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# Asymmetric 1,3-Dipolar Cycloadditions of Nitrones and Methacrolein Catalyzed by Chiral Bis-Titanium Lewis Acid: A Dramatic Effect of *N*-Substituent on Nitrone

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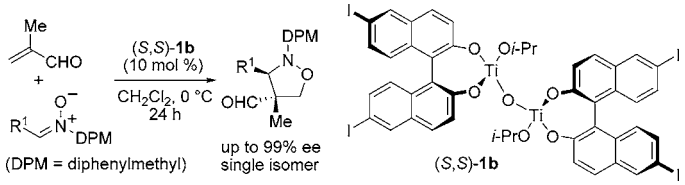
## ABSTRACT



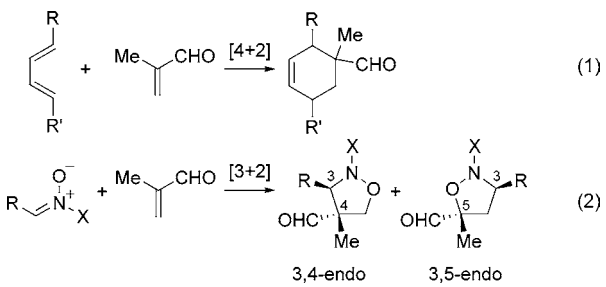

**Highly stereoselective 1,3-dipolar cycloadditions of methacrolein and nitrones could be realized by the use of bis-titanium chiral Lewis acid catalyst. Key to the success is the introduction of bulky *N*-substituent on nitrone to attenuate the undesired Lewis acid–nitrone complexation.**

The Lewis acid-catalyzed asymmetric Diels−Alder reaction of methacrolein and dienes is one of the most important and fundamental cycloaddition reactions, and enables the formation of one all-carbon quaternary stereocenter and additional stereocenters at one time depending on the substitution pattern of the diene (Scheme 1, eq 1).[1,2] This attractive feature of this catalysis has promoted the development of various chiral Lewis acid catalysts over the past decades.

In sharp contrast to its prosperity in the field of asymmetric catalysis, methacrolein has rarely been employed in the asymmetric 1,3-dipolar cycloadditions of nitrone, another important class of cycloadditions (Scheme 1, eq 2).[3] The main cause of this lack might be attributed to the long-standing substrate limitation of using bidentate dipolarophiles, such as 3-(2-alkenoyl)-2-oxazolidinone.[4] Namely, in the chiral Lewis acid activation of such bidentate carbonyl substrates, α-substitution of the carbonyl substrates is not normally amenable due to a problematic $A^{1,3}$ strain between the template and the α-substituent.[5]

The results of research focusing on the use of α,β-unsaturated aldehydes in the asymmetric 1,3-dipolar cy-

**Scheme 1.** Use of Methacrolein in [4 + 2] and [3 + 2] Cycloadditions




(1) For reviews on the Lewis acid-catalyzed asymmetric Diels−Alder reactions, see: (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (b) Corey, E. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1650.

(2) For reviews on the formation of quaternary stereocenters, see: (a) Trost, B. M.; Jiang, C. *Synthesis* **2006**, 369. (b) Christoffers, J.; Baro, A. *Adv. Synth. Catal.* **2005**, *347*, 1473. (c) Christoffers, J.; Baro, A., Eds. *Quaternary Stereocenters*: *Challenges and Solutions for Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2005. (d) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363.

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cloadditions of nitrone appeared recently, which offered an opportunity to implement the reaction of nitrone and methacrolein by the judicious choice of Lewis acids.[6,7] Although high endo selectivity was generally attained, these studies suffered from poor regioselectivity or the preferential formation of 3,5-endo isomer without exception. Thus, despite the intriguing structure of vicinally substituted 3,4-endo adduct including one all-carbon quaternary center, the 3,4-endo selective reaction still remains an elusive goal. It should also be noted that chiral organocatalysts do not provide a solution to this problem because of their poor ability to discriminate the enantiotopic face of methacrolein.[8,9]

Our approach to addressing this issue is the use of chiral bis-titanium Lewis acid (*S*,*S*)-**1a** (Figure 1), which has recently been revealed to catalyze various asymmetric transformations including 1,3-dipolar cycloadditions of *N*-benzyl nitrones and acrolein.[10] Along the line of this research, the reaction of methacrolein and *N*-benzylidenebenzylamine *N*-oxide **2** (R = $CH_2Ph$) was conducted in the presence of a catalytic amount of (*S*,*S*)-**1a**. The reaction was sluggish even at 0 °C, providing the cycloadduct only in disappointingly low yield with a moderate enantioselectivity of 75% ee (Table 1, entry 1). However, the sterically congested 3,4-endo adduct **3** was obtained exclusively, in contrast to the previous reports from other groups. Intrigued by this unusual outcome, we set out to realize a practical asymmetric 1,3-dipolar cycloaddition reaction of methacrolein and nitrones.

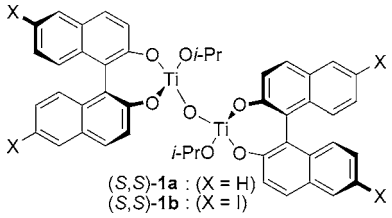
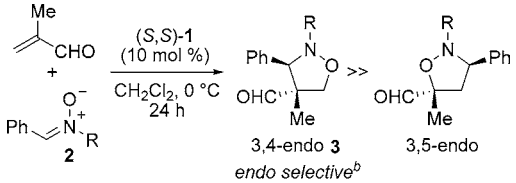



**Figure 1.** Chiral bis-titanium Lewis acids **1a** and **1b**.

**Table 1.** Comparison of the Reactivity and Selectivity of *N*-Substituted Nitrones[a]




| entry | R | catalyst | yield (%)[c] | ee (%)[d] |
|---|---|---|---|---|
| 1 | $PhCH_2$ | (*S*,*S*)-**1a** | 10 | 75 |
| 2 | $Ph_2CH$ | (*S*,*S*)-**1a** | 58 | 90 |
| 3 | $Ph_2CH$ | (*S*,*S*)-**1b** | 80 | 93 |
| 4 | 1-$NpCH_2$ | (*S*,*S*)-**1b** | 24 | 78 |
| 5 | (2-tolyl)$_2$CH | (*S*,*S*)-**1b** | trace | |

[a] The reaction of nitrones and methacrolein (3 equiv) was performed in the presence of 10 mol % of (*S*,*S*)-**1** in $CH_2Cl_2$. [b] Determined by $^1H$ NMR spectroscopy. [c] Isolated yield. [d] Determined by HPLC analysis with use of chiral columns after the reduction of the aldehyde moiety.

On the basis of the premise that poor reactivity of the Lewis acid-catalyzed 1,3-dipolar cycloadditions of nitrone is due to the unfavorable interaction of Lewis acid and electronegative oxygen of nitrone,[11] we assumed that kinetic destabilization of a Lewis acid−nitrone complex by steric repulsion between the *N*-substituent on nitrone and the ligand of Lewis acid catalyst might be an effective approach to increase the reactivity (Scheme 2).

With this consideration in mind, the *N*-benzyl group on nitrone was replaced by a sterically more demanding *N*-diphenylmethyl group, which was anticipated not to change the electronic property of the dipole significantly.[12] To our delight, the reaction proceeded smoothly and the cycloadduct was obtained in a remarkably higher yield of 58%, maintaining the preferential formation of one regio-

(3) For reviews, see: (a) Gothelf, K. V.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (b) Gothelf, K. V.; Jørgensen, K. A. *Chem. Commun.* **2000**, 1449. (c) Gothelf, K. V. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, Germany, 2002; Chapter 6, p 211. (d) Kanemasa, S. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, Germany, 2002; Chapter 7, p 249. (e) Pellissier, H. *Tetrahedron* **2007**, *63*, 3235.

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(6) (a) Viton, F.; Bernardinelli, G.; Kündig, E. P. *J. Am. Chem. Soc.* **2002**, *124*, 4968. (b) Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Org. Lett.* **2002**, *4*, 2457. (c) Ohtsuki, N.; Kezuka, S.; Kogami, Y.; Mita, T.; Ashizawa, T.; Ikeno, T.; Yamada, T. *Synthesis* **2003**, 1462. (d) Kezuka, S.; Ohtsuki, N.; Mita, T.; Kogami, Y.; Ashizawa, T.; Ikeno, T.; Yamada, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 2197. (e) Shirahase, M.; Kanemasa, S.; Oderaotoshi, Y. *Org. Lett.* **2004**, *6*, 675. (f) Carmona, D.; Lamata, M. P.; Viguri, F.; Rodríguez, R.; Oro, L. A.; Balana, A. I.; Lahoz, F. J.; Tejero, T.; Merino, P.; Franco, S.; Montesa, I. *J. Am. Chem. Soc.* **2004**, *126*, 2716. (g) Carmona, D.; Lamata, M. P.; Viguri, F.; Rodríguez, R.; Oro, L. A.; Lahoz, F. J.; Balana, A. I.; Tejero, T.; Merino, P. *J. Am. Chem. Soc.* **2005**, *127*, 13386. (h) Carmona, D.; Lamata, M. P.; Viguri, F.; Ferrer, J.; García, N.; Lahoz, F. J.; Martín, M. L.; Oro, L. A. *Eur. J. Inorg. Chem.* **2006**, 3155. (i) Carmona, D.; Lamata, M. P.; Viguri, F.; Rodríguez, R.; Fischer, T.; Lahoz, F. J.; Dobrinovitch, I. T.; Oro, L. A. *Adv. Synth. Catal.* **2007**, *349*, 1751.

(7) For a B3LYP/6-31G study, see: Barba, C.; Carmona, D.; García, J. I.; Lamata, M. P.; Mayoral, J. A.; Salvatella, L.; Viguri, F. *J. Org. Chem.* **2006**, *71*, 9831.

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(9) Sakakura, A.; Suzuki, K.; Ishihara, K. *Adv. Synth. Catal.* **2006**, *348*, 2457.

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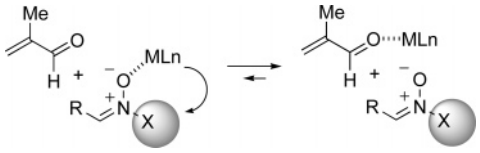
(11) For a similar strategy with achiral bulky Lewis acid, see: Kanemasa, S.; Ueno, N.; Shirahase, M. *Tetrahedron Lett.* **2002**, *43*, 657.

(12) Tamura, O.; Kanoh, A.; Yamashita, M.; Ishibashi, H. *Tetrahedron* **2004**, *60*, 9997.

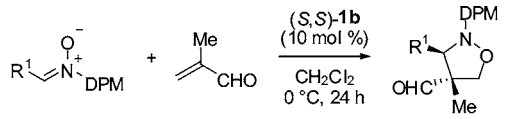
**Scheme 2.** Kinetic Destabilization of Lewis Acid−Nitrone Complex by Steric Repulsion



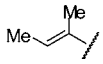

isomer; additionally, a high enantioselectivity of 90% was observed. Further improvement could be realized by the introduction of 6,6′-$I_2$-BINOL into the bis-titanium Lewis acid catalyst ((*S*,*S*)-**1b**) and, in this case, the cycloadduct **3** could be obtained in 80% yield with almost complete stereoselectivity (93% ee, endo/exo = >20/1, 3,4-endo/3,5-endo = >20/1). The reaction with less hindered *N*-(1-naphthylmethyl) nitrone led to a poor conversion (entry 4), and more sterically demanding *N*-bis(2-tolyl)methyl nitrone was inert under the reaction condition (entry 5).

The generality of this reaction was then examined employing various *N*-diphenylmethyl nitrones as illustrated in Table 2. The reaction system was applicable to nitrones bearing

**Table 2.** Asymmetric 1,3-Dipolar Cycloadditions of Methacrolein and Various Nitrones[a]




*endo/exo = >20/1*[b]
*3,4-endo/3,5-endo = >20/1*[b]

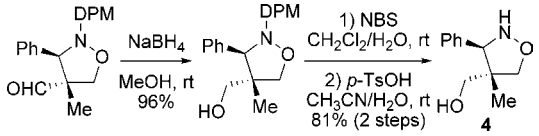
| entry | $R^1$ | yield (%)[c] | ee (%)[d] |
|---|---|---|---|
| 1 | Ph | 80 | 93 |
| 2 | 2-tolyl | 67 | 99 |
| 3 | 3-tolyl | 74 | 96 |
| 4 | 4-tolyl | 75 | 88 |
| 5 | 2-naphthyl | 51 | 95 |
| 6 | 4-$MeOC_6H_4$ | 49 | 94 |
| 7[e] | 4-$ClC_6H_4$ | 46 | 88 |
| 8[e] |  | 48 | 88 |
| 9 |  | 65 | 91 |

[a] The reaction of nitrones and methacrolein (3 equiv) was performed in the presence of 10 mol % of (*S*,*S*)-**1b** in $CH_2Cl_2$. [b] Determined by $^1H$ NMR spectroscopy. [c] Isolated yield. [d] Determined by HPLC analysis with use of chiral columns after the reduction of the aldehyde moiety. [e] Performed with 20 mol % of (*S*,*S*)-**1b**.

electronically neutral aromatic groups irrespective of the substitution patterns or the ring size, and the cycloadducts were obtained in high yields with an excellent level of enantioselection (entries 2−5). Electronic properties of the aromatic rings on nitrone slightly affected the reactivity and these reactions provided the cycloadducts in moderate yields with high enantioselectivities (entries 6 and 7). To further expand the utility of our methodology, nitrones incorporating alkenyl groups at the *C*-terminus of nitrone were investigated.[13] 1-Cyclopentenyl and 1-methyl-1-propenyl groups could be successfully incorporated into the products with 91% ee and 88% ee, respectively (entries 8 and 9). The modest yields observed in some cases imply the intervention of the Lewis acid inhibition by the substrate as well as the product inhibition, since prolongation of the reaction time did not improve the yield.

To strengthen the synthetic utility of 1,3-dipolar cycloadditions of *N*-diphenylmethyl nitrones, the procedure for the effective removal of the diphenylmethyl group in the cycloadduct was then surveyed. After several unfruitful attempts utilizing hydrogenation conditions, we succeeded in cleaving the C−N bond oxidatively as shown in Scheme 3.[14] Thus, after the reduction of the aldehyde moiety of the

**Scheme 3.** Removal of the *N*-Diphenylmethyl Group




cycloadduct, the alcohol was treated with 1.1 equiv of *N*-bromosuccinimide in $CH_2Cl_2$ followed by acidic hydrolysis of thus formed hemiaminal, which gave *N*-unprotected isoxazolidine **4** in 81% yield.

The relative and absolute stereochemistry of the cycloadduct was unequivocally determined by X-ray crystallographic analysis of the deprotected cycloadduct **4** after the complexation with (+)-(*S*)-camphorsulfonic acid (Figure 2).[15]

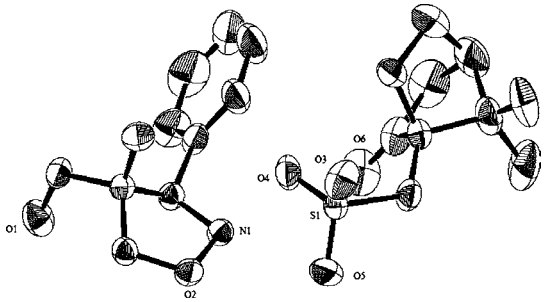



**Figure 2.** X-ray structure of **4**·(+)-(*S*)-camphorsulfonic acid complex. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are shown at the 50% probability level.

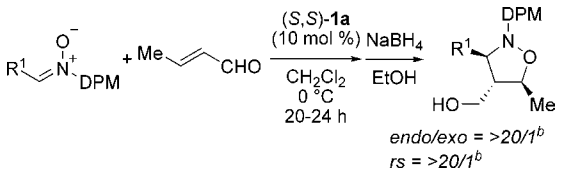
Further extension of this catalytic system was achieved by employing crotonaldehyde as the dipolarophile. As in the

(13) Use of *C*-isopropyl nitrone ($R^1$ = *i*-Pr) led to the formation of 3,5-isomer in low yield, suggesting the dominance of the steric factor over the electronic control.

(14) Laurent, M.; Belmans, M.; Kemps, L.; Cérésiat, M.; Marchand-Brynaert, J. *Synthesis* **2003**, 570.

(15) CCDC-655706 (**4**·(+)-(*S*)-camphorsulfonic acid complex) 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 3.** Asymmetric 1,3-Dipolar Cycloadditions of Crotonaldehyde and Nitrones[a]




| entry | $R^1$ | yield (%)[c] | ee (%)[d] |
|---|---|---|---|
| 1 | Ph | 82 (36)[e] | 87 (63)[e] |
| 2 | 4-tolyl | 93 | 89 |
| 3 | 4-$MeOC_6H_4$ | 83 | 88 |
| 4 | *t*-Bu | 50 | 89 |
| 5 | *i*-Pr | 83 | 92 |

[a] The reaction of nitrones and crotonaldehyde (1.5 equiv) was performed in the presence of 10 mol % of (*S*,*S*)-**1a** in $CH_2Cl_2$. [b] Determined by $^1H$ NMR spectroscopy. [c] Isolated yield after the reduction of the aldehyde moiety in situ, considering the possibility of epimerization at the C4 position. [d] Determined by HPLC analysis with use of chiral columns. [e] Performed with *N*-benzyl nitrone under otherwise identical conditions.

case of the reaction with methacrolein, use of *N*-diphenylmethyl nitrone was apparently advantageous providing the single isomer of the cycloadduct in 82% with 87% ee (entry 1, Table 3), while the reaction with *N*-benzyl nitrone gave the cycloadduct in 36% yield with 63% ee (entry 1 in parentheses). As a clear superiority of (*S*,*S*)-**1b** was not observed in this case, the generality was investigated with a simpler catalyst (*S*,*S*)-**1a**.

In summary, we have succeeded in 3,4-endo selective asymmetric 1,3-dipolar cycloadditions of nitrones and methacrolein by the use of chiral bis-titanium Lewis acids. The clear advantage of using *N*-diphenylmethyl nitrones was also demonstrated in the reaction with crotonaldehyde. This strategy offers a new benchmark reaction for the chiral Lewis acid catalyzed asymmetric 1,3-dipolar cycloadditions of nitrones.

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**Supporting Information Available:** Experimental details, characterization data for new compounds, and crystal data for compound **4**·(+)-(*S*)-camphorsulfonic acid complex. This material is available free of charge via the Internet at http://pubs.acs.org.

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