Asymmetric Friedel–Crafts reaction of N-heterocycles and nitroalkenes catalyzed by imidazoline–aminophenol–Cu complex†

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Catalytic asymmetric Friedel–Crafts reaction of pyrrole with nitroalkenes was smoothly catalyzed by newly synthesized nitro-substituted imidazoline–aminophenol (1b)–Cu complex to give the adduct with up to 92% ee.

As symbolized by the potent alkaloid strychnine, various highly functionalized N-heterocycles (*e.g.*, indoles and/or pyrroles) have been isolated from natural sources.[1] Because the structural complexity of these molecules is obviously linked to their significant biological activity, the development of an efficient method for the synthesis of N-heterocyclic derivatives in an optically active form is currently in high demand in organic chemistry. Moreover, a new class of artificial N-heterocyclic derivatives having an array of stereogenic centers would offer fascinating scaffolds for the design and exploration of novel biologically active compounds directed towards pharmaceutical research.

The catalytic asymmetric Friedel–Crafts reaction[2] is one of the most direct methods for introducing a new stereogenic center on an N-heteroaromatic compound. In the last few years, asymmetric Friedel–Crafts reaction employing a nitroalkene as the electrophilic partner has attracted considerable attention because the installation of a nitro group allows subsequent versatile transformations, and extensive progress has been achieved in this direction. After pioneering work which led to the SalenAlCl catalyst,[3] successful catalytic systems have since been reported for Friedel–Crafts reaction of indole and nitroalkene by using bis-sulfonamides,[4] thioureas,[5] phosphoric acids,[6] zinc,[7] and copper catalysts.[8] We have also succeeded in the development of an imidazoline–aminophenol (**1a**)–Cu complex for the catalytic asymmetric Friedel–Crafts reaction of indole (Scheme 1).[9]

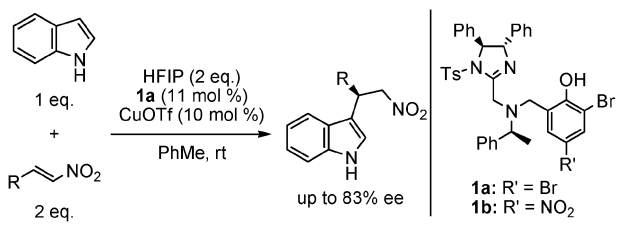
Herein, we report on the application of an imidazoline–aminophenol–Cu catalyst to the Friedel–Crafts reaction of pyrrole, for which only a limited number of successful examples have been reported.[10]

The study began with an examination of the original catalytic conditions required for the Friedel–Crafts reaction of indole and nitroalkenes. When using the **1a**–Cu catalyst in combination with 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), conversion to the Friedel–Crafts adduct **4a** occurred in low yield with moderate enantiomeric excess (Table 1, entry 1). One isolable by-product in entry 1 was a dialkylated adduct of pyrrole, which was formed by dual Friedel–Crafts reaction at both the 2- and 5-positions of pyrrole. An increase in the ratio of pyrrole to nitrostyrene improved the chemical yield of **4a** without affecting the enantioselectivity (Table 1, entry 2). We were impressed to note that, without use of HFIP, **4a** was obtained in 80% yield with a greatly improved selectivity of 80% ee (Table 1, entries 3 and 4). Other solvent systems (xylene, $CHCl_3$, AcOEt, THF) were not as effective as toluene (Table 1, entries 5–8).

In the **1a**–Cu catalysis, a reduction in the temperature lowered the chemical yield (Table 1, entries 9, 10). Because the Lewis acidity of the **1a**–CuOTf catalyst was not considered to be high enough to effectively promote the Friedel–Crafts reaction of pyrrole and nitroalkenes, we decided to modify the structure of **1a**. If the phenoxy functionality of the ligand binds to the Cu atom, the substituent *para* to the phenoxy group would significantly affect the Lewis acidity of the resulting Cu complex. Based on this reasoning, we planned to exchange the *para*-bromo functionality with an NO_2 group. DFT calculations based on the **1a**–CuOTf model suggested that the charge on the Cu-center would increase from +0.288 to +0.307 with a change in the ligand from **1a** to **1b** (see ESI†). The synthesis of ligand **1b** was readily accomplished using a method similar to that used in the preparation of **1a** (see details in ESI†).

The newly developed nitro-functionalized ligand **1b**–CuOTf catalyst successfully catalyzed the Friedel–Crafts reaction of **2** and **3a** at 0 °C, and **4a** was obtained in 73% yield with 90% ee after 27 h (other data shown in parentheses for comparison). The scope and generality of the **1b**–CuOTf catalyzed Friedel–Crafts reaction of pyrrole (**2**) and nitroalkene (**3**) are shown in Table 2.

For aromatic nitroalkenes, attachment of an electron withdrawing group at the 4-position on the phenyl ring gave the adducts in good yields with high enantiomeric excesses (Table 2, entries 2–6). The 4- and 3-substituted nitrostyrenes



Scheme 1 Asymmetric Friedel–Crafts reaction of indole and nitroalkenes catalyzed by imidazoline–aminophenol (**1a**)–CuOTf complex.

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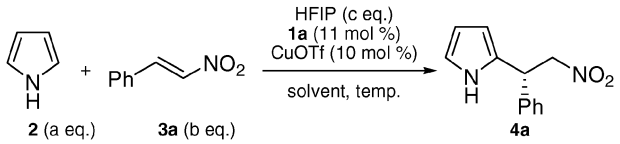
Table 1 Optimization of reaction conditions of **1a**–CuOTf catalyzed Friedel–Crafts reaction

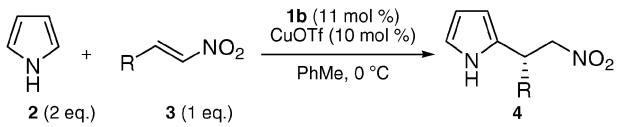


2 (a eq.) **3a** (b eq.) **4a**

Entry	*a*	*b*	*c*	Solvent	Temp./ °C	Time/ h	Yield (%)	ee (%)[a]
1	1	2	2	toluene	rt	37	29	40
2	3	1	2	toluene	rt	16	83	42
3	3	1	0	toluene	rt	17	80	80
4	2	1	0	toluene	rt	20	74	83
5	2	1	0	xylene	rt	15	71	75
6	2	1	0	$CHCl_3$	rt	20	88	50
7	2	1	0	AcOEt	rt	72	38	56
8	2	1	0	THF	rt	71	34	12
9	2	1	0	toluene	0	43	53	87
10	2	1	0	toluene	−10	44	21	91

[a] Enantiomeric excess was determined by chiral HPLC using a Chiralpak AD-H column.

Table 2 **1b**–CuOTf catalyzed asymmetric Friedel–Crafts reaction of pyrrole and nitroalkenes



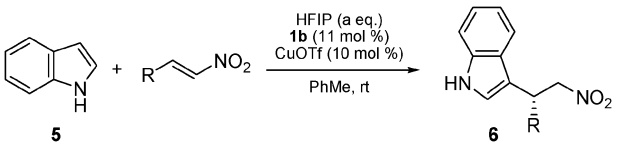
2 (2 eq.) **3** (1 eq.) **4**

Entry	R	Time/h[a]	Yield (%)[a]	ee (%)[a,b]
1	Ph (**a**)	27 (43)	73 (53)	90 (87)
2	4-FC_6H_4 (**b**)	24 (42)	81 (48)	91 (89)[d]
3	4-ClC_6H_4 (**c**)	24 (38)	97 (64)	92 (89)
4	4-BrC_6H_4 (**d**)	12 (48)	99 (87)	91 (85)[d]
5	4-$NO_2C_6H_4$ (**e**)	20 (24)	67 (44)	86 (81)[d]
6	4-$CF_3C_6H_4$ (**f**)	12 (24)	91 (73)	88 (91)[d]
7	4-$MeOC_6H_4$ (**g**)	48 (38)	55 (33)	81 (83)[d]
8	4-$CH_3C_6H_4$ (**h**)	24 (72)	78 (34)	80 (83)[d]
9	3-$NO_2C_6H_4$ (**i**)	17 (69)	81 (61)	80 (71)[d]
10	2-BrC_6H_4 (**j**)	17 (43)	96 (96)	56 (10)[d]
11	1-naphthyl (**k**)	24 (43)	70 (44)	66 (78)[d]
12	2-naphthyl (**l**)	24 (41)	81 (43)	81 (81)[d]
13	2-thienyl (**m**)	24 (43)	66 (52)	80 (52)[d]
14	$PhCH_2CH_2$ (**n**)	24 (43)	81 (81)	83 (66)[d]
15[c]	*c*-C_6H_{11} (**o**)	24 (48)	71 (74)	64 (60)[d]
16[c]	*i*-Pr (**p**)	24 (21)	61 (10)	75 (55)[d]

[a] The value in parentheses is the result using **1a** under the same conditions. [b] Enantiomeric excess was determined by chiral HPLC using a Chiralpak AD-H, AS-H column or Chiralcel OD-H column. [c] The reaction was performed at rt. [d] The absolute configuration is presented by analogy with the products obtained in entries 1 and 3.

generally gave good results; however, a drastic reduction in the ee was observed using a 2-substituted nitroalkene (Table 2, entry 10). The reaction using 2-naphthyl nitroalkene gave better enantiomeric excess than the reaction of 1-naphthyl nitroalkene. Aliphatic nitroalkenes were also applicable, giving the adduct in up to 83% ee (Table 2, entry 14). In general, the current Cu catalysis seemed sensitive to a bulky substituent neighboring the β-position of the nitroalkene.

Table 3 Catalytic asymmetric Friedel–Crafts reaction of indole and nitroalkenes



5 **6**

Entry	R	*a*	Time/ h[a]	Yield (%)[a]	ee (%)[a,b]
1	Ph	0	48 (48)	99 (69)	70 (74)
2	Ph	2	8 (47)	98 (99)	72 (75)
3	4-$NO_2C_6H_4$	2	12 (20)	99 (99)	81 (80)[c]
4	4-BrC_6H_4	2	12 (9)	99 (99)	76 (75)[c]
5	4-$MeOC_6H_4$	2	7 (18)	99 (97)	54 (55)[c]
6	*c*-C_6H_{11}	2	72 (98)	80 (50)	80 (85)[c]
7	$PhCH_2CH_2$	2	15 (28)	99 (97)	81 (83)[c]
8	*n*-pentyl	2	16 (23)	92 (97)	79 (78)[c]

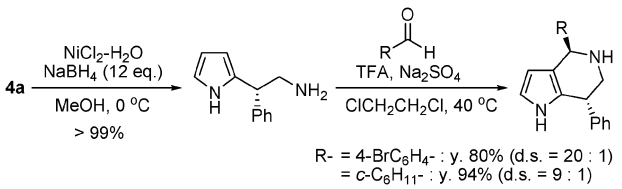
[a] The value in parentheses is the result using **1a** under the same conditions. [b] Enantiomeric excess was determined by chiral HPLC using Chiralpak AD-H and Chiralcel OD-H columns. [c] The absolute configuration is presented by analogy with the product obtained in entry 1.

Importantly, in most cases, the **1b**–Cu catalyst gave better chemical yields with higher enantiomeric excesses for the Friedel–Crafts adducts than those obtained by using **1a** as the ligand. A remarkable example is shown in entry 10, in which the stereoselectivity is improved to 56% ee using **1b** as compared to 10% using **1a**.[11]

The effect of the **1b**–CuOTf catalyst on the previously reported Friedel–Crafts reaction of indole and nitroalkene was also examined. In the case of indole, the addition of HFIP was effective in enhancing the catalytic cycle (Table 3, entries 1 and 2). With the assistance of HFIP, the **1b**–CuOTf catalyst also showed better catalyst activity than **1a**–CuOTf, while the products were obtained with almost the same stereoselectivities as those obtained using **1a**–CuOTf. Thus, the **1b**–CuOTf catalyst is a powerful and general Lewis acid catalyst for the Friedel–Crafts reaction of N-heterocycles and nitroalkenes.

Although the role of HFIP is not clear, in the **1b**–CuOTf catalyzed Friedel–Crafts reactions of both pyrrole and indole, the N-heterocycle is known to attack the β-carbon atom of the nitroalkene from the *Si* face.[12]

The synthetic utility of the product obtained in the Friedel–Crafts reaction of pyrrole was examined as shown in Scheme 2.[13] After reduction of the nitro group of the adduct using Ni-boride, which maintained the enantiomeric excess, Pictet–Spengler cyclization using aldehydes provided the pyrrolo[3,2-*c*]pyridine derivatives with high diastereoselectivity.



Scheme 2 Reduction and Pictet–Spengler reaction of Friedel–Crafts adduct.

In conclusion, we have achieved catalytic asymmetric Friedel–Crafts reaction of pyrrole with various nitroalkenes catalyzed by newly developed imidazoline–aminophenol ligand **1b**–CuOTf complex. The catalyst activity and selectivity were increased by introducing a nitro-functionality on the phenol ring of the ligand. Further application of the imidazoline–aminophenol–metal catalyst and a detailed study of the catalytic mechanism are in progress.

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11 The **1b**–CuOTf catalyzed Friedel–Crafts reaction of 2-ethylpyrrole and **3a** gave the adduct in 83% yield with 17% ee (0 °C, 48 h).

12 Based on the group-order rule, although the adducts **4** are assigned as (*S*)-form and adducts **6** are assigned as (*R*)-form, both **4** and **6** have the same stereogenic center. Our determination of the absolute configuration of **4** agrees with the result reported in ref. 10*b*. See the determination of absolute configuration in ESI†.

13 During the preparation of this manuscript, You *et al.* reported an excellent example of asymmetric Friedel–Crafts reaction of 4,7-dihydroindoles: Y.-F. Sheng, G.-Q. Li, Q. Kang, A.-J. Zhang and S.-L. You, *Chem.–Eur. J.*, 2009, **15**, 3351.