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Enantioselective Michael-Type Friedel–Crafts Reactions of Indoles to Enones Catalyzed by a Chiral Camphor-Based Brønsted Acid

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Chiral Brønsted acid, D-camphorsulfonic acid, was found to be practical and efficient in the catalysis of the enantioselective Michael-type Friedel–Crafts reactions of indoles with aromatic enones to afford the corresponding β-indolyl ketones in excellent yields and moderate enantioselectivities. A surprising synergistic effect was discovered between BmimBr and D-CSA which leads to active catalytic systems for the Friedel–Crafts reaction. The efficiency of these systems might result from the catalytic Lewis acid activation of the Brønsted acids.

The addition of aromatic substrates to electron-deficient alkenes, such as enones, is an important type of reaction in synthetic organic chemistry for the formation of new C–C bonds, which may be considered a Friedel–Crafts (FC) type alkylation or a Michael-type FC reaction in many respects.[1] Among the FC reactions, the Michael-type FC reaction of indoles is a widely investigated process because it is involved in the total synthesis of a class of bioactive indole alkaloids, for example the hapalindoles and other 3-substituted indoles, which are significant substructures and building blocks for the synthesis of natural products and therapeutic agents.[2]

Since the pioneering study published by Casnati and Casiraghi[3] on the enantioselective orthohydroxy alkylation of phenol with aldehydes catalyzed by stoichiometric amounts of chiral aluminum complexes, many efforts have been devoted to the exploitation of new catalytic stereocontrolled FC procedures.[4] Although numerous and significant advances have been achieved,[5] the asymmetric conjugate addition of aromatic compounds to simple α,β-unsaturated ketones (FC-type reactions) under efficient catalytic conditions is still a considerable challenge. In FC reactions, enones are particularly attractive and are widely used as Michael acceptors because their ketone moieties are strong electron-withdrawing groups that can be readily transformed into a range of different functionalities. Up to now, with the best of our knowledge, only Bandini and Umani-Ronchi have reported the enantioselective Al(Salen)Cl-catalyzed conjugate addition of indoles to simple alkyl α,β-unsaturated ketones with moderate-to-high enantioselectivities.[6]

Previously, we reported an efficient organic Brønsted acid (2,6-pyridinedicarboxylic acid) which catalyzed Michael-type FC reactions of indoles.[7] As a part of our ongoing research on organic Brønsted acid controlled reactions of appropriately functionalized heteroatom-containing compounds, we report here our new results of enantioselective Michael-type FC additions of indoles to aromatic enones catalyzed by easily available D-camphorsulfonic acid (D-CSA) and its derived BmimBr–CSA complex. Although D-CSA has been recognized as an excellent catalyst in various organic transformations, such as Diels–Alder reactions and the oxidation of sulfides,[8] there is no report about its stereoselectivity in previous studies.

Initially, we aimed to examine the asymmetric-induced effect of a chiral Brønsted acid in the promotion of this Michael-type FC reaction (Scheme 1). Interestingly, in CH_3CN the reaction was found to proceed spontaneously in the presence of a catalytic amount of D-CSA to give the corresponding product with excellent yield. D-CSA displayed a moderate but promising asymmetric induction (18% *ee*; Table 1, Entry 1) to the products. We also found that aprotic solvents, such as CH_2Cl_2 or toluene, had a negative influence on the enantioselectivity, as well as ethereal solvents such as THF on the catalytic activity to give product **3a**. As predicted, the reactions in water or CH_3OH gave a much poorer conversion or a lower enantioselectivity, respectively (Table 1, Entries 5,7). By lowering to 0 °C, we found that the temperature had a negative effect on the conversion, whereas a slight improvement in the enantioselectivity of the reaction was observed (Table 1, Entry 8). The absolute stereochemistry was assigned as the (*S*)-stereoisomer by comparison of the optical rotation with

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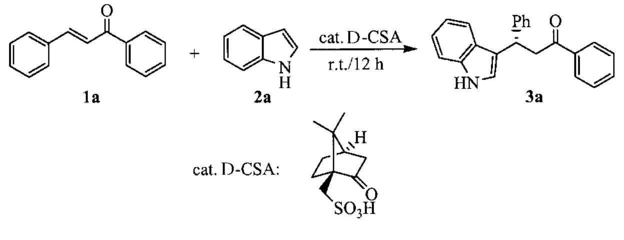
the reported values.[6] It is no doubt that the present commercial Brønsted acid is a powerful catalyst for the activation of carbonyl groups in this Michael-type FC reaction of indole with chalcone.



Scheme 1. Addition of indole **2a** to enone **1a** to give access to optically active 2-indole-1-ketone derivative **3a**.

Table 1. Solvent effect on the D-CSA-catalyzed Michael-type Friedel–Crafts reaction of indole with chalcone.

Entry[a]	Solvent	Yield [%][b]	*ee* [%][c]
1	CH_3CN	78	18
2	THF	60	19
3	toluene	33	11
4	CH_2Cl_2	88	10
5	H_2O	trace	–
6	H_2O/THF (1:10)	trace	–
7	CH_3OH	98	0
8[d]	CH_3CN	60	24

[a] Experimental conditions: To a solution of enone (0.5 mmol) and indole (0.55 mmol) in solvent (3 mL), catalyst (0.05 mmol) was added. All the reactions were carried out at room temp. for 12 h except Entry 8. [b] Isolated yields. [c] Determined by chiral stationary phase HPLC. [d] The reaction was carried out at 0 °C for 24 h.

In the last decades, room temperature ionic liquids have been described as one of the most promising new reaction mediums.[9] Ionic liquids are being used as green solvents because of their unique properties, for example wide liquid range, good dissolubility, tunable polarity, and high thermal stability, etc. Attractively, their properties can be regulated to satisfy specific chemical tasks. As a result of their green credentials and potential to enhance rates and selectivities, ionic liquids, which are used as dual solvent–catalysts, are finding increased application in organic synthesis.[10] Recently, the studies on ionic liquids used as catalysts in organic reactions have attracted more and more chemists. Moreover, Brønsted acidic ionic liquids are specially alluring because they behave as dual solvent–catalysts in some reactions and display excellent catalytic activities in the esterification of acids, carbonylation of toluene, Mannich reactions, etc.[11] In fact, these ionic liquids are special Brønsted acids that can be reused several times. With the consideration that various Brønsted acids have proven to be effective catalysts similar to CSA in the Michael-type FC reactions of indoles, we wish to investigate the combination of an ionic liquid with a chiral Brønsted acid and investigate its catalytic activity and its asymmetric induction effect in Michael-type FC reactions of indoles.

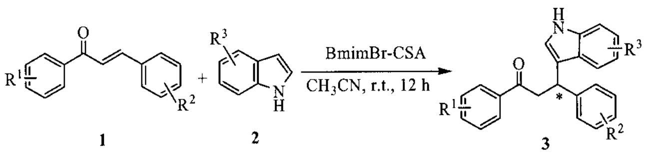
Further investigation allowed us to find that the ionic liquid (molten salt) 1-butyl-3-methyl-1*H*-imidazolium bromide (BmimBr) was an effective promoter in this reaction. In our successive work, a novel chiral Brønsted acidic BmimBr–CSA complex was prepared according to a literature procedure.[12] The obtained pale yellow liquid was not soluble in ether. Its catalytic activity in the Michael-type FC reactions of indole with chalcone was then investigated. We were pleased to find that the BmimBr–CSA complex was also an efficient catalyst and provided a better yield (96%) than that observed(78%) by using only D-CSA as a catalyst and a moderate level of stereoselectivity (19% *ee*) was obtained. However, if BmimBr was added to the mixture of indole, chalcone, and D-CSA catalyst in CH_3CN directly, there was no improvement in the conversion or the stereoselectivity of the reaction. Furthermore, the combination of D-CSA with inorganic salts such as KBr and NaBr, or an organic base such as phosphane did not lead to active catalytic systems.

From a mechanistic point of view, we believe that the observed synergistic effects might proceed: (1) by a purely Brønsted acid catalysis, (2) by a molecular interaction between CSA and BmimBr, which generates a stable molecular complex, (3) by a Lewis acid promoted Brønsted acid catalysis (LBA),[13] which results in the double-activation of the enone and indole.

Next, we expanded the range of substrates by using two different Brønsted acids, D-CSA and its derived BmimBr–CSA complex, as catalysts under the optimized reaction conditions. Table 2 summarizes the chemical and optical results for the 1,4-addition of indoles to enones. Except for Entries 3–4 and 7–8, substrates gave nearly the same levels of enantioselectivity. In Entries 7–8, although indole **2a** afforded corresponding product **3d** in good yields, the enantioselectivities contrasted greatly. D-CSA gave no enantioselectivity whereas the BmimBr–CSA complex gave a moderate *ee* of 29%. Similarly, in Entries 3–4, the *ee* improved remarkably from 37 to 58% when the BmimBr–CSA complex was used as the catalyst. At the same time, the yields of all entries suggested that the BmimBr–CSA complex had a slightly better catalytic activity than that of D-CSA. So, it is worthy to note that the BmimBr–CSA complex showed better catalytic activity in both the conversion and stereochemistry than D-CSA. We also tested the reactions of 2-cyclohexen-1-one and 2-cyclopenten-1-one catalyzed by BmimBr–CSA. The yields were 15 and 88%, respectively. Unfortunately, no *ee* was observed in the product of the reaction of 2-cyclopenten-1-one. Although the novel catalyst system (BmimBr–CSA) is not soluble in ether, the recovery and reuse of the catalyst is difficult. When the ionic liquid BmimBr–CSA was recovered and reused once the corresponding yield and *ee* was 55% and 25%, respectively (Table 2, Entry 15).

In summary, we have found that chiral Brønsted acids, commercial D-CSA and its derived BmimBr–CSA complex, are effective catalysts in the enantioselective Michael-type Friedel–Crafts reactions of indoles with enones. By mixing a Brønsted acid with BmimBr a new set of active catalysts (LBA)[13] for this reaction are generated. This simple process provides easy access to a large library of highly functionalized β-indolyl ketones containing a stereocenter in the

Table 2. Michael-type Friedel–Crafts reactions of indoles with enones catalyzed by D-CSA and its acidic BmimBr–CSA complex.



Entry[a]	Catalyst	Enones	Indoles	Yield [%][b]	*ee* [%][c]
1	D-CSA	R^1 = H; R^2 = H	R^3 = H	**3a**: 78	18
2	BmimBr–CSA	R^1 = H; R^2 = H	R^3 = H	**3a**: 96	19
3	D-CSA	R^1 = H; R^2 = *p*-Cl	R^3 = H	**3b**: 92	37
4	BmimBr–CSA	R^1 = H; R^2 = *p*-Cl	R^3 = H	**3b**: 90	58
5	D-CSA	R^1 = *p*-OCH_3; R^2= H	R^3 = H	**3c**: 75	21
6	BmimBr–CSA	R^1 = *p*-OCH_3; R^2 = H	R^3 = H	**3c**: 85	26
7	D-CSA	R^1 = H; R^2 = *o*-Cl	R^3 = H	**3d**: 96	0
8	BmimBr–CSA	R^1 = H; R^2 = *o*-Cl	R^3 = H	**3d**: 92	29
9	D-CSA	R^1 = H; R^2 = H	R^3 = 5-Br	**3e**: 96	22
10	BmimBr–CSA	R^1 = H; R^2 = H	R^3 = 5-Br	**3e**: 96	24
11	D-CSA	R^1 = H; R^2 = *p*-Cl	R^3 = 5-Br	**3f**: 77	25
12	BmimBr–CSA	R^1 = H; R^2 = *p*-Cl	R^3 = 5-Br	**3f**: 76	21
13	D-CSA	R^1 = H; R^2 = *p*-OCH_3	R^3 = H	**3g**: 75	8
14	BmimBr–CSA	R^1 = H; R^2 = *p*-OCH_3	R^3 = H	**3g**: 74	13
15[d]	BmimBr–CSA	R^1 = H; R^2 = *p*-Cl	R^3 = H	**3b**: 55	25

[a] Experimental conditions: To a solution of enone (0.5 mmol) and indole (0.55 mmol) in solvent (3 mL), catalyst (0.05 mmol of D-CSA or 0.12 mmol of BmimBr–CSA complex) was added. All reactions were carried out at room temp. for 12 h. [b] Isolated yields. [c] Determined by chiral stationary phase HPLC. [d] The catalyst was recovered and used for a second time.

β-position in excellent yields and moderate enantiomeric excesses. Further investigation into the novel chiral sulfonic acid catalyst is now in progress.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and spectral data for all new compounds.

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