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ARTICLE TYPE

# Enantioselective Friedel-Crafts Reaction of 4,7-Dihydroindoles with $\beta$ -CF<sub>3</sub>- $\beta$ -disubstituted Nitroalkenes

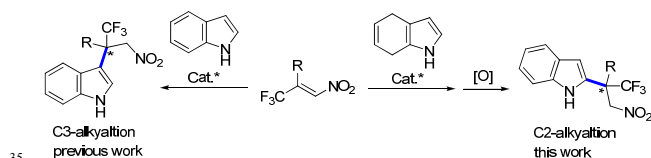
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Using Ni(ClO<sub>4</sub>)<sub>2</sub>-bisoxazoline complex as a catalyst, the enantioselective Friedel-Crafts alkylation of 4,7-dihydroindoles with  $\beta$ -CF<sub>3</sub>- $\beta$ -disubstituted nitroalkenes was furnished in high enantioselectivities (up to 91%) to give alkylated dihydroindoles bearing trifluoromethylated all-carbon quaternary stereocenters in good yields. The corresponding chiral C2 alkylated indoles were obtained with complete preservation of enantiopurities through the oxidation by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

Indole is a privileged structural motif existing in many biologically active compounds and natural products.<sup>1</sup> Therefore, extensive effort has been devoted to the synthesis of optically active indolic compounds. Catalytic asymmetric Friedel-Crafts alkylation reaction is undoubtedly an attractive approach for this purpose through the direct functionalization of indole ring.<sup>2</sup> Predominant examples have been documented for C3 alkylations of indole ring.<sup>2</sup> In comparison, Friedel-Crafts alkylation of indole at the C2 position was difficult due to the higher nucleophilicity of C3 position of indole ring.<sup>3</sup> Therefore, an indirect strategy has been developed for the synthesis of chiral 2-alkylated indoles via enantioselective Friedel-Crafts alkylation of 4,7-dihydroindoles at the pyrrolic C2 position and followed by an oxidation reaction. A range of electrophiles have been successfully applied in the Friedel-Crafts alkylations of 4,7-dihydroindoles.<sup>4-7</sup> However, the construction of all-carbon quaternary stereocenter at the C2 position of indole ring has remained unexploited. Efficient approach developed toward this challenge would be highly valuable.



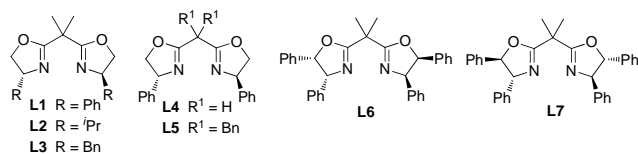
Recently, success has been achieved in the enantioselective construction of all-carbon quaternary stereogenic center via asymmetric Friedel-Crafts C3 alkylation reaction of indole.<sup>8</sup> Kwiatkowski and co-workers disclosed a high-pressure accelerated Friedel-Crafts reaction of indole with enone in modest enantioselectivities.<sup>9</sup> Excellent results were then

presented by Liu and Zhang in the reactions with isatin-derived  $\alpha,\beta$ -unsaturated aldehydes as alkylating reagents,<sup>10</sup> both of which applied chiral amine as a catalyst. At the same time, Arai's group and our group independently reported the chiral Lewis-acid catalyzed Friedel-Crafts reactions of indoles with  $\beta,\beta$ -disubstituted nitroalkenes (isatin-derived nitroalkenes and  $\beta$ -CF<sub>3</sub>- $\beta$ -disubstituted nitroalkenes), leading to the desired products in excellent enantioselectivities.<sup>11</sup> Followed success appeared in the Friedel-Crafts reactions of indoles with  $\alpha$ -substituted- $\beta$ -nitroacrylates, which were communicated by the groups of Meggers, Akiyama, and us, respectively.<sup>12</sup> Inspired by the above progress, we envisioned the Friedel-Crafts alkylation of 4,7-dihydroindole with  $\beta,\beta$ -disubstituted unsaturated substrates and subsequent oxidation would provide a good opportunity to prepare chiral 2-alkylated indoles bearing all-carbon quaternary stereocenters (Scheme 1).<sup>13</sup> Herein, we presented our primary result on the Friedel-Crafts alkylation of 4,7-dihydroindoles with  $\beta$ -CF<sub>3</sub>- $\beta$ -disubstituted nitroalkenes.

Table 1 Optimization of the reaction condition<sup>a</sup>

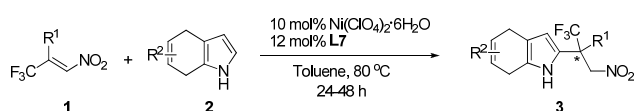
Entry	LA	L*	Solvent	T(°C)	Yield (%) <sup>b</sup>	Ee(%) <sup>c</sup>
1	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L1	Toluene	80	85	59
2	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L2	Toluene	80	78	23
3	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L3	Toluene	80	83	55
4	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L4	Toluene	80	80	69
5	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L5	Toluene	80	77	14
6	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L6	Toluene	80	89	43
7	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L7	Toluene	80	94	91
8	Zn(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L7	Toluene	80	80	84
9	Ni(OTf) <sub>2</sub>	L7	Toluene	80	82	67
10	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L7	DCE <sup>d</sup>	80	65	89
11	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L7	Ether	80	78	87
12 <sup>e</sup>	Ni(ClO <sub>4</sub> ) <sub>2</sub> ·6H <sub>2</sub> O	L7	Toluene	50	75	88

<sup>a</sup> Reaction condition: **1a** (0.2 mmol), **2a** (0.3 mmol), Lewis acid (LA) (10 mol%), and chiral ligand (L\*) (12 mol%) in toluene (2.0 mL) at 80 °C for 24 h. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by chiral HPLC. <sup>d</sup> DCE = 1,2-dichloroethane. <sup>e</sup> 48 h.



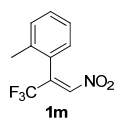
Initially, (*E*)-1-phenyl-1-trifluoromethyl-2-nitroethene (**1a**) and 4,7-dihydroindole (**2a**) were selected as the model substrates to study the Friedel–Crafts reaction. To our delight, the reaction proceeded smoothly to give the desired product in 85% yield and 59% ee in the presence of 10 mol % Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O and 12 mol% ligand **L1** in toluene at 80 °C (entry 1, Table 1). Different chiral bisoxazolone ligands were then investigated. Poor to modest enantioselectivities were detected when modifying the chiral substituents and the link groups of ligand **L1** (entries 2-6). Gratifyingly, the reaction with **L7** bearing trans-diphenyl groups as a ligand gave the highest ee value (entry 7). Lewis acid Zn(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O could also promote this reaction with slightly lower enantioselectivity, while Ni(OTf)<sub>2</sub> gave inferior result (entries 8-9). Finally, solvent change and lowering the temperature did not improve the enantioselectivity (entries 10-12).

**Table 2** Substrate scope of the enantioselective Friedel–Crafts reaction<sup>a</sup>



Entry	R <sup>1</sup>	R <sup>2</sup>	Yield(%) <sup>b</sup>	Ee(%) <sup>c</sup>	
1	Ph ( <b>1a</b> )	H ( <b>2a</b> )	<b>3aa</b>	94	91
2	3-Me-Ph ( <b>1b</b> )	H ( <b>2a</b> )	<b>3ba</b>	95	85
3	4-Me-Ph ( <b>1c</b> )	H ( <b>2a</b> )	<b>3ca</b>	92	88
4	4-MeO-Ph ( <b>1d</b> )	H ( <b>2a</b> )	<b>3da</b>	90	88
5	3,5-Me <sub>2</sub> -Ph ( <b>1e</b> )	H ( <b>2a</b> )	<b>3ea</b>	90	84
6	4-Cl-Ph ( <b>1f</b> )	H ( <b>2a</b> )	<b>3fa</b>	89	81
7	3-F-Ph ( <b>1g</b> )	H ( <b>2a</b> )	<b>3ga</b>	92	85
8	4-CF <sub>3</sub> -Ph ( <b>1h</b> )	H ( <b>2a</b> )	<b>3ha</b>	88	86
9	3-Thienyl ( <b>1i</b> )	H ( <b>2a</b> )	<b>3ia</b>	86	68
10	2-Naphthyl ( <b>1j</b> )	H ( <b>2a</b> )	<b>3ja</b>	85	82
11	2-Phenylethyl ( <b>1k</b> )	H ( <b>2a</b> )	<b>3ka</b>	84	71
12	1-Octyl ( <b>1l</b> )	H ( <b>2a</b> )	<b>3la</b>	88	62
13	Ph ( <b>1a</b> )	5-Me ( <b>2b</b> )	<b>3ab</b>	90	88
14	Ph ( <b>1a</b> )	5-F ( <b>2c</b> )	<b>3ac</b>	87	88
15	Ph ( <b>1a</b> )	6-F ( <b>2d</b> )	<b>3ad</b>	89	88

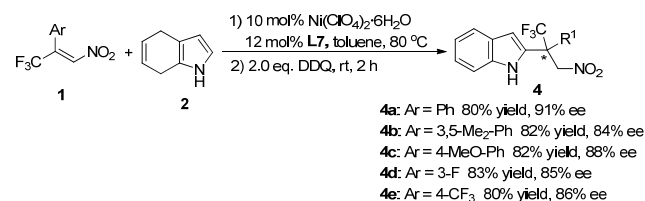
<sup>a</sup> Reaction condition: **1** (0.2 mmol), **2** (0.3 mmol), 10 mol% Ni(ClO<sub>4</sub>)<sub>2</sub>·6H<sub>2</sub>O and 12 mol% **L7** in 2.0 mL toluene at 80 °C for 24–48 h. <sup>b</sup> Isolated yield. <sup>c</sup> Determined by chiral HPLC.



With the optimal conditions in hand, we then checked the substrate scope. A range of substituted nitroalkenes and 4,7-

dihydroindoles were investigated. As shown in Table 2, either electron-donating or electron-withdrawing substituents in the *para*- or *meta*-position on the phenyl ring of nitroalkenes were well-tolerated, and their reactions with 4,7-dihydroindole smoothly afforded the corresponding products with excellent yields and good to excellent enantioselectivities (entries 2-8, Table 2). However, the reactivity was sharply influenced by the steric effect of nitroalkene and no reaction was observed for the substrate **1m**, indicating the limitation of the present method. Besides, 3-thienyl and 2-naphthyl products **3ia** and **3ja** were isolated in good yields but the enantioselectivity of **3ia** was lower (entries 9 and 10). Modest enantioselectivities were also observed in the reactions of alkylated nitroalkenes **1k** and **1l** though good yields were obtained (entries 11-12). The reaction was successfully extended to 4,7-dihydroindoles bearing 5-Me, 5-F, and 6-F substituents, achieving good yields and enantioselectivities in their reactions with nitroalkene **1a** (entries 13-15).

To disclose the practicality of the present method for synthesizing chiral 2-substituted indole derivatives, a one-pot process combining the Friedel–Crafts alkylation and the sequential oxidation was developed. As shown in Scheme 2, the direct addition of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to the reaction mixture after completion of the Friedel–Crafts alkylation led to the corresponding 2-alkylated indoles in good yields. The enantioselectivities of the 2-alkylated indoles were kept the same as the original Friedel–Crafts adducts, indicating the perfect preservation of the stereochemistry during the oxidation step.



**Scheme 2** One-pot synthesis of 2-alkylated indoles **4**<sup>14</sup>

## 60 Conclusions

In summary, we have developed a highly enantioselective Friedel–Crafts reaction of 4,7-dihydroindoles with  $\beta$ -CF<sub>3</sub>- $\beta$ -disubstituted nitroalkenes by employing a Ni(ClO<sub>4</sub>)<sub>2</sub>-bisoxazolone complex as a catalyst. The reaction produced 2-substituted 4,7-dihydroindoles bearing trifluoromethylated all-carbon quaternary stereocenters in good yields and modest to excellent enantioselectivities. Moreover, a one-pot process combining alkylation and sequential oxidation was developed to prepare the optically active 2-alkylated indoles in good yields and no loss of enantioselectivity was observed in the oxidation reaction. Further extension of this methodology for organic synthesis is currently underway in our laboratory.

## Notes and references

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† Electronic Supplementary Information (ESI) available: Preparation of substrates, characterization data, <sup>1</sup>H, <sup>13</sup>C NMR, HRMS. See DOI: 10.1039/b000000x/

- 1 (a) M. d'Ischia, A. Napolitano and A. Pezzella, *Comprehensive Heterocyclic Chemistry III*, 2008, **3**, 353; (b) A. J. Kochanowska-Karamyan and M. T. Hamann, *Chem. Rev.*, 2010, **110**, 4489; (c) S. E. O'Connor and J. J. Maresh, *Nat. Prod. Rep.*, 2006, **23**, 532.
- 15 2 For a book on the asymmetric Friedel-Crafts reaction, see: (a) *Catalytic Asymmetric Friedel-Crafts Alkylations*, M. Bandini and A. Umani-Ronchi, Wiley-VCH, Weinheim, 2009. For reviews, see: (b) T. B. Poulsen and K. A. Jørgensen *Chem. Rev.*, 2008, **108**, 2903; (c) S.-L. You, Q. Cai, M. Zeng, *Chem. Soc. Rev.*, 2009, **38**, 2190; (d) M. Bandini, A. Eichholzer, *Angew. Chem., Int. Ed.*, 2009, **48**, 9608; (e) V. Terrasson, R. M. Figueiredo and J. M. Campagne, *Eur. J. Org. Chem.*, 2010, 2635.
- 3 For the reactions of 3-substituted indole, see: (a) H.-G. Cheng, L.-Q. Lu, T. Wang, Q. -Q. Yang, X.-P. Liu, Y. Li, Q.-H. Deng, J.-R. Chen and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2013, **52**, 3250; (b) Y.-L. Zhang, X.-H. Liu, X.-H. Zhao, J.-L. Zhang, L. Zhou, L.-L. Lin and Feng, X.-M., *Chem. Commun.*, 2013, **49**, 11311.
- 4 For  $\alpha,\beta$ -unsaturated carbonyl compounds: (a) D. A. Evans, K. R. Fandrick, H. J. Song, K. A. Scheidt and R. Xu, *J. Am. Chem. Soc.*, 2007, **129**, 10029; (b) G. Blay, I. Fernández, J. R. Pedro and C. Vila, *Tetrahedron Lett.*, 2007, **48**, 6731; (c) M. Zeng, Q. Kang, Q.-L. He and S.-L. You, *Adv. Synth. Catal.*, 2008, **350**, 2169; (d) L. Hong, C. Liu, W. Sun, L. Wang, K. Wong and R. Wang, *Org. Lett.*, 2009, **11**, 2177; (e) L. Hong, W. Sun, C. Liu, L. Wang, K. Wong and R. Wang, *Chem. Eur. J.*, 2009, **15**, 11105; (f) T. Sakamoto, J. Itoh, K. Mori and T. Akiyama, *Org. Biomol. Chem.*, 2010, **8**, 5448.
- 5 For  $\beta$ -monosubstituted nitroalkenes: (a) Y.-F. Sheng, G.-Q. Li, Q. Kang, A.-J. Zhang and S.-L. You, *Chem. Eur. J.*, 2009, **15**, 3351; (b) N. Takenaka, J. Chen, B. Captain, R. S. Sarangthem and A. Chandrakuma, *J. Am. Chem. Soc.*, 2010, **132**, 4536.
- 6 For active ketones: (a) T. Wang, G. W. Zhang, Y. Teng, J. Nie, Y. Zheng and J.-A. Ma, *Adv. Synth. Catal.*, 2010, **352**, 2773; (b) G. Blay, I. Fernández, M. C. Muñoz, J. R. Pedro, A. Recuenco and C. Vila, *J. Org. Chem.*, 2011, **76**, 6286.
- 45 7 For imines: (a) Q. Kang, X.-J. Zheng and S.-L. You, *Chem. Eur. J.*, 2008, **14**, 3539; (b) J. Feng, W. Yan, D. Wang, P. Li, Q. Sun and R. Wang, *Chem. Commun.*, 2012, **48**, 8003.
- 8 For reviews of catalytic asymmetric construction of all-carbon quaternary stereocenters, see: (a) E. J. Corey, A. Guzman-Perez, *Angew. Chem., Int. Ed.*, 1998, **37**, 388; (b) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. U.S.A.*, 2004, **101**, 5363; (c) J. Christoffers and A. Baro, *Adv. Synth. Catal.*, 2005, **347**, 1473; (d) B. M. Trost and C. Jiang, *Synthesis*, 2006, 369; (e) C. Hawner and A. Alexakis, *Chem. Commun.*, 2010, **46**, 7295.
- 55 9 D. Lyzwa, K. Dudzinski and P. Kwiatkowski, *Org. Lett.* 2012, **14**, 1540.
- 10 R. Liu and J. Zhang, *Org. Lett.*, 2013, **15**, 2266.
- 11 (a) J.-R. Gao, H. Wu, B. Xiang, W.-B. Yu, L. Han and Y.-X. Jia, *J. Am. Chem. Soc.* 2013, **135**, 2983; (b) T. Arai, Y. Yamamoto, A. Awata, K. Kamiya, M. Ishibashi and A. Arai, *Angew. Chem. Int. Ed.* 2013, **52**, 2486.
- 12 (a) K. Mori, M. Wakazawa and T. Akiyama, *Chem. Sci.*, 2014, **5**, 1799; (b) L.-A. Chen, X. Tang, J. Xi, W. Xu, L. Gong and E. Meggers, *Angew. Chem., Int. Ed.*, 2013, **52**, 14021; (c) J.-Q. Weng, Q.-M. Deng, L. Wu., K. Xu, H. Wu, R.-R. Liu, J.-R. Gao and Y.-X. Jia, *Org. Lett.*, 2014, **16**, 776.
- 13 M. G. Banwell, D. A. S. Beck and A. C. Willis, *ARKIVOC*, 2006, **iii**, 163.
- 14 The absolute configuration of product **4a** was assigned to be *S*, see supporting information.