ORGANIC LETTERS

2012
Vol. 14, No. 24
6230–6233

A Facile Access to Enantioenriched Isoindolines *via* One-Pot Sequential Cu(I)-Catalyzed Asymmetric 1,3-Dipolar Cycloaddition/Aromatization

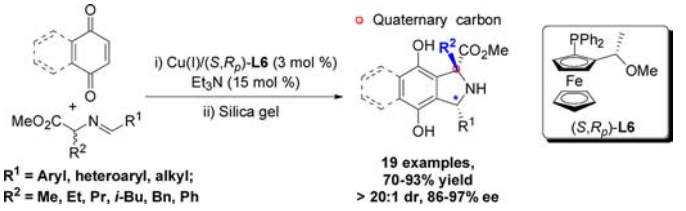
Zhaolin He,[†] Tanglin Liu,[†] Haiyan Tao,[†] and Chun-Jiang Wang*[,†,‡]

College of Chemistry and Molecular Sciences, Wuhan University, 430072, China, and State Key Laboratory of Elemento-organic Chemistry, Nankai University, 300071, China

cjwang@whu.edu.cn

Received October 30, 2012

ABSTRACT



Facile access to enantioenriched isoindolines bearing a quaternary stereogenic center and a tertiary stereogenic center was successfully developed *via* highly efficient Cu(I)/(*S*,*Rp*)-PPFOMe-catalyzed asymmetric 1,3-dipolar cycloaddition of azomethine ylide with quinone derivatives followed by silica-gel-promoted aromatization in a one-pot reaction protocol. The present catalytic system exhibited high diastereoselectivity, excellent enantioselectivity, and a broad substrate scope under mild conditions.

Catalytic enantioselective 1,3-dipolar cycloaddition of azomethine ylides to electron-deficient alkenes is a powerful and atom-economical carbon−carbon bond-forming reaction that facilitates the synthesis of a range of structurally and stereochemically rich pyrrolidines.[1] Because the resulting highly substituted pyrrolidines are prevalent in many natural alkaloids, compounds of pharmaceutical significance, organocatalysts, and biologically important building blocks in organic synthesis,[2] recent research has focused on the catalytic asymmetric version of the 1,3-dipolar cycloaddition of azomethine ylides.[3] Since the first catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides to electron-deficient alkenes reported by Zhang using Ag^{I}/Xylyl-FAP,[3a] and Jørgensen employing the Zn^{II}/bisoxazo-line complex,[3b] catalytic asymmetric 1,3-dipolar cycloaddition has been one of the most powerful and diversity-oriented syntheses (DOS)[4] for the construction of a range of structurally and stereochemically rich pyrrolidines. Despite excellent results achieved for this transformation,

[†] Wuhan University.
[‡] Nankai University.

(1) For recent reviews about 1,3-dipolar cycloaddition reactions of azomethine ylides, see: (a) Engels, B.; Christl, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7968. (b) Stanley, L. M.; Sibi, M. P. *Chem. Rev.* **2008**, *108*, 2887. (c) Alvarez-Corral, M.; Munoz-Dorado, M.; Rodrıguez-Garcıa, I. *Chem. Rev.* **2008**, *108*, 3174. (d) Naodovic, M.; Yamamoto, H. *Chem. Rev.* **2008**, *108*, 3132. (e) Nair, V.; Suja, T. D. *Tetrahedron* **2007**, *63*, 12247. (f) Adrio, J.; Carretero, J. C. *Chem. Commun.* **2011**, *47*, 6784.

(2) (a) Pyne, S. G.; Davis, A. S.; Gates, N. J.; Nicole, J.; Hartley, J. P.; Lindsay, K. B.; Machan, T.; Tang, M. *Synlett* **2004**, 2670. (b) Harwood, L. M.; Vickers, R. J. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W., Eds.; Wiley & Sons: New York, 2002. (c) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139.

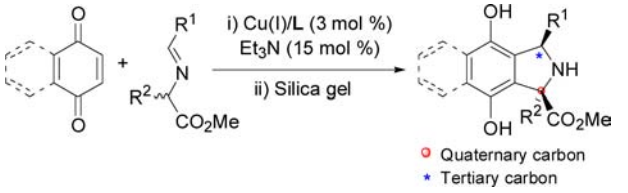
(3) For the first catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides to activated alkenes, see: (a) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400. (b) Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4236. For the very recent examples, see: (c) Kim, H. Y.; Li, J.-Y.; Kim, S.; Oh, K. *J. Am. Chem. Soc.* **2011**, *133*, 20750. (d) He, L.; Chen, X.-H.; Wang, D.-N.; Luo, S.-W.; Zhang, W.-Q.; Yu, J.; Ren, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2011**, *133*, 13504. (e) Bai, J.-F.; Wang, L.-L.; Peng, L.; Guo, Y.-L.; Ming, J.-N.; Wang, F.-Y.; Xu, X.-Y.; Wang, L.-X. *Eur. J. Org. Chem.* **2011**, 4472. (f) Robles-Machin, R.; Alonso, I.; Adrio, J.; Carretero, J. C. *Chem.—Eur. J.* **2011**, *17*, 13109. (g) Wu, H.; Wang, B.; Liu, H.; Wang, L. *Tetrahedron* **2011**, *67*, 1210. (h) Reboredo, S.; Reyes, E.; Vicario, J. L.; Badía, D.; Carrillo, L.; Cózar, A.; Cossío, F. P. *Chem.—Eur. J.* **2012**, *18*, 7179. (i) Han, M.-L.; Wang, D.-Y.; Zeng, P.-W.; Zheng, Z.; Hu, X.-P. *Tetrahedron: Asymmetry* **2012**, *23*, 306.

(4) Schreiber, S. L. *Science* **2000**, *287*, 1964.

10.1021/ol302987h
Published on Web 11/30/2012

most dipolarophiles applied in these reactions are the derivatives of conjugated unsaturated esters or enones, maleimides, vinyl sulfones, and nitroalkenes.[1,3]

Scheme 1. Catalytic Asymmetric Synthesis of Isoindoline Derivatives



However, readily available quinone derivatives, which contain two electron-withdrawing carbonyl groups and were employed successfully as dienophiles in asymmetric Diels–Alder reactions,[5] have been seldom applied as dipolarophiles in the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides probably due to the challenging synthetic difficulties associated with enantio-/diastereoselectivity control. Recently, Gong et al. reported an elegant procedure[6] for the first organocatalytic asymmetric 1,3-dipolar cycloaddition of quinone derivatives with *in situ* formed azomethine ylides followed by subsequential base-promoted isomerization leading to the asymmetric synthesis of biologically active isoindoline derivatives[7] with excellent diastereo- and enantioselectivity. Nevertheless, despite this recent advance in the application of quinones as dipolarophiles, limitations still persist in this area, particularly in the context of efficient construction of enantioenriched isoindoline derivatives[8] bearing a quaternary stereogenic center.[9] In this communication, we reported a facile and one-pot approach to isoindolines bearing a quaternary stereogenic center *via* highly efficient Cu(I)-catalyzed 1,3-dipolar cycloaddition followed by sequential aromatization with excellent diastereoselectivity and high enantioselectivity (Scheme 1).

Recently, we reported that Cu(I) or Ag(I)/chiral TF-BiphamPhos complexes exhibited excellent results in the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides with various electron-deficient alkenes.[10] It would be reasonable that quinone derivatives could also be employed as dipolarophiles in such a catalytic system considering its structural similarity with the commonly used dipolarophile dimethyl maleate. Unfortunately, as outlined in eq 1 in Scheme 2, no desired product was observed when the reaction of glycinate derived imino ester **1** with naphthoquinone **2** was examined with AgOAc/PPh_3 as the catalyst and Et_3N as the base at rt, and the pyrole **3** was formed unexpectedly in high yield. Isolation of pyrrole indicated that the possible pyrrolidine intermediate did form through a 1,3-dipolar cycloaddition reaction pathway; however, this labile species was easily oxidized to deliver the corresponding pyrrole.[11] We envisaged that treatment of an α-substituted imino ester under the same reaction conditions would significantly inhibit the above-mentioned undesired oxidation, as further reaction could be efficiently suppressed by the formed quaternary carbon stereogenic center adjacent to the N-atom of the five-membered pyrrolidine ring. Then, (±)-phenylalanine-derived imino ester **4a** was tested, and the reaction was finished in less than 4 h at rt. To our surprise, although two newly formed spots were detected on the TLC plate, only isoindoline **5a** corresponding to the less polar spot could be isolated. Later, we found the more polar compound rapidly turned into the less polar isoindoline **5a** when mixing the reaction mixture with silica gel. Based on these results, we postulate that the more polar compound may be the labile keto-isomer of **5a**, that is, the normal 1,3-dipolar cycloaddition adduct, and the more stable isoindoline **5a** was easily fully achieved *via* a subsequent silica-gel-promoted aromatization in a one-pot reaction protocol (Scheme 2, eq 2).

Scheme 2. Initial Test Employing Glycinate-Derived Imino Ester **1** and Phenylalaninate-Derived Imino Ester **4a** as the Dipolar Precursor in the Reaction with Naphthoquinone

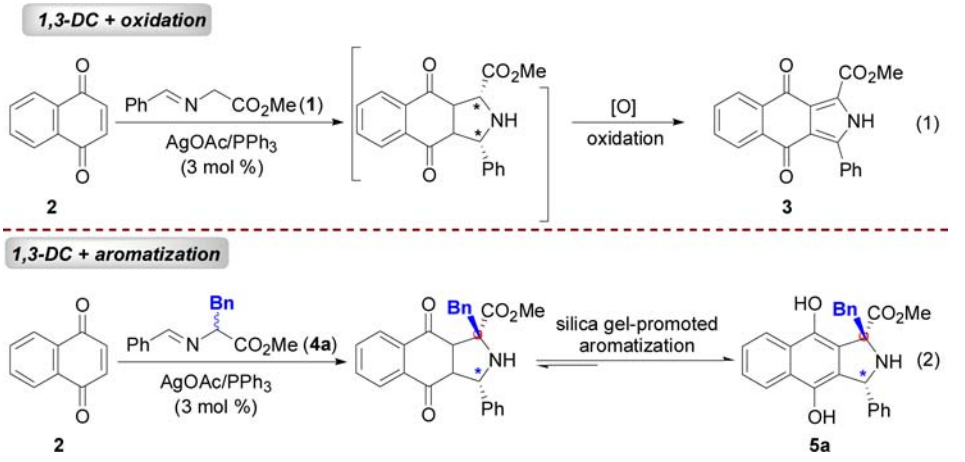
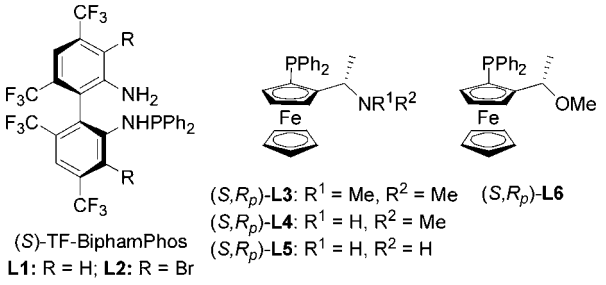


Table 1. Optimization of One-Pot and Sequential Catalytic Asymmetric 1,3-DC/Aromatization of Imino Ester **4a** with Naphthoquinone **2**[a]

entry	L	[M]	solvent	*t*/°C	time/h	yield (%)[b]	ee (%)[c]
1	**L1**	AgOAc	CH_2Cl_2	rt	6	81	20
2	**L1**	$CuBF_4$	CH_2Cl_2	rt	6	87	9
3	**L2**	AgOAc	CH_2Cl_2	rt	6	86	27
4	**L2**	$CuBF_4$	CH_2Cl_2	rt	6	85	37
5	**L3**	AgOAc	CH_2Cl_2	rt	4	76	9
6	**L3**	$CuBF_4$	CH_2Cl_2	rt	4	85	71
7	**L4**	$CuBF_4$	CH_2Cl_2	rt	4	69	69
8	**L5**	$CuBF_4$	CH_2Cl_2	rt	4	74	22
9	**L6**	$CuBF_4$	CH_2Cl_2	rt	4	85	78
10	**L6**	$CuBF_4$	CH_2Cl_2	-20	12	89	87
11	**L6**	$CuBF_4$	Ether	-20	24	43	97
12	**L6**	$CuBF_4$	THF	-20	24	65	95
13	**L6**	$CuBF_4$	PhMe	-20	12	87	95



[a] All reactions were carried out with 0.26 mmol of **4a** and 0.20 mmol of **2** in 2 mL of solvent. $CuBF_4$ = $Cu(CH_3CN)_4BF_4$. [b] Isolated yield. [c] Ee was determined by HPLC analysis.

Encouraged by these results, we then investigated the asymmetric version of this one-pot and sequential 1,3-dipolar cycloaddition/aromatization reaction to evaluate the enantioselectivity with chiral ligands, and the results were summarized in Table 1. Having exhibited excellent stereoselective control in the 1,3-dipolar cycloaddition of azomethine ylides, chiral TF-BiphamPhos[10a] developed in this research group was first tested in this reaction. Combined with chiral TF-BiphamPhos **L1** and **L2**, both $CuBF_4$ and AgOAc show high catalytic activities and afforded the desired product in good yields with excellent diastereoselectivities albeit with low enantioselectivities (Table 1, entries 1−4). Other commercially available chiral ligands such as BINAP and Monophos were also tested in this transformation affording unsatisfied results (see Supporting Information for more details). Next, readily available Ugi amine[12]-derived ferrocenyl ligands **L3**−**L6** were identified as promising chiral ligands. (S,R_p)-PPFOMe[13] **L6** exhibited the best performance in terms of the reaction rate and enantioselectivity among the tested ligands, giving rise to the isoindoline **5a** as the sole isomer in 85% yield with excellent diastereoselectivity (>20:1 dr) and 78% ee (entry 9). Reducing the reaction temperature from rt to −20 °C led to reaction completion in good yield with 87% ee (entry 10). Solvent effects were investigated for this transformation, and toluene was revealed to be the best solvent in terms of the reaction rate, yield, and enantioselectivity (entry 13).

Next, the scope and generality of this one-pot and sequential 1,3-dipolar cycloaddition/aromatization of naphthoquinone **2** with a variety of imino esters **4** were investigated under the optimized experimental conditions. As shown in Table 2, imino esters bearing electron-rich (entries 6−10), electron-neutral (entries 1 and 11), and electron-deficient groups (entries 2−5) on the aryl ring reacted with naphthoquinone **2** smoothly affording the corresponding cycloadducts (**5a**−**5k**) exclusively in good yields (79−93%) and high enantioselectivities (92−97%) at −20 °C within 12−24 h. The substitution pattern and electronic property of the phenyl ring have little effect on the enantioselectivity. It is noteworthy that comparable results were still achieved for the sterically hindered *ortho*-chloro, *ortho*-methyl, and *ortho*-methoxyl imino esters **4c**, **4g**, and **4j** in terms of diastereo-/enantioselectivity and reactivity (entries 3, 7, and 10). Additionally, the heteroaryl substituted imino ester **4l** derived from 2-furylaldehyde also works in this transformation leading to a 76% yield and 94% ee (entry 12). Notably, the less reactive imino

(5) (a) Choi, S.; Hwang, H.; Lee, P. H. *Eur. J. Org. Chem.* **2011**, 1351. (b) Mohamed, Y. A. M.; Inagaki, F.; Takahashi, R.; Mukai, C. *Tetrahedron* **2011**, *67*, 5133. (c) Evans, D. A.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10162. (d) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388.

(6) Wang, C.; Chen, X. H.; Zhou, S. M; Gong, L. Z. *Chem. Commun.* **2010**, *46*, 1275.

(7) (a) Kukkola, P. J.; Bilci, N. A.; Ikler, T.; Savage, P.; S. Shetty, S.; DelGrande, D.; Jeng, A. Y. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1737. (b) Ewing, D. F.; Len, C.; Mackenzie, G.; Petit, J. P.; Ronco, G.; Villa, P. *J. Pharm. Pharmacol.* **2001**, *53*, 945. (c) Van der Veken, P.; Soroka, A.; Brandt, I.; Chen, Y.-S.; Maes, M.-B.; Lambeir, A.-M.; Chen, X.; Haemers, A.; Scharpé, S.; Augustyns, K.; De Meester, I. *J. Med. Chem.* **2007**, *50*, 5568.

(8) For very recent examples on the asymmetric construction of isoindolines, see: (a) Enders, D.; Narine, A. A.; Toulgoat, F.; Bisschops, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 5661. (b) Williams, F. J.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2011**, *50*, 4459. (c) Takizawa, S.; Inoue, N.; Hirata, S.; Sasai, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 9725.

(9) (a) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388. (b) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591.

(10) (a) Wang, C.-J.; Liang, G.; Xue, Z.-Y.; Gao, F. *J. Am. Chem. Soc.* **2008**, *130*, 17250. (b) Wang, C.-J.; Xue, Z.-Y.; Liang, G.; Lu, Z. *Chem. Commun.* **2009**, 2905. (c) Liu, T.-L.; He, Z.-L.; Tao, H.-Y.; Cai, Y.-P.; Wang, C.-J. *Chem. Chem* **2011**, *47*, 2616. (d) Liu, T.-L.; He, Z.-L.; Tao, H.-Y.; Wang, C.-J. *Chem.—Eur. J.* **2012**, *18*, 8042.

(11) Gilgen, P.; Jackson, B.; Hansen, H.-J.; Heimgartner, H.; Schmid, H. *Helv. Chim. Acta* **1974**, *57*, 2634.

(12) (a) Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389. (b) Gokel, G.; Marquarding, D.; Ugi, I. *J. Org. Chem.* **1972**, *37*, 3052.

(13) Hayashi, T.; Mise, T.; Fukushima, M.; Kagotani, M.; Nagashima, N.; Hamada, Y.; Matsumoto, A.; Kawakami, S.; Konishi, M.; Yamamoto, K.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1138.

Table 2. Substrate Scope of One-Pot and Sequential Asymmetric 1,3-DC/Aromatization of Imino Ester **4** with Napthoquinone **2**[a]

entry	R^1	R^2	**5**	yield (%)[b]	*ee* (%)[c]
1	Ph (**4a**)	Bn	**5a**	86	96
2	*p*-Cl-C_6H_4 (**4b**)	Bn	**5b**	89	95
3	*o*-Cl-C_6H_4 (**4c**)	Bn	**5c**	87	94
4	*m*-Cl-C_6H_4 (**4d**)	Bn	**5d**	87	94
5[d]	*p*-CF_3-C_6H_4 (**4e**)	Bn	**5e**	87	92
6	*p*-Me-C_6H_4 (**4f**)	Bn	**5f**	93	95
7	*o*-Me-C_6H_4 (**4g**)	Bn	**5g**	81	93
8	*m*-Me-C_6H_4 (**4h**)	Bn	**5h**	86	97
9	*p*-MeO-C_6H_4 (**4i**)	Bn	**5i**	81	96
10	*o*-MeO-C_6H_4 (**4j**)	Bn	**5j**	85	94
11[d]	2-naphthyl (**4k**)	Bn	**5k**	79	97
12	2-furyl (**4l**)	Bn	**5l**	76	94
13	Cy (**4m**)	Bn	**5m**	70	94
14	Ph (**4n**)	Me	**5n**	82	89
15	Ph (**4o**)	Et	**5o**	90	94
16[d]	Ph (**4p**)	Pr	**5p**	77	90
17[d]	Ph (**4q**)	*i*-Bu	**5q**	74	93
18[d]	Ph (**4r**)	Ph	**5r**	86	93

[a] Unless otherwise noted, the reaction was carried out with 0.26 mmol of **4** and 0.20 mmol of **2** in 2 mL of toluene at −20 °C. [b] Isolated yield. [c] Ee was determined by HPLC analysis. [d] Carried out at 0 °C.

ester **4m** from aliphatic cyclohexane-carbaldehyde was tolerated in this reaction, and the corresponding adduct could be obtained in 70% yield and, remarkably, 94% ee (entry 13). To further expand the synthetic utility of this transformation, imino esters derived from other α-substituted amino acids have also been examined. Under the optimal reaction conditions, high yields and excellent diastereoselectivities were uniformly observed for the aldimino esters derived from (±)-alanine, (±)-2-aminobutyric acid, (±)-2-aminopentanoic acid, (±)-leucine, and (±)-2-phenylglycine (entries 14−18).

The absolute configuration of adduct **5b** achieved by Cu(I)/(S,R_p)-PPFOMe was unequivocally determined as (1*R*,3*R*) by X-ray crystallographic analysis of a single crystal (Figure 1). Those of other adducts are tentatively proposed on the basis of these results.

The potential of this catalytic approach is further demonstrated by the reaction of benzoquinone **6** with imino ester **4a** under the optimized reaction conditions to afford

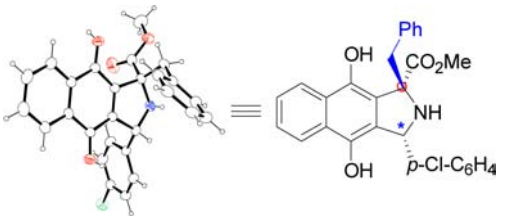
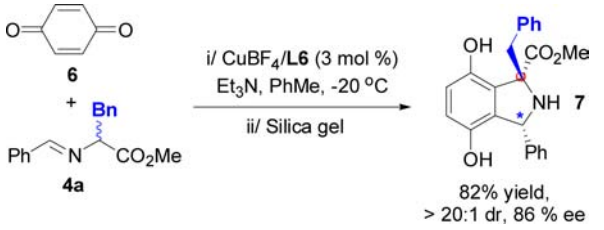


Figure 1. X-ray structure of (1*R*,3*R*)-**5b**.

the cycloadduct **7** in excellent diastereoselectivity and good enantioselectivity (Scheme 3).

Scheme 3. Catalyst Asymmetric One-Pot Sequential 1,3-DC/Aromatization of Benzoquinone **6** and Imino Ester **4a**



In conclusion, we have successfully developed a facile access to enantioenriched isoindolines *via* highly efficient Cu(I)-catalyzed asymmetric 1,3-dipolar cycloaddition followed by silica-gel-promoted aromatization in a one-pot reaction protocol. The success of this methodology relies on logic design and rational optimization which led to utilizing α-substituted imino esters as the dipoles. The highly efficient Cu(I)/(S,R_p)-PPFOMe combined with silica gel exhibited excellent performances, providing enantioenriched isoindolines containing a quaternary and a tertiary stereogenic center in high yield, and excellent stereoselectivities. Further investigations of the scope and synthetic application of this methodology are ongoing, and the results will be reported in due course.

Acknowledgment. This work is supported by the 973 Program (2011CB808600), NSFC (21172176), NCET-10-0649, IRT1030, and Large-scale Instrument And Equipment Sharing Foundation of Wuhan University. We thank Prof. Hua Li at Wuhan University for solving the crystal structure.

Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.