ORGANIC LETTERS

2013
Vol. 15, No. 7
1508–1511

Asymmetric Michael Addition of *N-tert*-Butanesulfinyl Imidate with α,β-Unsaturated Diesters: Scope and Application to the Synthesis of Indanone Derivatives

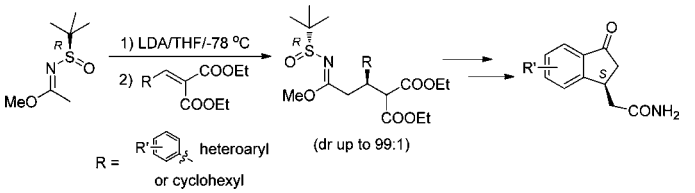
Jinfang Wang, Yu Zhou,* Lei Zhang, Zeng Li, Xianjie Chen, and Hong Liu*

State Key Laboratory of Drug Research, CAS Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zuchongzhi Road, Shanghai 201203, P. R. China

zhouyu@mail.shcnc.ac.cn; hliu@mail.shcnc.ac.cn

Received January 30, 2013

ABSTRACT



An additive-free and highly diastereoselective Michael addition reaction of an *N-tert*-butanesulfinyl imidate to α,β-unsaturated diesters has been developed using LDA as a base with good to excellent yields. The utility of this chemistry is further demonstrated by the asymmetric synthesis of 3-substituted indanone derivatives 8a, 8d, 8e, and 8i with high enantiomeric excess, which are potential building blocks for preparing biologically active lead compounds.

The addition of metalloenamines to electrophiles is one of the most important strategies in the preparation of diverse amine-containing derivatives.[1] Recently, the highly diastereoselective addition of metalloenamines derived from *N-tert*-butanesulfinyl imines to aldehydes,[2,3] trifluoromethyl ketones,[4] alkyl halides,[5] and imines[6] has been developed for the asymmetric synthesis of 1,3-amino alcohols, β-hydroxy-β-trifluoromethyl imines, α-alkyl imidates, and α-chloro-β-amino-*N*-sulfinylimidates, respectively. However, the asymmetric addition of *N-tert*-butanesulfinyl metalloenamines to other electrophiles, especially Michael addition of the metalloenamines to α,β-unsaturated ketones or esters, is still a challenging area of organic chemistry.[7] This is in part attributed to the strong electron-withdrawing character of the sulfinyl group, which attenuates the nucleophilicity of the metalloenamines, the low electrophilicity and the competitive deprotonation[7] of simple α,β-unsaturated ketones or esters. In 2005, Ellman et al. reported the first Michael conjugate addition of *N-tert*-butanesulfinyl metalloenamines to α,β-unsaturated ketones,[7] LDA was used as a base and only moderate yields were obtained. $ZnBr_2$ was used as an additive to overcome the competitive

(1) (a) Mangelinckx, S.; Giubellina, N.; De Kimpe, N. *Chem. Rev.* **2004**, *104*, 2353. (b) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron*. **2002**, *58*, 2253. (c) Lanter, J. C.; Chen, H. F.; Zhang, X. Q.; Sui, Z. H. *Org. Lett*. **2005**, *7*, 5905. (d) Colpaert, F.; Mangelinckx, S.; De Kimpe, N. *Org. Lett*. **2010**, *12*, 1904. (e) Schenkel, L. B.; Ellman, J. A. *Org. Lett*. **2004**, *6*, 3621. (f) Zhao, C. H.; Liu, L.; Wang, D.; Chen, Y. J. *Eur. J. Org. Chem*. **2006**, *13*, 2977. (g) Dessole, G.; Bernardi, L.; Bonini, B. F.; Capito, E.; Fochi, M.; Herrera, R. P.; Ricci, A.; Cahiez, G. *J. Org. Chem*. **2004**, *69*, 8525.

(2) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc*. **2002**, *124*, 6518.

(3) Kochi, T.; Tang, T. P.; Ellman, J. A. *J. Am. Chem. Soc*. **2003**, *125*, 11276.

(4) Liu, Z. J.; Mei, Y. Q.; Liu, J. T. *Tetrahedron* **2007**, *63*, 855.

(5) (a) Kochi, T.; Ellman, J. A. *J. Am. Chem. Soc*. **2004**, *126*, 15652. (b) Colpaert, F.; Mangelinckx, S.; De Kimpe, N. *J. Org. Chem*. **2011**, *76*, 234. (c) Colpaert, F.; Mangelinckx, S.; Verniest, G.; De Kimpe, N. *J. Org. Chem*. **2009**, *74*, 3792.

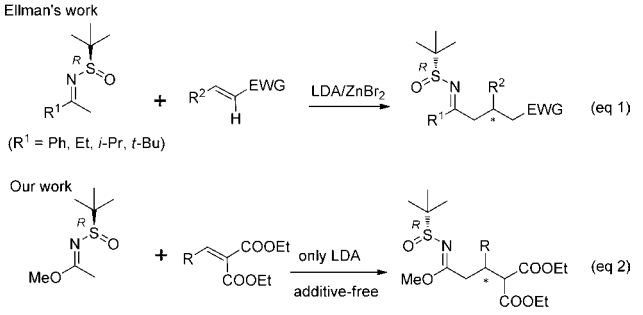
(6) Colpaert, F.; Mangelinckx, S.; Debrabandere, S.; De Kimpe, N. *J. Org. Chem*. **2011**, *76*, 2204.

(7) Peltier, H. M.; Ellman, J. A. *J. Org. Chem*. **2005**, *70*, 7342.

10.1021/ol400277h © 2013 American Chemical Society
Published on Web 03/25/2013

deprotonation of the Michael acceptor and to give improved yields and diastereoselectivities (Scheme 1, eq 1). Therefore, we envisioned that more nucleophilic metalloenamines derived from *N*-sulfinyl imidates and more electrophilic α,β-unsaturated diesters derived from diethyl arylidenemalonates would more effectively facilitate the Michael addition reaction (Scheme 1, eq 2).

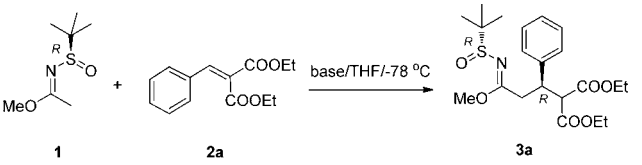
Scheme 1. Michael Additions to α,β-Unsaturated Compounds



Successful Michael additions to α,β-unsaturated diesters **2** would be of particular interest because the addition products **3** could potentially be converted to chiral 3-substituted-1-indanones **8** by simple deprotection, decarboxylation, and cyclization reactions (Scheme 4). Substituted indanone rings are well-known privileged structures which are widely distributed in natural products and biologically synthetic compounds.[8] They exhibit a wide spectrum of biological activities, such as smooth muscle relaxant, anticancer, anti-inflammatory activity, and acetylcholinesterase (AChE) inhibition.[9] Although some advances have been achieved for the asymmetric synthesis of 3-substituted-1-indanones, most of them suffered from the use of precious metal catalysts and unreadily available ligands.[10]

In our ongoing efforts to develop efficient methods to construct potential bioactive chiral heterocyclic compounds,[11] we herein describe an additive-free and highly diastereoselective Michael addition reaction of *N*-*tert*-butanesulfinyl imidate to diethyl arylidenemalonates using LDA as a base to generate diethyl 2-(3-((*R*)-*tert*-butylsulfinylimino)-3-methoxy-1-arylpropyl)-malonates. The application of this chemistry was further demonstrated through the efficient synthesis of 3-substituted 1-indanone derivatives with high enantiomeric excess, which are potential building blocks of biologically active lead compounds.

Table 1. Optimization of the Reaction Conditions of Synthesis of **3a**[a]



entry	base (equiv)	time (h)	yield (%)	dr
1[b]	NaHMDS (1.5)	2	95	85:15
2[c]	KHMDS (1.5)	2	93	87:13
3[d]	LiHMDS (1.5)	2	94	90:10
4	LDA (1.5)	2	90	93:7
5	LDA (1.2)	2	90	95:5
6	LDA (1.0)	2	73	96:4
7	LDA (1.8)	2	89	88:12
8	LDA (1.2)	5	87	96:4
9	LDA (1.2)	12	85	95:5
10[e]	LDA (1.2)	2	85	96:4
11[f]	LDA (1.2)	2	94	98:2
12[g]	LDA (1.2)	2	84	97:3

[a] Unless otherwise stated, all reactions were carried out using **1** (1.0 equiv, 0.2 mmol), **2a** (1.5 equiv, 0.3 mmol), and 0.5 mol/L of LDA as base at −78 °C in 5 mL of THF. [b] 1.0 mol/L of NaHMDS was used as base. [c] 1.0 mol/L of KHMDS was used as base. [d] 1.0 mol/L of LiHMDS was used as base. [e] 10 mL of THF was used as solvent. [f] 0.5 mol/L of LDA was diluted to 0.25 mol/L. [g] 1.1 equiv of **2a** was used.

N-*tert*-Butanesulfinyl imidate **1** and **2a** were chosen as model substrates for exploring the optimum reaction conditions for the synthesis of optically pure diethyl 2-(3-((*R*)-*tert*-butylsulfinylimino)-3-methoxy-1-arylpropyl)malonate (**3a**) via asymmetric Michael addition (Table 1). First, *N*-*tert*-butanesulfinyl imidate **1** was synthesized through condensation of (*R*)-*tert*-butanesulfinamide with the corresponding ortho ester in the presence of a catalytic amount of *p*-TsOH without solvent.[5c] Subsequently, the Michael addition reaction of **1** and **2a** was systematically optimized by changing the reaction conditions (Table 1). Commercially available NaHMDS was initially used as the base, and full conversion of **1** was observed after 2 h at −78 °C (95%) (Table 1, entry 1). However, the diastereoselectivity (dr = 85:15) was not satisfactory. Replacement of NaHMDS with KHMDS also resulted in a disappointing diastereoselectivity (Table 1, entry 2). However, using LiHMDS as base gave an improved diastereoselectivity (dr = 90:10) (Table 1, entry 3). To further increase the diastereoselectivity, 0.5 mol/L of LDA in THF was freshly prepared. To our delight, the use of LDA greatly improved the diastereoselectivity (Table 1, entries 4−12). When 1.5 equiv of LDA was used, **3a** was obtained

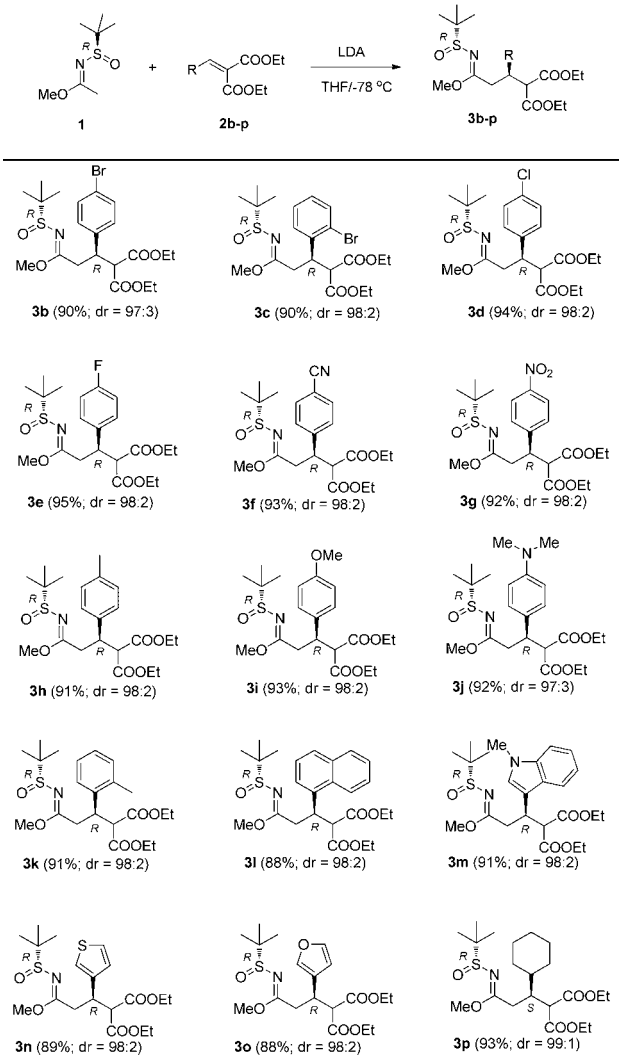
(8) (a) Satake, T.; Murakami, T.; Yokote, N.; Saiki, Y.; Chen, C. M. *Chem. Pharm. Bull.* **1985**, *33*, 4175. (b) Saito, M.; Umeda, M.; Enomoto, M.; Hatanaka, Y.; Natori, S. *Experientia* **1975**, *31*, 829.

(9) (a) Sheridan, H.; Frankish, N.; Farrell, R. *Eur. J. Med. Chem.* **1999**, *34*, 953. (b) Nagle, D. G.; Zhou, Y. D.; Park, P. U.; Paul, V. J.; Rajbhandari, I.; Duncan, C. J. G.; Pasco, D. S. *J. Nat. Prod.* **2000**, *63*, 1431. (c) Tumiatti, V.; Vincenza, A.; Banzi, R.; Bartolini, M.; Minarini, A.; Rosini, M.; Melchiorre, C. *J. Med. Chem.* **2004**, *47*, 6490. (d) Ssaravanan, V. S.; Selvan, P. S.; Gopal, N.; Gupat, J. K. *Asian J. Chem.* **2006**, *18*, 2597.

(10) (a) Shintani, R.; Takatsu, K.; Hayashi, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 3735. (b) Shintani, R.; Yashio, K.; Nakamura, T.; Okamoto, K.; Shimada, T.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 2772. (c) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482. (d) Kundu, K.; McCullagh, J. V.; Morehead, A. T., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 16042. (e) Matsuda, T.; Shigeno, M.; Makino, M.; Murakami, M. *Org. Lett.* **2006**, *8*, 3379.

(11) Chen, X. J.; Zhu, W.; Qian, W. K.; Feng, E. G.; Zhou, Y.; Wang, J. F.; Jiang, H. L.; Yao, Z. J.; Liu, H. *Adv. Synth. Catal.* **2012**, *354*, 2151.

Scheme 2. Asymmetric Michael Addition of *N-tert*-Butanesulfinyl Imidate with Diethyl Arylidenemalonates[a]

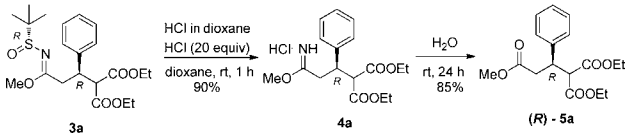


[a] All reactions were carried out using **1** (1.0 equiv, 0.2 mmol), **2b**−**p** (1.5 equiv, 0.3 mmol), and 0.25 mol/L of LDA as base at −78 °C in 5 mL of THF for 2 h. The dr value was determined by LC/MS.

with good diastereoselectivity (dr = 93:7) and high yield (90%) (Table 1, entry 4). Further studies demonstrated that better diasteroselectivity could be obtained when 1.0 equiv of LDA was used, but the yield of **3a** was decreased dramatically (73%) (Table 1, entry 6), which indicated that a small excessive base was necessary for the reaction to go on smoothly. However, increasing the amount of LDA to 1.8 equiv led to decreased diastereoselectivity (Table 1, entry 7). Overall, 1.2 equiv of LDA could give a higher yield and better diastereoselectivity (Table 1, entry 5). The yields decreased slightly when the reaction time was prolonged to 5 and 12 h, respectively (Table 1, entries 8 and 9). In addition, the concentration of the substrate also affected the reaction, the yield of **3a** was slightly decreased after dilution of the substrate (Table 1, entry 10). Similarly, the concentration of base was also crucial to this Michael reaction, diluting LDA to 0.25 mol/L provided the best diastereoselectivity (dr = 98:2) and excellent yield (94%) (Table1, entry 11). Besides, we screened the amount of substrate **2a** and excellent diastereoselectivity (dr = 97:3) was obtained when 1.1 equiv of **2a** was used but with moderate yield (84%) (Table1, entry 12). Altogether, the optimum result (dr = 98:2; 94% yield) was obtained by treating *N-tert*-butanesulfinyl imidate **1** (0.2 mmol) in 5 mL of THF with 1.2 equiv of LDA (0.25 mol/L) at −78 °C for 45 min followed by reaction with **2a** (0.3 mmol) for another 2 h.

Under the aforementioned optimized reaction conditions, we examined the substrate scope of this Michael reaction by various substituted diethyl 2-arylidenemalonates (Scheme 2). A variety of novel diethyl 2-(3-((*R*)-*tert*-butylsulfinylimino)-3-methoxy-1-arylpropyl)malonates **3b**−**o** were prepared with good to excellent reaction yields (88%-95%) and excellent diastereoselectivities (dr = 97:3 to 98:2). A range of substituted diethyl arylidenemalonates with electron-withdrawing or -donating groups were all successfully transformed into the corresponding Michael adducts, with high dr values and good to excellent yields (**3b**−**l**). These results indicated that the electronic property of the substituents and the substituted-positions on the benzene ring of diethyl arylidenemalonates have no

Scheme 3. Determination of the Absolute Stereochemistry of **3a**



significant influence on the yields and diastereoselectivities of these Michael adducts. Some heterocyclic systems, such as *N*-methylindole, furan, or thiofuran, were also introduced to the Michael reaction acceptors (**2m**−**o**), and high yields and excellent diastereoselectivities were also obtained (**3m**−**o**). In addition, when 2-cyclohexylmethylenemalonate was used as the Michael acceptor, high yield (93%) and excellent diastereoselectivity of **3p** (dr > 99:1) were obtained.

In order to determine the absolute stereochemistry of the Michael adducts, 2-phenylpropane-1,1,3-tricarboxylate **5a** was synthesized from **3a** according to the literature procedures (Scheme 3).[5c] First, compound **3a** was treated with saturated HCl in dioxane to afford the corresponding imidate hydrochloride **4a**, which was stirred in water at room temperature for 24 h to generate the desired compound **5a** at high yield (85%). 2-Phenylpropane-1,1,3-tricarboxylate **5a** has been characterized by Jørgensen's group.[12] Therefore, we compared optical rotation of **5a** ($[\alpha]_D^{25}$ −31.3 (*c* 1.0, $CHCl_3$)) to those published in the literature (*R*-**5a**, $[\alpha]_D^{25}$ −29 (*c* 1.0, $CHCl_3$)), and confirmed that the absolute stereochemistry of compounds **3a**−**p** are *R*-configuration.

The stereoselectivity of the Michael addition of *N-tert*-butanesulfinyl imidate with diethyl arylidenemalonates

(12) Brandau, S.; Landa, A.; Franzen, J.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 4305.

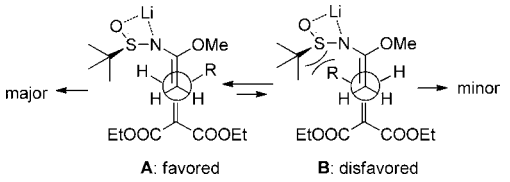


Figure 1. Proposed transition-state model.

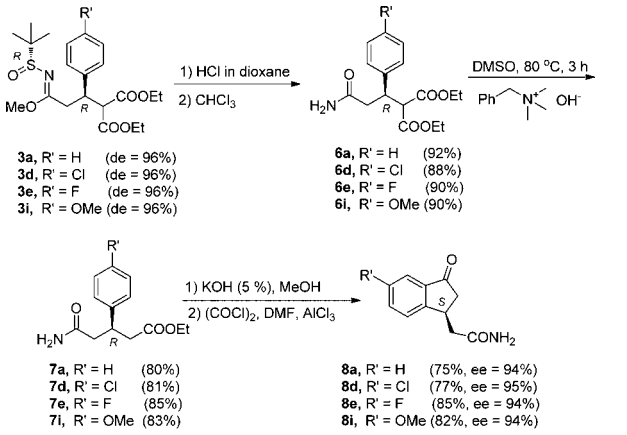
could be explained with a proposed transition-state model that is shown in Figure 1. Chelation of the metal with the nitrogen and sulfinyl oxygen occurred upon deprotonation of imidate **1**. The steric repulsion between the *tert*-butyl group of **1** and the *R*-group of the diethyl arylidenemalonates in the transition state **B** led to the diastereomers formed via transition state **A** as major products.

Furthermore, we demonstrated the utility of this methodology by transforming the addition products into 3-substituted indanone derivatives **8a**, **8d**, **8e**, and **8i**. As shown in Scheme 4, treatment of **3a**, **3d**, **3e**, and **3i** with HCl/dioxane resulted in the cleavage of the sulfinyl group and formed the imidate hydrochlorides which were excellent intermediates for an easy transformation to **6a**, **6d**, **6e**, and **6i** via heating at reflux temperature in $CHCl_3$ for 16 h. Then, the resulting amides were heated with Triton-B (benzyltrimethyl ammonium hydroxide in methanol solution) in DMSO at 80 °C for 3 h[13] afforded the deethoxycarbonylation products **7a**, **7d**, **7e**, and **7i** which were further hydrolyzed by KOH (5%) and followed by Friedel–Crafts reactions to prepare the target products **8a**, **8d**, **8e**, and **8i** with good yields (75%, 77%, 85%, and 82%, respectively) and enantiomeric excesses (ee = 94% for **8a**, **8e**, and **8i** and ee = 95% for **8d**).

In summary, we have developed an efficient methodology for a highly diastereoselective Michael addition reaction of *N*-*tert*-butanesulfinyl imidate with diethyl arylidenemalonate derivatives. This strategy was proved to be tolerant to the diversified diethyl arylidenemalonates containing aryl

(13) Melo, J. O. F.; Pereir, E. H. T.; Donnici, C. L.; Wladislaw, B.; Marzorati, L. *Synth. Commun.* **1998**, *28*, 4179.

Scheme 4. Synthesis of Chiral Indanones **8** from **3**



groups, heterocyclic substituents and alicyclic groups. By comparing optical rotation with known compound, the absolute stereochemistry of the Michael adducts was confirmed as *R*-configuration. As evidenced by the asymmetric synthesis of 3-substituted indanone derivatives, our method could be readily extended to an efficient asymmetric synthesis of a wide variety of 3-substituted indanone derivatives, which are valuable building blocks for preparing potential biologically active compounds.

Acknowledgment. We gratefully acknowledge financial support from the National Natural Science Foundation of China (Grant Nos. 21021063, 91229204, 81102307, and 81025017), National S&T Major Projects (2012ZX09103-101-072), and the China-EU Science and Technology Cooperation Project (1109).

Supporting Information Available. Detailed experimental procedures including spectroscopic and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.