## Highly Diastereo- and Enantioselective Tandem Reaction toward Functionalized Pyrrolidines with Multiple Stereocenters

## ORGANIC LETTERS

2011 Vol. 13, No. 20 5596–5599

Shengmei Guo,<sup>†</sup> Yinjun Xie,<sup>†</sup> Xinquan Hu,<sup>†,‡</sup> and Hanmin Huang<sup>\*,†</sup>

State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou, 730000, P. R. China, and College of Chemical Engineering and Materials Science, Zhejiang University of Technology, Hangzhou, 310014, P. R. China

hmhuang@licp.cas.cn

## Received August 26, 2011



An efficient asymmetric tandem dual Michael reaction that constructs three contiguous stereocenters in acyclic open-chain systems with very high enantioselectivity and diastereoselectivity has been developed. This protocol provides a reliable and rapid approach for synthesis of chiral pyrrolidines with multiple stereocenters.

Catalytic asymmetric tandem reactions have proven to be an efficient and powerful access for synthesis of complex chiral molecules of interest.<sup>1</sup> These reactions are particularly important for synthesis of stereodefined compounds with multiple stereocenters, which are usually difficult to achieve through conventional stepwise processes. A critical feature for construction of such an efficient tandem reaction is the identification of a catalyst system capable of generation of reactive species and that could be compatible with or activate the subsequent reactants. In this context, copper-catalyzed asymmetric conjugate addition of dialkylzinc to enones has been successfully explored as an efficient fundamental reaction for constructing a variety of tandem reactions combined with various electrophiles.<sup>2</sup> However, most of these protocols have been inevitably limited to the cyclic enones.<sup>3</sup> This limitation arises owing to the difficulty to control the enolate geometry in the acyclic enolate, which is likely due to the s-*cis*/s-*trans* conformational flexibility inherent to open-chain enoyl systems.<sup>4</sup>

Over the years, enolates have been a research topic of great interest to synthetic chemists.<sup>5</sup> While a number of asymmetric reactions with enolates as nucleophiles have been developed, a practical method for controlling the

<sup>&</sup>lt;sup>†</sup>Lanzhou Institute of Chemical Physics.

<sup>&</sup>lt;sup>‡</sup> Zhejiang University of Technology.

For reviews, see: (a) Ho, T.-L. Tandem Organic Reactions; Wiley: New York, 1992. (b) Bunce, R. A. Tetrahedron 1995, 51, 13103. (c) Tietze, L. F. Chem. Rev. 1996, 96, 115. (d) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. Chem. Commun. 2003, 551. (e) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. Chem. Rev. 2005, 105, 1001. (f) Ramón, D. J.; Yus, M. Angew. Chem., Int. Ed. 2005, 44, 1628. (g) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. Angew. Chem., Int. Ed. 2006, 45, 7134. (h) Enders, D.; Grondal, C.; Hüttl, M. R. M. Angew. Chem., Int. Ed. 2007, 46, 1570.

<sup>(2)</sup> For a review, see: (a) Guo, H.-C.; Ma, J.-A. Angew. Chem., Int. Ed. 2006, 45, 354. For selected examples, see: (b) Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R. Tetrahedron Lett. 1996, 37, 5141. (c) Feringa, B. L.; Pineschi, M. L.; Arnold, A.; Imbos, R.; de Vries, A. H. M. Angew. Chem., Int. Ed. Engl. 1997, 36, 2620. (d) Keller, E.; Maurer, J.; Nassz, R.; Schader, T.; Meetsma, A.; Feringa, B. L. Tetrahedron: Asymmetry 1998, 9, 2409. (e) Arnold, L. A.; Nassz, R.; Minnaard, A. J.; Feringa, B. L. J. Org. Chem. 2002, 67, 7244. (f) Naasz, R.; Arnold, L. A.; Pineschi, M.; Keller, E.; Feringa, B. L. J. Am. Chem. Soc. **1999**, *121*, 1104. (g) Mizutani, H.; Degrado, S. J.; Hoveyda, A. H. J. Am. Chem. Soc. **2002**, 124, 779. (h) Rathgeb, X.; March, S.; Alexakis, A. J. Org. Chem. 2006, 71, 5737. (i) Oliver, K.; Alexakis, A. Org. Lett. 2002, 4, 3835. (j) Alexakis, A.; March, S. J. Org. Chem. 2002, 67, 8753. (k) Agapiou, K.; Cauble, D. F.; Krische, M. J. J. Am. Chem. Soc. 2004, 126, 4528. (1) Li, K.; Alexakis, A. Tetrahedron Lett. 2005, 46, 5823. (m) Li, K.; Alexakis, A. Chem.-Eur. J. 2007, 13, 3765. (n) Xu, Y.-J.; Liu, Q.-Z.; Dong, L. Synlett 2007, 273.

<sup>(3)</sup> For the control of three stereocenters in an acyclic system, see: (a) Howell, G. P.; Fletcher, S. P.; Geurts, K.; ter Horst, B.; Feringa, B. L. J. Am. Chem. Soc. 2006, 128, 14977. (b) Arai, T.; Yokoyama, N. Angew. Chem., Int. Ed. 2008, 47, 4989. (c) Anderson, J. C.; Stepney, G. J.; Mills, M. R.; Horsfall, L. R.; Blake, A. J.; Lewis, W. J. Org. Chem. 2011, 76, 1961.

<sup>(4)</sup> Alexakis, A.; Benhaim, C. Eur. J. Org. Chem. 2002, 3221.

geometry of acyclic enolate remains elusive. Recently, we have established an asymmetric tandem reaction based on the copper-catalyzed conjugate addition reaction, in which the chiral zinc enolate was involved.<sup>6</sup> The excellent diastereoselectivities and enantioselectivities observed there suggested that the geometry of the chiral enolate was completely controlled by the catalyst system, which guaranteed the subsequent trapping reaction to proceed in high stereoselectivity. To further explore such an approach for facile control of the geometry of the acyclic enolate, we therefore selected nitroalkenes as electrophiles for trapping the zinc enolates formed in the copper-catalyzed conjugate addition of diethylzinc to acyclic enones to examine the feasibility of this approach. Herein we report a highly diastereoselective and enantioselective tandem reaction via copper-catalyzed dual Michael addition reactions that affords  $\gamma$ -nitro ketones with three contiguous acyclic stereogenic centers in high stereoselectivities (Scheme 1). Thanks to the versatility of the nitro group,<sup>7</sup> the importance of the dual Michael addition reaction is demonstrated in the elaboration of the  $\gamma$ -nitro ketones into chiral pyrrolidines with multiple stereocenters using a two-step procedure.

Scheme 1. Cu-Catalyzed Tandem Conjugate Dual Michael Reaction



We first investigated the tandem Michael/Michael addition reaction of  $Et_2Zn$  to chalcone **1a** and  $\beta$ -nitrostyrene **2a** in the presence of copper catalyst with phosphite–pyridine **L2** as chiral ligand and neutral CuBr as copper source.<sup>8</sup> A sequential one-pot procedure was employed in which the reagents were added step by step in one pot. After complete conversion of the chalcone **1a** to the zinc enolate in the presence of the chiral catalyst was confirmed by TLC, the nitroalkene **2a** was added to the reaction mixture to trap the chiral enolate. To our delight, high yield with excellent diastereoselectivity and enantioselectivity were observed **Table 1.** Optimized Reaction Conditions for the Tandem DualMichael Reaction $^a$ 

0	Et <sub>2</sub> Zn		ЛнΩ
	+NO2 -	CuX <sub>n</sub> / L*	Ph Ph
Ph <sup>2</sup> Ph	Ph Ph	solvent, -20 °C	Ph NO2
1a	2a		н За

entry	$\mathrm{CuX}_n$	solvent	yield <sup><math>b</math></sup> (%)	$\mathrm{d}\mathbf{r}^c$	$\operatorname{ee}^{d}(\%)$
1	CuBr	$Et_2O$	79	95:5	94
<b>2</b>	$CuBr_2$	$Et_2O$	78	91:9	92
3	CuCl	$Et_2O$	82	>99:1	97
4	$CuCl_2$	$Et_2O$	85	93:7	94
5	$Cu(OAc)_2$	$Et_2O$	72	90:10	94
6	$Cu(CH_3CN)_4BF_4\\$	$Et_2O$	32	83:17	-30
7	$Cu(OTf)_2$	$Et_2O$	43	50:50	20
8	CuCl	CPME	85	95:5	96
9	CuCl	$Bu_2O$	82	98:2	96
10	CuCl	TBME	67	95:5	63
11	CuCl	$CH_2Cl_2$	21	97:3	80
12	CuCl	toluene	44	96:4	96
$13^e$	CuCl	$Et_2O$	78	97:3	96

<sup>*a*</sup> Reaction conditions: chalcone **1a** (0.5 mmol),  $Et_2Zn$  (0.6 mmol), nitroalkene **2a** (0.6 mmol),  $CuX_n$  (0.005 mmol), L (0.006 mmol),  $Et_2O$  (2.0 mL), -20 °C, 24 h. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> Determined by <sup>1</sup>H NMR and HPLC. <sup>*d*</sup> Determined by chiral HPLC, and for the major isomer. <sup>*e*</sup> With L1 as ligand.

(Table 1, entry 1). As expected, with L2 as chiral ligand, the less electrophilic neutral copper catalysts with more coordinating counterions, such as CuBr and CuCl, proved to be more suitable, and among all those tested, CuCl led to the best results with respect to both diastereoselectivity and enantioselectivity. In contrast, the copper sources with fewer coordinating counterions, such as Cu(CH<sub>3</sub>CN)<sub>4</sub>BF<sub>4</sub> and Cu(OTf)<sub>2</sub>, gave poor results in this catalytic process (Table 1, entries 6 and 7). Further screening of solvents indicated that reactions performed in ether solvents led to good results, and Et<sub>2</sub>O was the best choice for this transformation. The chiral ligand L1 could also be employed for this transformation, but with relative lower diastereoselectivity (Table 1, entry 13). Under the optimal reaction conditions and using CuCl/L2 as the catalyst (Table 1, entry 3), the desired adduct  $\gamma$ -nitro ketone 3a was obtained in 82% yield with excellent stereoselectivity.

After having identified the optimal reaction conditions, we first investigated the substrate scope of nitroalkenes in this one-pot sequence of reaction. A series of aromatic nitroalkenes bearing electron-donating or electron-with-drawing groups in the aryl moiety were first subjected to the optimal conditions using chalcone **1a** and Et<sub>2</sub>Zn. As summarized in Table 2, the corresponding adducts were obtained in good yields (66–90%) and with excellent enantioselectivities (94–97% ee). In each case, the reaction was highly diastereoselective with almost only one of four possible diastereomers observed (>20:1 dr, Table 2, entries 1–8). Besides the substituted phenyl nitroalkenes **2i** and **2j** 

<sup>(5)</sup> For reviews, see: (a) Evans, D. A. In Asymmetric Synthesis; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 1–110.
(b) Heathcock, C. H. Modern Enolate Chemistry: Regio- and Stereoselective Formation of Enolates and the Consequence of Enolate Configuration on Subsequent Reactions; VCH: Weinheim, 1992. (c) Arya, P.; Qin, H. Tetrahedron 2000, 56, 917.

<sup>(6)</sup> Guo, S.; Xie, Y.; Hu, X.; Xia, C.; Huang, H. Angew. Chem., Int. Ed. 2010, 49, 2728.

<sup>(7) (</sup>a) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001. (b) Larock, R. C. *Comprehensive Organic Transformation*; VCH, New York, 1989; p 411.

<sup>(8)</sup> Hu, Y.; Liang, X.; Wang, J.; Zheng, Z.; Hu, X. J. Org. Chem. 2003, 68, 4542.

Table 2. Cu-Catalyzed Tandem Dual Michael Reaction<sup>a</sup>

$Ar^{1}$ $Ar^{2}$		NO <sub>2</sub> <u>L2</u> 2	Ar <sup>1</sup>	$Ar^{1} \xrightarrow[\bar{H}]{} Ar^{2} Ar^{2}$	
entry	$1(\mathrm{Ar}^1,\mathrm{Ar}^2)$	<b>2</b> (R)	$\operatorname{yield}^{b}(\%)$	$\mathrm{dr}^c$	$\operatorname{ee}^{d}(\%)$
1	Ph, Ph	Ph	<b>3a</b> , 82	>99:1	97
2	Ph, Ph	4-ClPh	<b>3b</b> , 76	>20:1	96
3	Ph, Ph	4-BrPh	<b>3c</b> , 80	>20:1	96
4	Ph, Ph	4-FPh	<b>3d</b> , 72	>20:1	97
5	Ph, Ph	4-CH <sub>3</sub> Ph	<b>3e</b> , 78	>20:1	96
6	Ph, Ph	4-MeOPh	<b>3f</b> , 66	>20:1	95
7	Ph, Ph	3-ClPh	<b>3g</b> , 79	>20:1	96
8	Ph, Ph	3,4-(MeO) <sub>2</sub> Ph	<b>3h</b> , 90	>20:1	94
9	Ph, Ph	1-naphthyl	<b>3i</b> , 59	>20:1	97
10	Ph, Ph	2-furyl	<b>3j</b> , 69	>20:1	96
11	Ph, Ph	c-C <sub>6</sub> H <sub>11</sub>	<b>3k</b> , 52	>20:1	96
$12^e$	Ph, Ph	AcNH	<b>31,</b> 68	>20:1	94
13	Ph, Ph	E-PhCH=CH	<b>3m</b> , 55	>20:1	97
14	4-CH <sub>3</sub> Ph, Ph	Ph	<b>3n</b> , 85	>20:1	96
15	4-MeOPh, Ph	Ph	<b>30</b> , 64	>20:1	95
16	4-ClPh, Ph	Ph	<b>3p</b> , 87	>20:1	96
17	4-BrPh, Ph	Ph	<b>3q</b> , 83	>20:1	95
18	4-FPh, Ph	Ph	<b>3r</b> , 88	>20:1	97
19	3-ClPh, Ph	Ph	<b>3s</b> , 82	17:1	91
20	Ph, 4-ClPh	Ph	<b>3t</b> , 85	>20:1	96
21	Ph, 4-BrPh	Ph	<b>3u</b> , 85	>20:1	95
22	4-MeOPh, Ph	4-BrPh	<b>3v</b> , 81	>20:1	95

<sup>*a*</sup> Reaction conditions: chalcone **1** (0.5 mmol), Et<sub>2</sub>Zn (0.6 mmol), nitroalkene **2** (0.6 mmol), CuCl (0.005 mmol), **L2** (0.006 mmol), Et<sub>2</sub>O (2.0 mL), -20 °C, 24 h. <sup>*b*</sup> Isolated yield. <sup>*c*</sup> Determined by <sup>1</sup>H NMR. <sup>*d*</sup> Determined by chiral HPLC. <sup>*e*</sup> (*Z*)-Type nitroalkene was used.

could also react smoothly, generating the corresponding products **3i** and **3j** in good yields and excellent stereoselectivities. The aliphatic nitroalkene **2k** was also shown to be compatible in this reaction and provided the corresponding adduct **3k** with excellent stereoselectivity (Table 2, entry 11). It is notable that the current reaction could be extended to some functionalized nitroalkenes. The (Z)-nitroalkene **2l**<sup>9</sup> bearing an amide functional group as well as **2m** containing alkenyl moiety reacted with **1a** in good yields with high diastereoselectivities and enantioselectivities (Table 2, entries 12 and 13). The formation of aminated and alkylated adducts are attractive because those functional groups could be easy convert to some important chiral compounds.

To further demonstrate the general applicability of the current tandem reaction, a broad spectrum of chalcones were also tested under the optimal reactions. As Table 2 shows, changing the electronic properties of the aromatic substituent in the enone had no major effect on the stereoselectivity of this transformation. Electron-withdrawing as well as electron-donating groups could be attached to the aromatic moiety and afforded the corresponding adducts

, 1., Ivia,

5598

3n-v with excellent diastereoselectivities and enantioselectivities in the range of 91–97% ee. Only in the case of 3-(3chlorophenyl)-1-phenylprop-2-en-1-one 2s was a slight decrease in diastereoselectivity and enantioselectivity observed (Table 2, entry 19).

The absolute configuration of the major stereoisomer was determined to be 2S, 3S, 2'R by single-crystal X-ray analysis of the bromo-containing product 3v.<sup>10</sup> The assigned absolute configuration indicated that the initial Michael addition takes place from the Re face of the enone through the control of the catalyst which was identical to the original 1,4-addition protocol catalyzed by copper catalyst with the same chiral ligand.<sup>8</sup> On the basis of this information, the absolute configuration of the adduct 31 which produced by the (Z)-nitroalkene could also be determined as (2S,3S,4S) by the single-crystal X-ray analysis, which holds the same relative configuration as that of 3v.<sup>11</sup> These results indicated that the geometry of the nitroalkene did not affect chiral environment in the transition state and suggested that the (E)-enolate was involved in the second Michael reaction. Based on these results,<sup>12</sup> we propose an eight-membered cyclic Zimmer-Traxler-like transition state (Scheme 2) to account for the observed stereoselectivity,  $1^{13}$  in which the chiral (E)-enolate is involved and the aryl or alkyl group of the nitroalkene adopts a pseudoequatorial position to give the anti product during the second Michael reaction. The nitro group of the nitroalkene might be able to coordinate with the Cu center and thus make the carbon-carbon double bond more electrophilic toward the enolate from its Re face to facilitate an substrate-induced enantioselective Michael addition and give the  $\gamma$ -nitro ketone products with high levels of stereochemical control.





The obtained  $\gamma$ -nitro ketone contains the versatile nitro group and therefore could be readily converted to structurally diverse pyrrolidine derivatives through well-established methods. As outlined in Scheme 3, after reductive cyclization of the **3a** and **3l** by the known method, the corresponding dihydropyrroles **4a** and **4l** were then hydrogenated under the catalysis of Pd/C to furnish the chiral pyrrolidines **5a** and **5l** containing four stereocenters in a

<sup>(9)</sup> For synthesis of and using this nitroalkene, see: Zhu, S.; Yu, S.; Wang, Y.; Ma, D. Angew. Chem., Int. Ed. **2010**, 49, 4656.

single isomer. The relative configuration of the newly formed chiral center was determined by 2D NMR (see the

Scheme 3. Synthesis of Chiral Pyrrolidine Derivatives



Supporting Information). Both dihydropyrrole **4l** and pyrrolidine **5l** contain the useful acetamide functional

(10) CCDC 834880 (**3v**), 834881 (**3l**), and 834882 (**7a**) contain 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/conts/datarequest/cif.

(11) The difference of absolute configuration of 3v and 3l resulted from the sequence difference of the Ar group and AcNH group according to the sequence rule.

(12) A control experiment was carried out: the conjugate addition product **8a** with 92% ee was reacted with LDA at -78 °C for generation of the enolate, which was then subjected to react with the nitroalkene in the absence of copper catalyst. The desired dual Michael adduct **3a** was obtained in lower yield with high enantioselectivity (92% ee for major isomer) but relative lower diastereoselectivity. These results indicated that the absolute configuration of the final adduct was determined by the chiral enolate and the Cu catalyst could accelerate the second Michael reaction but may not exert chiral induction in this step.



group, which should find applications in the design of new catalysts<sup>14</sup> and biologically active molecules.<sup>15</sup> In addition, the adduct **3a** was also successfully transformed into the chiral acids **6a** and **7a** in high yields. The structure of **7a** was confirmed by single-crystal X-ray analysis.<sup>10</sup>

In summary, we have successfully established an efficient method for assembling of two distinct electrophiles into one molecule through the copper-catalyzed dual Michael addition reaction. The reaction is applicable to a wide array of  $\alpha$ , $\beta$ -unsaturated ketones as well as nitroalkenes and proceeds with excellent diastereoselectivity and enantioselectivity for obtaining  $\gamma$ -nitro ketones with three contiguous stereocenters. In addition, the dramatic effect of neutral copper in the tandem reactions has been disclosed, which provided evidence that the electrophilic of catalyst precursor plays a crucial role in the control of stereoselectivity. These finds may suggest an efficient strategy for controlling geometry of acyclic enolate.

Acknowledgment. Financial support provided by the National Natural Science Foundation of China (21172226, 21133011) and the Chinese Academy of Sciences is gratefully acknowledged.

**Supporting Information Available.** Experimental details and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) (a) Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, *13*, 1. (b) Heathcock, C. H. In *Comprehensive Carbanion Chemistry, Part B*; Elsevier: Amsterdam, 1984; p 177.

(14) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. Chem. Rev. 2007, 107, 5471.

(15) Pearson, W. H. In *Studies in Natural Product Chemistry*; Rahman, A. U., Ed.; Elsevier: New York, 1998; Vol. 1, p 323.