 12).

The scope of α-iodoaldehydes was next explored (Table 2). Under the optimized reaction conditions, α-iodoaldehydes with linear alkyl substituents proceeded in the [4 + 1] annulation smoothly to afford optically active isoxazoline *N*-oxides **3** in good yields (64−94%), with excellent enan-

(6) For reference of asymmetric [4 + 1] annulation reactions using chiral reactants, see: (a) Zheng, J.-C.; Zhu, C.-Y.; Sun, X.-L.; Tang, Y.; Dai, L.-X. *J. Org. Chem.* **2008**, *73*, 6909. (b) Lu, L.-Q.; Zhang, J.-J.; Li, F.; Cheng, Y.; An, J.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4495.

(7) For reference of catalytic asymmetric [4 + 1] annulation reactions, see: Son, S.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 1046.

(8) For reviews of enamine chemistry, see: (a) List, B. *Acc. Chem. Res.* **2004**, *37*, 548. (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471.

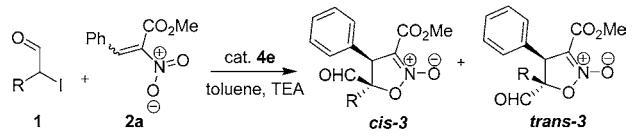
(9) Zhong, G.; Fan, J.; Barbas III, C. F. *Tetrahedron Lett.* **2004**, *45*, 5681.

(10) For general review of a nitro group, see: Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.

(11) For more detailed optimization, see the Supporting Information.

(12) For selected references of chiral pyrrolidine derivative catalyzed reactions, see: (a) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjrsgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296. (b) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212. (c) Xie, H.; Zu, L.; Li, H.; Wang, J.; Wang, W. *J. Am. Chem. Soc.* **2007**, *129*, 10886. (d) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (e) Shibatomi, K.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 5796. (f) Zhu, D.; Lu, M.; Dai, L.; Zhong, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 60892. (g) Tan, B.; Zeng, X.; Lu, Y.; Chua, P. J.; Zhong, G. *Org. Lett.* **2009**, *11*, 1927. (h) The catalyst **4e** was used in: Tan, B.; Zhu, D.; Zhang, L.; Chua, P. J.; Zeng, X.; Zhong, G. *Chem.−Eur. J.* **2010**, *16*, 3842. (i) The catalyst **4e** was prepared using a modification of the method described in: Olivares-Romero, J. L.; Juaristi, E. *Tetrahedron* **2008**, *64*, 9992.

Table 2. Scope of α-Iodoaldehydes[a]



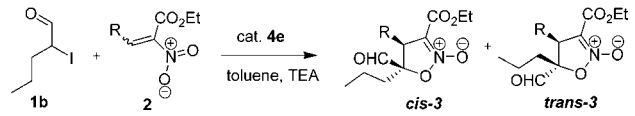
entry	1 (R)	yield (%)[b]	dr[c]	ee (%)[d]
1	**1a** (ethyl)	**3a** 64	10:1	95
2	**1b** (propyl)	**3b** 68	11:1	94
3	**1c** (butyl)	**3c** 94	11:1	>99
4	**1d** (heptyl)	**3d** 84	9:1	92
5	**1e** (benzyloxymethyl)	**3e** 75	18:1	99
6	**1f** (benzyl)	**3f** 70	8:1	99

[a] Unless otherwise noted, reactions were performed at rt on a 0.2 mmol scale, in 2.0 mL of toluene, with a molar ratio of α-iodohexanal/**2a**/TEA/**4e** = 4:1:1.1:0.2. [b] The sum of both diastereoisomers. [c] dr = *cis*/*trans*, determined by ^{1}H NMR. [d] Determined by chiral HPLC for *cis*-isomer.

tioselectivities (92 to >99% ee's) and good diastereoselectivities (9:1−11:1 dr, entries 1−4). Furthermore, aryl-substituted α-iodoaldehydes proved to be good donors, affording desired products in good yields and remarkable stereocontrol (entries 5 and 6).

To further evaluate the versatility of this reaction, a variety of 2-nitroacrylates were used (Table 3). Aromatic and

Table 3. Scope of 2-Nitroacrylates[a]



entry	2 (R, *E*/*Z*)	yield of 3 (%)[b]	dr[c]	ee (%)[d]
1	**2g** (Ph, 1:1)	**3g** 87	9:1	91
2	**2h** (*o*-MePh, 1.2:1)	**3h** 81	11:1	97
3	**2i** (*o*-ClPh, 1.5:1)	**3i** 64	11:1	96
4	**2j** (*m*-MePh, 1.8:1)	**3j** 80	11:1	92
5	**2k** (*m*-ClPh, Z)	**3k** 63	>20:1	96
6	**2l** (*p*-BrPh, *Z*)	**3l** 78	14:1	94
7	**2m** (*p*-MePh, 2:1)	**3m** 81	10:1	92
8	**2n** (*p*-MeOPh, 4:1)	**3n** 73	13:1	91
9	**2o** (1-naphthyl, 1.5:1)	**3o** 62	12:1	94
10[e]	**2p** (2-naphthyl, 1.7:1)	**3p** 74	11:1	87 (>99)[f]
11[g]	**2q** (3-furanyl, 2:1)	**3q** 67	>20:1	85
12	**2r** (2-furanyl, 1:1)	**3r** 61	11:1	84

[a] Unless otherwise noted, reactions were performed at rt, on a 0.2 mmol scale, in 2.0 mL of toluene, with a molar ratio of **1b**/**2**/TEA/**4e** = 4:1:1.1:0.2, for 9−24 h. [b] The sum of both diastereoisomers. [c] dr = *cis*/*trans*, determined by ^{1}H NMR. [d] Determined by chiral HPLC for *cis*-isomer. [e] Methyl ester **2p** was used. [f] After a simple recrystallization. [g] α-Iodohexanal was employed.

heteroaromatic substrates were observed to be suitable acceptors in this [4 + 1] annulation process. Systematic tuning of electron-withdrawing and electron-donating substituents at ortho-, meta- and para-positions of the aromatic ring gave rise to densely functionalized isoxazoline *N*-oxides in good yields, and with high stereoselectivities (entries 2−8). Notably, electron-rich substrates delivered higher yields compared to electron-poor substrates, thus demonstrating that the electronic nature of the aromatic substrates had drastic effects. However, longer reaction times were needed (entries 2 and 3). Interestingly, for all cases, comparable results were obtained, regardless of the double bond geometry of the 2-nitroacrylate substrates. This may be due to isomerization of the 2-nitroacrylate during the course of the reaction,[13] which was proved by the detection of benzenaldehyde in the reaction system, and subsequently resulted in relatively low yields of isoxazoline *N*-oxides for some cases. The absolute configuration of the major diastereomer *cis*-**3l** was determined to be (4*S*,5*R*) by X-ray crystallography (Figure 1).

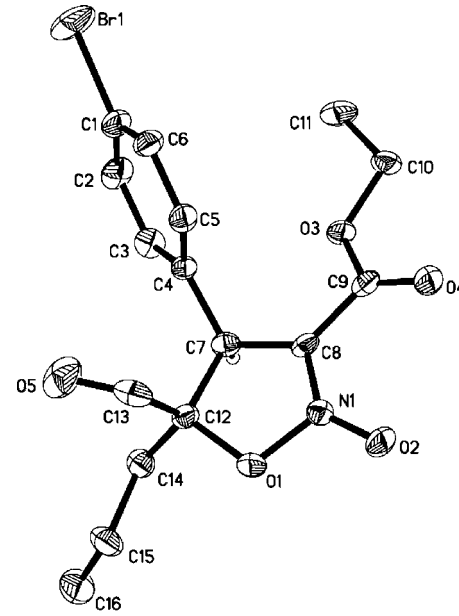


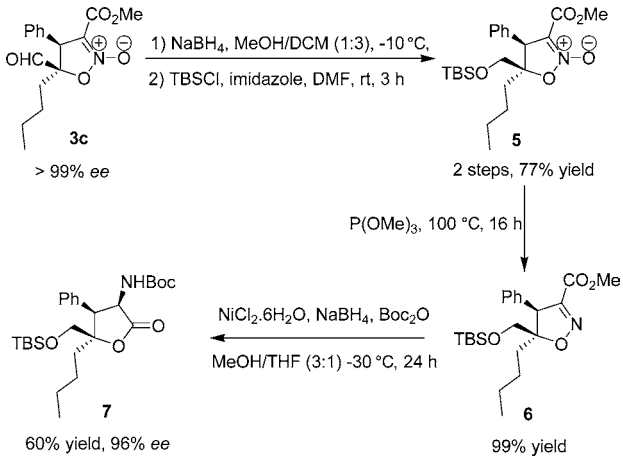
Figure 1. Absolute configuration of *cis*-**3l** determined by X-ray diffraction crystallography.

Having established the catalytic asymmetric formal [4 + 1] annulation methodology of 2-nitroacrylates and α-iodoaldehydes, the synthetic utilities of these previously undocumented *cis*-isoxazoline *N*-oxides were further explored. Apart from the typical transformation of the chiral isoxazoline core into numerous valuable synthons, such as β-amino acids,[1] γ-hydroxy-α-amino acids, and amino alcohols,[2] a concise approach to a densely functionalized chiral γ-lactone **6**, an important building block in the synthesis of natural products and biologically active compounds,[14] was realized (Scheme 2).

(13) For selected reference of similar double bond geometric isomerization, see: Wang, J.; Yu, F.; Zhang, X.; Ma, D. *Org. Lett.* **2008**, *10*, 2561.

(14) For selected references of biologically active natural products containing 2-amino-γ-lactones as core, see: (a) Matic, V.; Kosowska, K.; Bozdogan, B.; Kelly, L. M.; Smith, K.; Ednie, L. M.; Lin, G.; Credito, K. L.; Clark, C. L.; McGhee, P.; Pankuch, G. A.; Jacobs, M. R.; Appelbaum, P. C. *Antimicrob. Agents Chemother.* **2004**, *48*, 4103. (b) Kosowska, K.; Credito, K.; Pankuch, G. A.; Hoellman, D.; Lin, G.; Clark, C.; Dewasse, B.; McGhee, P.; Jacobs, M. R.; Appelbaum, P. C. *Antimicrob. Agents Chemother.* **2004**, *48*, 4113. (c) Bringmann, G.; Gulder, T. A. M.; Schmitt, G.; Lang, S.; Stöhr, R.; Wiese, J.; Nagel, K.; Imhoff, J. F. *Mar. Drugs* **2007**, *5*, 23.

Scheme 2. Transformation of *cis*-Isoxazoline *N*-Oxide into Densely Functionalized γ-Lactone[a]

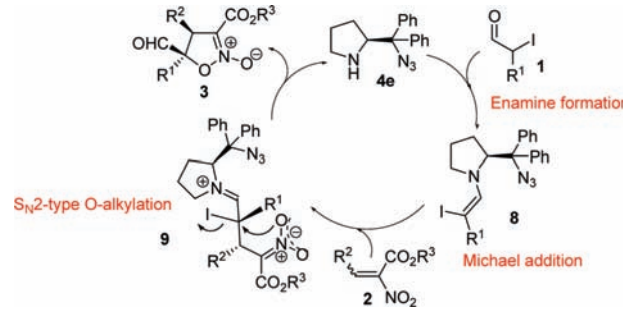


[a] TBS = *tert*-butyldimethylsilyl, Boc = *tert*-butoxycarbonyl.

Optically pure *cis*-isoxazoline *N*-oxide **3c** was readily converted to intermediate **5** by simple reduction and protection. A deoxygenation was then carried out to provide isoxazoline **6** in quantitative yield. This was followed by treatment of **6** with nickel borohydride which was formed in situ, to give highly substituted 2-amino-γ-lactone **7** as a single diastereoisomer in good yield, albeit with slight loss of optical purity.

It is proposed that the tandem sequence[15,16] is initiated by condensation of α-iodoaldehyde **1** and catalyst **4e**, to generate enamine **8**, which then undergoes a Michael addition with 2-nitroacrylate **2** (Scheme 3). The oxyanion of intermediate **9** then proceeds via an intramolecular S_N2-type O-alkylation to complete the catalytic cycle.[17]

Scheme 3. Proposed Mechanism of the Fomal [4 + 1] Annulation Reaction



In conclusion, we have presented the first catalytic asymmetric [4 + 1] annulation of 2-nitroacrylates and α-iodoaldehydes for the highly stereoselective synthesis of valuable *cis*-isoxazoline *N*-oxides with readily available substrates with novel use of the catalyst **4e**. Racemic α-iodoaldehydes, which were rarely employed as nucleophiles, proved to be suitable donors for this enamine cyclization process. Moreover, a concise synthetic approach to the biologically and medicinally relevant building block, chiral 2-amino-γ-lactone, has been developed. This catalytic platform has opened up a new entry to the construction of five-membered ring systems. Additional investigations of the mechanism and other synthetic utilities of this protocol, such as extension to three-membered ring formation as well as total synthesis of natural products, are currently underway.

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Supporting Information Available: Experimental procedures, characterization, spectra, chiral HPLC conditions, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) For selected references of tandem reactions, see: (a) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (b) Tan, B.; Shi, Z.; Chua, P.; Li, Y.; Zhong, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 758. (c) Lu, M.; Zhu, D.; Lu, Y.; Hou, Y.; Tan, B.; Zhong, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 10187. (d) Zhang, C.; De, C. K.; Mal, R.; Seidel, D. *J. Am. Chem. Soc.* **2007**, *130*, 416. (e) Zhu, D.; Lu, M.; Chua, P. J.; Tan, B.; Wang, F.; Yang, X.; Zhong, G. *Org. Lett.* **2008**, *10*, 4585. (f) Wang, J.; Yu, F.; Zhang, X.; Ma, D. *Org. Lett.* **2008**, *10*, 5425. (g) Cao, C.; Zhou, Y.; Zhou, J.; Sun, X.; Tang, Y.; Li, Y.; Li, G.; Sun, J. *Chem.—Eur. J.* **2009**, *15*, 11384. (h) Belot, S.; Vogt, K. A.; Besnard, C.; Krause, N.; Alexakis, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 8923.

(17) For selected references involving intramolecular nucleophilic substitution, see: (a) Marigo, M.; Bertelsen, S.; Landa, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 5475. (b) Enders, D.; Wang, C.; Bats, J. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 7539. (c) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450.