Multicomponent Reactions

DOI: 10.1002/anie.200801373

Tandem Catalytic Asymmetric Friedel–Crafts/Henry Reaction: Control of Three Contiguous Acyclic Stereocenters**

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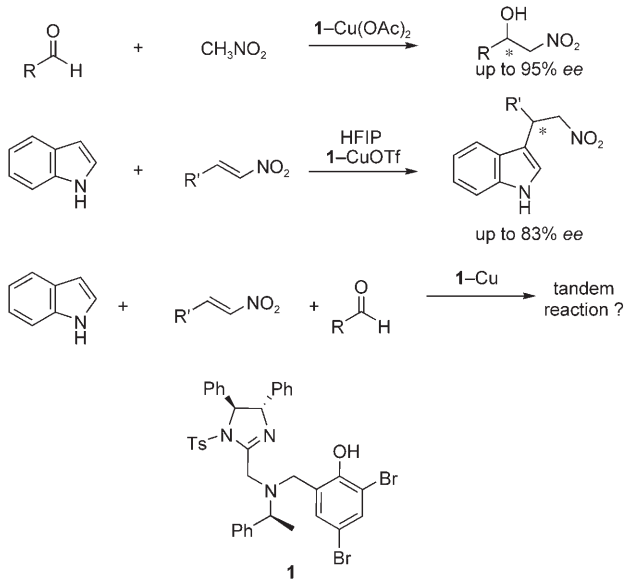
Highly functionalized, optically pure compounds are in strong demand in the pharmaceutical and agricultural industries. Catalytic asymmetric tandem reactions[1] are powerful tools for providing such complex molecules. They minimize the number of steps required in target-oriented synthesis, and the compounds obtained, which may have multiple stereogenic centers, serve as a fascinating scaffold for diversity-oriented synthesis.[2] The impressive work of Enders et al.[3a] on cascade organocatalytic reactions demonstrated the fundamental importance of the conformational stability of cyclic compounds in the construction of multiple contiguous stereocenters.[3] However, the control of multiple contiguous stereocenters in acyclic products is difficult even in modern chemistry.

Herein, we report the catalytic asymmetric tandem Friedel–Crafts/Henry (FCH) reaction of indoles, nitroalkenes, and aldehydes catalyzed by the imidazoline–aminophenol catalyst **1**–CuOTf. To the best of our knowledge, this is the first successful demonstration of the formation of chiral acyclic products with three contiguous stereocenters in a tandem FCH reaction.

In a recent study aimed towards the identification of a new asymmetric catalyst, we developed the chiral imidazoline–aminophenol ligand **1**.[4] The **1**–$Cu(OAc)_2$ complex catalyzed the enantioselective Henry reaction to give the adduct with up to 95% *ee*.[5,6] Furthermore, **1**–CuOTf was an effective catalyst in the Friedel–Crafts (FC) reaction of indole with nitroalkenes (Scheme 1).[7]

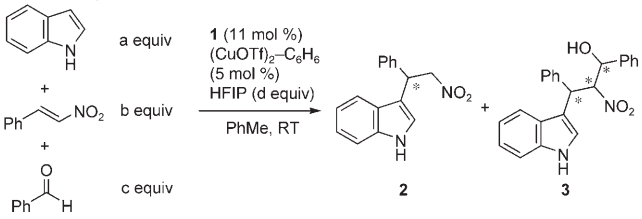
In contrast, the FC reaction of indole with aldehydes was relatively slow. On the basis of these experimental results, we envisioned that it would be possible to carry out a highly stereocontrolled tandem FCH reaction with the **1**–Cu catalyst.



Scheme 1. Asymmetric reactions with the imidazoline–aminophenol–Cu catalyst. Tf = trifluoromethanesulfonyl, Ts = *p*-toluenesulfonyl.

When benzaldehyde (1 equiv) was added to the conventional FC reaction mixture of indole and nitrostyrene (1:1), the desired three-component-coupling product **3** was obtained in 37% yield (Table 1, entry 1). Although **3** was formed with only moderate diastereoselectivity (2:4:1), the major adduct of **3** was obtained with 99% *ee*. (In the current

Table 1: Optimization of the reaction conditions for the FCH reaction.



Entry	a/b/c/d	Yield [%] 2[a]	3[b]	3 d.r.[c]	3 *ee* [%][d,e]
1	1/1/1/0	28 (82)	37	2:4:1	99
2	2/1/2/0	8 (85)	38	1:2:1	99
3	2/1/2/1	7 (70)	73	1:5:0	99
4	2/1/2/2	17 (70)	79	1:19:0	99
5	2/1/2/3	13 (70)	73	1:5:0	99

[a] The value in parentheses is the *ee* value of **2**. [b] Combined yield of the diastereomers. [c] Determined by ^{1}H NMR spectroscopic analysis. [d] The *ee* value of the major diastereomer is given. [e] The *ee* value was determined by HPLC by using a chiralcel OD-H column.

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[**] This research was supported by the Industrial Technology Research Grant Program in 2006 from the New Energy and Industrial Technology Development Organization (NEDO) of Japan and by a Grant-in Aid for Scientific Research on Priority Areas (No. 19028007, "Chemistry of Concerto Catalysis") from the Ministry of Education, Culture, Sports, Science and Technology (Japan). We thank Prof. Akira Yanagisawa at Chiba University for helpful discussions.

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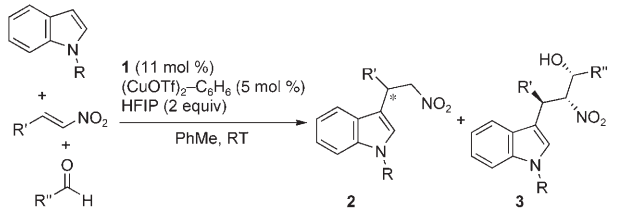
study, only three of the four possible diastereomers were detected.) The result was not improved when the amounts of indole and aldehyde were increased (Table 1, entry 2). Encouragingly, the addition of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP; 2 equiv) was effective in enhancing the catalytic reaction, with the adduct now formed in up to 79% yield. Importantly, the use of HFIP promotes the reaction in a highly diastereoselective manner to give the adducts **3** in the ratio 1:19:0, with the major isomer formed with 99% *ee*.

By using these optimized conditions, we were able to confirm the generality of the current FCH reaction (Table 2). Electron-deficient aldehydes, such as 4-bromobenzaldehyde,

Table 2: FCH reaction with various substrates.



Entry	R	R′	R″	*t* [h]	Yield [%] **2**[b]	**3**[c]	d.r.[d]	**3** *ee* [%][e]
1	H	C_6H_5	C_6H_5	16	17 (70)	79	1:19:0	99
2	H	C_6H_5	4-BrC_6H_4	3	2 (7)	29	1:9:0	87
3[a]	H	C_6H_5	4-BrC_6H_4	14	trace	84	1:16:0	90 (99)[f]
4[a]	H	C_6H_5	4-ClC_6H_4	17	2	82	1:10:0	90 (99)[f]
5[a]	H	C_6H_5	4-$NO_2C_6H_4$	15	10 (18)	90	1:10:0	89 (99)[f]
6	H	C_6H_5	*n*-C_5H_{11}	14	14 (77)	82	1:3:0	99
7	H	C_6H_5	*c*-C_6H_{11}	21	21 (70)	79	1:7:0	99
8	H	*n*-C_5H_{11}	C_6H_5	15	4	76	1:2:0	98 (97)[g]
9[a]	H	*n*-C_5H_{11}	4-BrC_6H_4	17	–	66	3:4:0	99 (99)[g]
10	H	PhC_2H_4	C_6H_5	15	12	83	2:3:0	90
11[a]	Me	C_6H_5	C_6H_5	13	–	72	2:3:0	99 (99)[g]

[a] The reaction was performed at 0 °C. [b] The value in parentheses is the *ee* value of **2**. [c] Combined yield of the diastereomers. [d] Determined by ^{1}H NMR spectroscopic analysis. [e] The *ee* value of the major diastereomer was determined by HPLC by using a chiralcel OD-H or chiralpak AS-H column. [f] The *ee* value of the major diastereomer after a single recrystallization from *i*PrOH is given in parentheses. [g] The *ee* value of the minor diastereomer is given in parentheses.

provided the adduct in poor yield at room temperature because of the generation of bisindole as an undesired side product (Table 2, entry 2). However, when the reaction was performed at 0 °C, the corresponding FCH product was obtained in 84% yield with 90% *ee* (Table 2, entry 3). Other electron-deficient aldehydes were converted into the desired products under similar conditions with high enantioselectivities (Table 2, entries 4 and 5). A single recrystallization from *i*PrOH afforded the products with 99% *ee* (Table 2, entries 3–5). The FCH reaction is also applicable to aliphatic aldehydes; the corresponding adducts were obtained with excellent enantioselectivities (Table 2, entries 6 and 7). When the reaction was examined with aliphatic nitroalkenes, the FCH products were obtained as a mixture of diastereomers. However, the two diastereomers obtained were formed with high enantioselectivities (Table 2, entries 8 and 9). *N*-Methylindole can also be used as a substrate with the current catalytic system; in this case, the FCH adduct was produced in 72% yield, and the two diastereomers obtained exhibited 99% *ee* (Table 2, entry 11).

The relative configuration of the major product obtained in entry 6 of Table 2 was determined by X-ray diffraction analysis to be 1*R**,2*R**,3*R**, and the absolute configuration at the benzylic position was determined to be 1*R* after conversion into the known FC product **2** by a retro-Henry reaction (Figure 1).

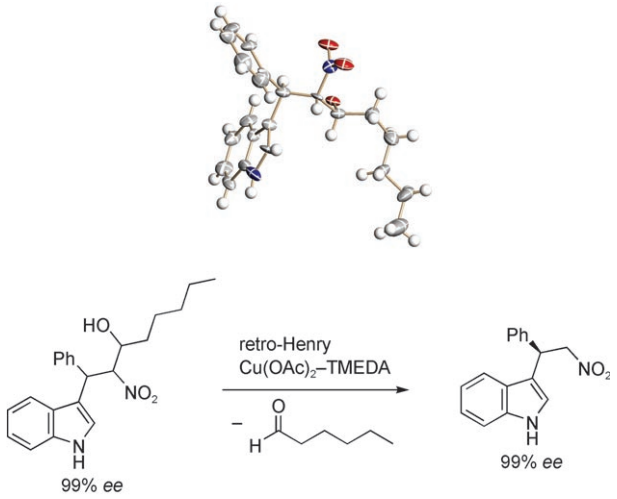
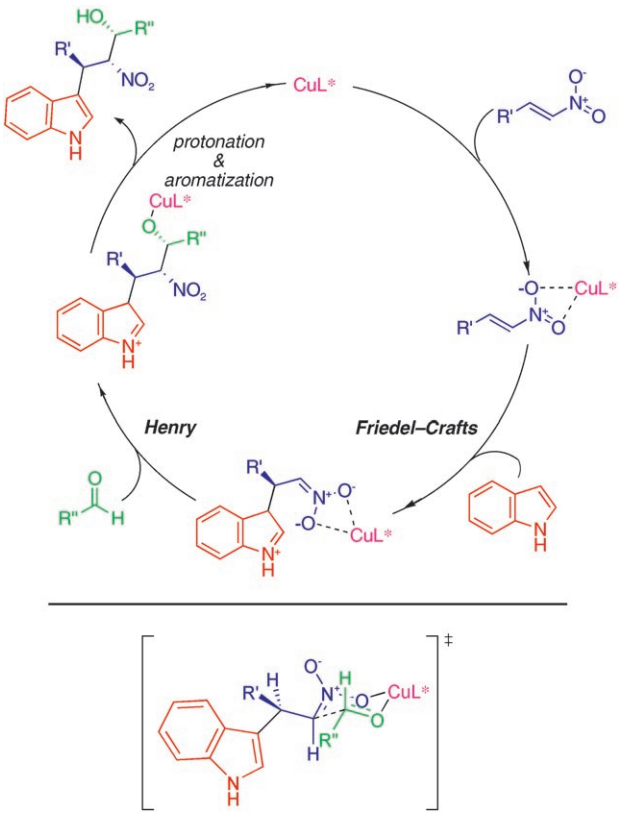


Figure 1. ORTEP structure and retro-Henry reaction of an FCH product (major product in Table 2, entry 6). TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.

Scheme 2 shows a plausible reaction mechanism. In the first step, the nitroalkene is activated by the Lewis acid catalyst **1**–Cu to start the enantioselective Friedel–Crafts reaction. The diastereoselective Henry reaction is then promoted by the Cu nitronate functionality of the intermediate that results from the FC addition.[8] The isolated FC product **2** did not react with the aldehyde under the reaction conditions. Moreover, the *ee* value of **3** was greatly improved to 99% from the 70% *ee* observed for the FC adduct **2** (Table 2, entry 1). Thus, the Henry reaction appears to proceed directly from the Cu nitronate intermediate and is accompanied by kinetic resolution of the nitronate.

The **1**–CuOTf-catalyzed FC reaction provided *R*-enriched **2**; therefore, the major *R* Cu–nitronate intermediate reacts with the aldehyde to give the Cu–alkoxide of the 1*R* FCH product. The formation of the 1*R*,2*R*,3*R* product indicates that the diastereoselective Henry reaction proceeds in a *syn*-selective manner. This *syn* selectivity can be explained well by considering an intermediate with a Cu-containing six-membered ring (see the structure below the catalytic cycle in Scheme 2). The relatively strong Lewis acidity of the CuOTf catalyst would favor the diastereoselective Henry reaction via this cyclic transition state. Finally, protonation of the Cu–alkoxide and aromatization furnishes the desired FCH product and regenerates the **1**–Cu catalyst. The additive HFIP enhances the release of the FCH product from the catalyst.



Scheme 2. Plausible reaction mechanism. CuL* represents the **1**–Cu catalyst.

In conclusion, we have developed a three-component tandem reaction of indole, nitroalkenes, and aldehydes to construct acyclic products with three contiguous stereocenters. We also tested other conventional Lewis acids (BEt_3, $Ti(OiPr)_4$) and a base ($KOtBu$) in the FCH reaction; however, the use of these catalysts resulted in the formation of only the FC product or bisindole, or both (see the Supporting Information). Our results clearly show the potential for the application of the **1**–Cu catalyst in the construction of multiple contiguous acyclic stereocenters. The well-organized **1**–Cu catalyst satisfies the requirement of the activation of the reaction intermediates at the appropriate times in the catalytic cycle. A variety of transformations of these highly functionalized FCH products can be envisaged readily, such as the synthesis of hydroxytryptamines by reduction of the nitro group, and Pictet–Spengler cyclization reactions to give polycyclic alkaloids. The novel FCH reaction developed herein has significant potential in chemistry and chemical biology.

Experimental Section

General procedure: A solution of **1** (14.9 mg, 19 μmol) in toluene (0.43 mL) was added to $(CuOTf)_2{\cdot}C_6H_6$ (4.4 mg, 8.7 μmol) under Ar, and the mixture was stirred for 2 h at room temperature. HFIP (35 μL, 0.34 mmol), the aldehyde (0.34 mmol), the nitroalkene (0.17 mmol), and indole (0.34 mmol) were added sequentially to the resulting clear green solution. The reaction mixture was stirred at the indicated temperature for the time indicated, then purified by column chromatography on silica gel to afford the adduct. The *ee* values of the products were determined by HPLC by using a Daicel chiralcel OD-H or chiralpak AS-H column.

Received: March 21, 2008
Published online: June 2, 2008

Keywords: asymmetric catalysis · domino reactions · Friedel–Crafts reaction · Henry reaction · multicomponent reactions

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