

# Asymmetric Friedel–Crafts Alkylation of Methoxyfuran with Nitroalkenes Catalyzed by Diphenylamine-Tethered Bis(oxazoline)–Zn(II) Complexes

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## ABSTRACT



The first catalytic asymmetric Friedel–Crafts reaction of 2-methoxyfuran with nitroalkenes was developed under the catalysis of diphenylamine-tethered bis(oxazoline)–Zn(OTf)<sub>2</sub> complexes. The reaction conditions and ligands were optimized, and the scope of the reaction was tested by varying the nitroalkenes. For most of aromatic and heteroaromatic nitroalkenes, good yields and high enantioselectivities (86–96% ee) were obtained. The methoxyfuran group in the product can be transformed to carboxylic acid via oxidative fragmentation with full retention of the configuration.

Asymmetric Friedel–Crafts reaction is an efficient way to construct chiral centers on the  $\alpha$  or  $\beta$  position of different kinds of aromatic systems.<sup>1</sup> During the past decade, indole and its derivatives have been demonstrated to be good substrates for the asymmetric Friedel–Crafts reaction with unsaturated aldehydes,<sup>2a,b</sup> unsaturated ketones,<sup>2c,d</sup> unsaturated 2-acyl imidazoles,<sup>2e</sup> unsaturated ketophosphonates,<sup>2f</sup> epoxides,<sup>3</sup> ketoesters,<sup>4</sup> glyoxylate,<sup>4a,b</sup> imines,<sup>5a–c</sup> enamines,<sup>5f</sup> and

electron-deficient olefins, such as nitroalkenes,<sup>6</sup> alkylidene malonates,<sup>7</sup> and ethenetetracarboxylates.<sup>8</sup> Many efficient catalytic asymmetric systems have been developed, including chiral ligand–metal complexes, imidazolidinones, thioureas, bis-sulfonamides, and phosphoric acids. Recently, the substrates have been expanded successfully to electron-rich

(3) Bandini, A.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 84.

(4) For some recent examples, see: (a) Li, H.; Wang, Y.-Q.; Deng, L. *Org. Lett.* **2006**, *8*, 4063. (b) Zhuang, W.; Poulsen, T. B.; Jorgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 3284. (c) Torok, B.; Abid, M.; London, G.; Esquibel, J.; Torok, M.; Mhadgut, S. C.; Yan, P.; Prakash, G. K. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3086. (d) Lyle, M. P. A.; Draper, N. D.; Wilson, P. D. *Org. Lett.* **2005**, *7*, 901. (e) Zhuang, W.; Gathergood, N.; Hazell, R. G.; Jorgensen, K. A. *J. Org. Chem.* **2001**, *66*, 1009.

(5) For some recent examples, see: (a) Wang, Y.-Q.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156. (b) Jia, Y.-X.; Xie, J.-H.; Duan, H.-F.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2006**, *8*, 1621. (c) Kang, Q.; Zhao, Z.-A.; You, S.-L. *J. Am. Chem. Soc.* **2007**, *129*, 1484. (d) Rowland, G. B.; Rowland, E. B.; Liang, Y.; Perman, J. A.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 2609. (e) Terada, M.; Yokoyama, S.; Sorimachi, K.; Uraguchi, D. *Adv. Synth. Catal.* **2007**, *349*, 1863. (f) Terada, M.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 292.

(1) For recent reviews, see: (a) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550. (b) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199. (c) Wang, Y.; Ding, K.-L. *Chin. J. Org. Chem.* **2001**, *21*, 763. (d) Jorgensen, K. A. *Synthesis* **2003**, 1117.

(2) For some recent examples, see: (a) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (b) Li, C.-F.; Liu, H.; Liao, J.; Cao, Y.-J.; Liu, X.-P.; Xiao, W.-J. *Org. Lett.* **2007**, *9*, 1847. (c) King, H. D.; Meng, Z.; Denhart, D.; Mattson, R.; Kimura, R.; Wu, D.; Gao, Q.; Macor, J. E. *Org. Lett.* **2005**, *7*, 3437. (d) Bandini, M.; Fagioli, M.; Melchiorre, P.; Melloni, A.; Umani-Ronchi, A. *Tetrahedron Lett.* **2003**, *44*, 5843. (e) Evans, D. A.; Fandrick, K. R.; Song, H.-J. *J. Am. Chem. Soc.* **2005**, *127*, 8942. (f) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. J. *J. Am. Chem. Soc.* **2003**, *125*, 10780.

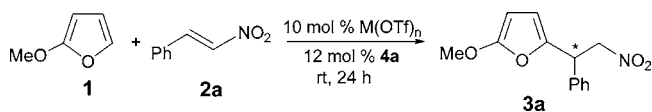
benzenes<sup>2f,4e,9</sup> and five-membered aromatic heterocycles.<sup>2e,4e,10</sup> In contrast, the asymmetric Friedel–Crafts reaction of furan derivatives with electron-deficient olefins has not been fully developed. In 2004, Terada et al. reported the first asymmetric Friedel–Crafts reaction of 2-methoxyfuran with tosylamines.<sup>10d</sup> In 2005, Evans et al. reported the reaction of 2-methoxyfuran with 2-acyl imidazoles.<sup>2e</sup> Since (1) the nitroalkenes are important Michael-acceptors in different asymmetric reactions,<sup>11</sup> (2) the nitro group has diverse transformations,<sup>12</sup> and (3) the furan is an important bioactive heterocycle, we speculate that it will be important to investigate the asymmetric Friedel–Crafts reaction of furan derivative with nitroalkenes. Herein, we would like to document our recent results about the diphenylamine-tethered bis(oxazoline)–metal complexes<sup>13</sup> catalyzed asymmetric Friedel–Crafts reaction of 2-methoxyfuran with nitroalkenes.

Our research began with the optimization of the model reaction between 2-methoxyfuran **1** and  $\beta$ -nitrostyrene **2a**. The results are summarized in Tables 1 and 2.

After the screening of metal salts, it was found that Zn(OTf)<sub>2</sub> is the suitable choice. Rare earth triflates and Cu(I/II) triflates led to both low yields and low enantioselectivities, while no formation of desired product **3a** was observed when other metal triflates were used (Table 1, entries 1–8). Under the catalysis of **4a**–Zn(II) complex, a significant solvent effect was observed. Xylene gave better results than toluene and dipolar solvents, while coordinative solvents inhibited the reactivity of the catalyst (Table 1, entries 9–14).

In order to improve the enantioselectivity of the asymmetric alkylation, we further optimized the ligands. Utilizing diphenylamine-tethered bis(oxazoline) (BOX) ligands (**4a**–**4d**) originally prepared by Guiry<sup>14a</sup> and bis(thiazoline) (BTH) ligands (**5a**–**5d**) originally developed by our group (Figure

**Table 1.** Effect of Metal Sources and Solvents<sup>a</sup>



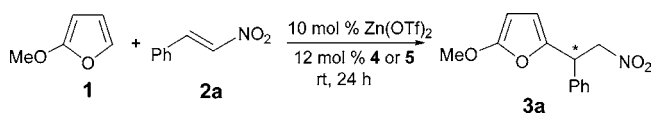
entry	metal salt	solvent	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	AgOTf	toluene	0	n.d.
2	Sc(OTf) <sub>3</sub>	toluene	0	n.d.
3	La(OTf) <sub>3</sub>	toluene	20	0
4	Yb(OTf) <sub>3</sub>	toluene	20	5
5	In(OTf) <sub>3</sub>	toluene	0	n.d.
6	CuOTf	toluene	19	2
7	Cu(OTf) <sub>2</sub>	toluene	5	24
8	Zn(OTf) <sub>2</sub>	toluene	64	85
9	Zn(OTf) <sub>2</sub>	xylene	65	87
10	Zn(OTf) <sub>2</sub>	THF	0	n.d.
11	Zn(OTf) <sub>2</sub>	CH <sub>3</sub> CN	14	1
12	Zn(OTf) <sub>2</sub>	DCM	34	38
13	Zn(OTf) <sub>2</sub>	DCE	20	36
14	Zn(OTf) <sub>2</sub>	hexane	28	21

<sup>a</sup> All data were obtained using 0.25 mmol substrates under the catalysis of 10 mol % ligand–metal triflate complex in 3 mL of solvent for 24 h.

<sup>b</sup> Isolated yields. <sup>c</sup> Determined by HPLC using a Chiracel OD-H column with hexane/isopropanol, 90:10, as eluent.

1),<sup>13a</sup> variable enantioselectivities were obtained in the reaction in catalyzing the asymmetric Friedel–Crafts alkylation reaction of 2-methoxyfuran with  $\beta$ -nitrostyrene. BOX ligands **4a**–**4c** and BTH ligands **5a**–**5c** gave comparable enantioselectivities (Table 2, entries 1–3 vs entries 9–11), whereas BOX **4d** is more active than the corresponding BTH **5d**. The new ligand **4f** with *trans*-diphenyl substitution on the oxazoline ring gave better results than its anomer **4e** formerly developed by our group,<sup>6c</sup> as well as other bis-

**Table 2.** Effect of Chiral Ligands<sup>a</sup>



entry	ligand	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	<b>4a</b>	65	87
2	<b>4b</b>	64	92
3	<b>4c</b>	31	78
4	<b>4d</b>	73	92
5	<b>4e</b>	70	94
6	<b>4f</b>	85	94
7	<b>4f</b>	74	94 <sup>d</sup>
8	<b>4f</b>	54	94 <sup>e</sup>
9	<b>5a</b>	66	84
10	<b>5b</b>	78	93
11	<b>5c</b>	15	67
12	<b>5d</b>	6	3

<sup>a</sup> All data were obtained using 0.25 mmol substrates under the catalysis of 10 mol % ligand–Zn(OTf)<sub>2</sub> complex in 3 mL of xylene for 24 h.

<sup>b</sup> Isolated yields. <sup>c</sup> Determined by HPLC using a Chiracel OD-H column with hexane/isopropanol, 90:10, as eluent. <sup>d</sup> Reaction performed at 0 °C.

<sup>e</sup> Reaction performed at 30 °C.

(6) (a) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6576. (b) Zhuang, W.; Hazell, R. G.; Jorgensen, A. K. *Org. Biomol. Chem.* **2005**, *3*, 2566. (c) Jia, Y.-X.; Zhu, S.-F.; Yang, Y.; Zhou, Q.-L. *J. Org. Chem.* **2006**, *71*, 75. (d) Bandini, M.; Garelli, A.; Rovinetti, M.; Tommasi, M.; Umani-Ronchi, A. *Chirality* **2005**, *17*, 522. (e) Lu, S.-F.; Du, D.-M.; Xu, J. *Org. Lett.* **2006**, *8*, 2115. (f) Fleming, E. M.; McCabe, T.; Connon, S. J. *Tetrahedron Lett.* **2006**, *47*, 7037. (g) Singh, P. K.; Bisai, A.; Singh, V. K. *Tetrahedron Lett.* **2007**, *48*, 1127.

(7) (a) Zhuang, W.; Hansen, T.; Jorgensen, K. A. *Chem. Commun.* **2001**, 347. (b) Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030. (c) Zhou, J.; Ye, M.-C.; Tang, Y. *J. Comb. Chem.* **2004**, *6*, 301. (d) Zhou, J.; Tang, Y. *Chem. Commun.* **2004**, 432.

(8) Yamazaki, S.; Iwata, Y. *J. Org. Chem.* **2006**, *71*, 739.

(9) For some recent examples, see: (a) Ishii, A.; Soloshonok, V. A.; Mikami, K. *J. Org. Chem.* **2000**, *65*, 1597. (b) Yuan, Y.; Wang, X.; Li, X.; Ding, K. *J. Org. Chem.* **2004**, *69*, 146.

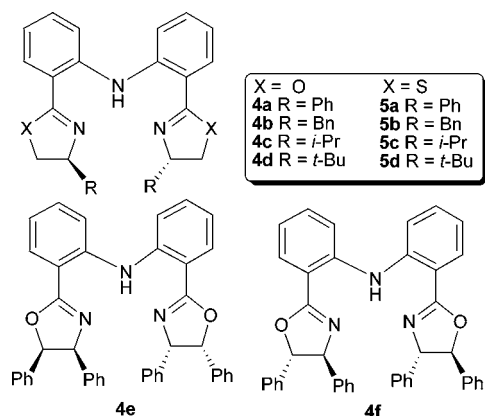
(10) (a) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370. (b) Palomo, C.; Oiarbide, M.; Kardak, B. G.; Garcia, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154. (c) Evans, D. A.; Fandrick, K. R. *Org. Lett.* **2006**, *8*, 2249. (d) Uruguchi, D.; Sorimachi, K.; Terada, M. *J. Am. Chem. Soc.* **2004**, *126*, 11804. (e) Li, G.; Rowland, G. B.; Rowland, E. B.; Antilla, J. C. *Org. Lett.* **2007**, *9*, 4065.

(11) For recent reviews, see: Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877 and refs therein.

(12) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.

(13) (a) Lu, S.-F.; Du, D.-M.; Zhang, S.-W.; Xu, J. *Tetrahedron: Asymmetry* **2004**, *15*, 3433. (b) Du, D.-M.; Lu, S.-F.; Fang, T.; Xu, J. *J. Org. Chem.* **2005**, *70*, 3712. (c) Lu, S.-F.; Du, D.-M.; Xu, J.; Zhang, S.-W. *J. Am. Chem. Soc.* **2006**, *128*, 7418.

(14) (a) McManus, H. A.; Guiry, P. J. *J. Org. Chem.* **2002**, *67*, 8566. (b) McManus, H. A.; Cozzi, P. G.; Guiry, P. J. *Adv. Synth. Catal.* **2006**, *348*, 551.

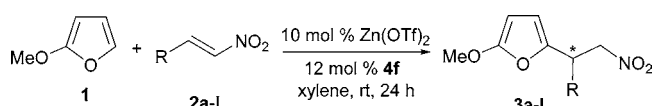


**Figure 1.** Diphenylamine-tethered bis(oxazoline) and bis(thiazoline) ligands.

(oxazoline) and bis(thiazoline) ligands. Obtained under the catalysis of 10 mol % **4f**–Zn(OTf)<sub>2</sub> within 24 h at room temperature were 85% yield and 94% ee (Table 2, entry 6). No product was formed when commercially available Pybox ligand was used. The yield decreased when the temperature varied, while no significant effect on the enantioselectivity was observed (Table 2, entries 7 and 8).

After the optimization of the reaction conditions, the scope of this asymmetric reaction was investigated. First, a variety of other electron-rich furans such as 2-methylfuran and 2-phenylfuran were tested with  $\beta$ -nitrostyrene, but these substrates cannot react with  $\beta$ -nitrostyrene. The low reactivity of furan derivatives can also be found from earlier reports;

**Table 3.** Catalytic Asymmetric Friedel–Crafts Reaction of 2-Methoxyfuran with Nitroalkenes<sup>a</sup>

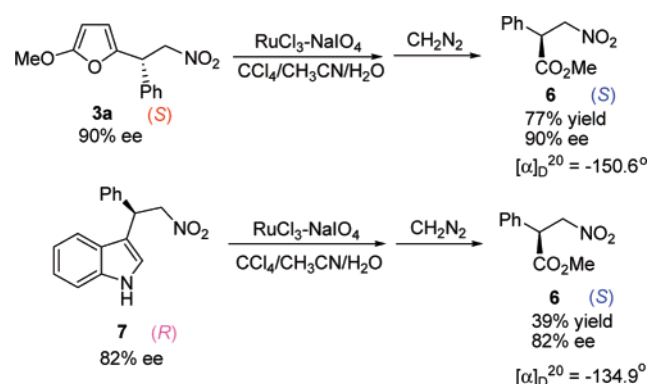


entry	R	product	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>
1	Ph	<b>3a</b>	85	94
2	4-MeC <sub>6</sub> H <sub>4</sub>	<b>3b</b>	75	94
3	4-MeOC <sub>6</sub> H <sub>4</sub>	<b>3c</b>	84	94
4	4-FC <sub>6</sub> H <sub>4</sub>	<b>3d</b>	69	95
5	4-ClC <sub>6</sub> H <sub>4</sub>	<b>3e</b>	73	95
6	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	<b>3f</b>	55	96 <sup>d</sup>
7	2-naphthyl	<b>3g</b>	70	88
8	3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	<b>3h</b>	86	96
9	2-furyl	<b>3i</b>	56	86
10	2-thienyl	<b>3j</b>	72	89
11	<i>o</i> -MeOC <sub>6</sub> H <sub>4</sub>	<b>3k</b>	56	81
12	PhCH <sub>2</sub> CH <sub>2</sub>	<b>3l</b>	49	62

<sup>a</sup> All data were obtained using 0.25 mol substrates under the catalysis of 10 mol % **4f**–Zn(OTf)<sub>2</sub> complex in 3 mL of xylene at room temperature for 24 h. <sup>b</sup> Isolated yields. <sup>c</sup> Determined by HPLC using Chiralcel OD-H or AS column. For details, see Supporting Information. <sup>d</sup> Compound **3f** does not have an adequate baseline resolution, the ee value in the chiral HPLC is an estimate.

there also only 2-methoxyfuran was used as the sole substrates.<sup>2e,10d</sup> Then a wide range of nitroalkenes **2a–l** were tested in the asymmetric Friedel–Crafts reaction with 2-methoxyfuran. The results are summarized in Table 3. Nitrostyrenes with both electron-donating and -withdrawing groups at the para position of the aromatic group gave excellent enantioselectivities in the range of 94–96% ee, with moderate-to-good yields that varied from 55% to 86%. No electronic effect was observed. Substituted groups on the meta position did not affect the yield and enantioselectivity significantly. Other aromatic or heteroaromatic groups, such as naphthalene, furan, and thiophene, could be successfully employed as the 2-substituent of the nitroethene to afford the corresponding products with good enantioselectivities (Table 3, entries 7, 9 and 10). However, the enantioselectivities decreased in the cases of **2k** and **2l**, for the unfavored interaction between the ortho substituted group and the ligand, and the high flexibility of the alkyl chain, respectively. Such a phenomenon was similar to one we have observed in the reaction of indole with nitroalkenes.<sup>6e</sup>

The absolute configuration of the product was determined through chemical correlation (Figure 2). After several

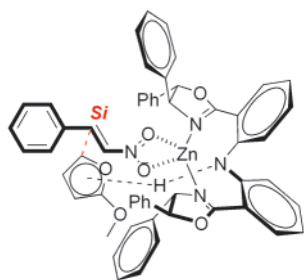


**Figure 2.** Oxidative fragmentation of the product and determination of the absolute configuration.

experiments, the product **3a** was transformed to methyl 2-nitro-1-phenylpropanoate **6** via oxidative fragmentation of the methoxyfuran group by RuCl<sub>3</sub>–NaIO<sub>4</sub>, which was recently used in the transformation of the furan group to carboxylic acid.<sup>15</sup> **6** can also be obtained from the known compound **7** which was formerly prepared through the asymmetric Friedel–Crafts reaction of indole with nitrostyrene under the catalysis of **4a**–Zn(OTf)<sub>2</sub>.<sup>6e</sup> The same *S* configuration of **6** derived from **3a** and **7** was elucidated by comparison of the optical rotation and retention time of the major enantiomer on HPLC (for details, see Supporting Information); thus, product **3a** should have the *S* configuration. The absolute configuration of other products **3b–3l** were assigned to be *S* by analogy.

On the basis of absolute configuration, the proposed transition state was illustrated in Figure 3. Similar to our

(15) Kohler, F.; Gais, H.-J.; Raabe, G. *Org. Lett.* **2007**, 9, 1231.



**Figure 3.** Proposed transition state for the asymmetric Friedel–Crafts alkylation.

former report, we believe that the catalyst works in a bifunctional form. Zinc(II) works as a Lewis acid to activate the nitrostyrene, while the NH group works as a H-bond donor via an  $\text{NH}\cdots\pi$  interaction to direct the attack of 2-methoxyfuran from the *si* face.<sup>16</sup>

In conclusion, the first catalytic asymmetric Friedel–Crafts alkylation of 2-methoxyfuran and nitroalkenes was developed. High enantioselectivities and good yields have been obtained for most of the aromatic and heteroaromatic

nitroalkenes. The transition state was proposed on the basis of the absolute configuration of the products. The product can be transformed to chiral methyl 2-nitropropanoate efficiently with full retention of the configuration via oxidative fragmentation. Further investigation on the application of the products are currently underway in our laboratory.

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**Supporting Information Available:** Experimental procedures and characterizations, copies of  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR of new compounds, and HPLC profiles. This material is available free of charge via the Internet at <http://pubs.acs.org>. OL702003X

(16) For examples of  $\text{NH}\cdots\pi$  interaction, see: (a) Arata, S.; Torigoe, H.; Iihoshi, T.; Matsumoto, N.; Dahan, F.; Tuchagues, J.-P. *Inorg. Chem.* **2005**, *44*, 9288. (b) Tsuzuki, S.; Honda, K.; Uchimaru, T.; Mikami, M.; Tanabe, K. *J. Am. Chem. Soc.* **2000**, *122*, 11450.