Regio and Enantioselective Organocatalytic Friedel–Crafts Alkylation of 4-Aminoindoles at the C7-Position

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Supporting Information

ABSTRACT: A chiral phosphoric acid catalyzed highly regio- and enantioselective Friedel–Crafts alkylation at the indole C7-position was developed via the introduction of an alkylamine moiety at the C4-position of the indole ring. The methodology is applicable to a wide range of 4-aminoindoles and β,γ-unsaturated α-ketimino esters to furnish the corresponding C7-position functionalized chiral indole derivatives in high yields with moderate to excellent enantioselectivities. Furthermore, the α-ketimino ester moiety in the products is a versatile building block and enables many further transformations.

Being regarded as one of the most intriguing heterocycles, the indole framework is present in a number of naturally occurring products and pharmaceutical compounds. Consequently, many methods have been developed for the regioselective direct functionalization of the indole ring, among which the catalytic enantioselective Friedel–Crafts reaction has proven to be one of the most efficient and practical approaches for the synthesis of chiral indole derivatives. In this regard, most efforts have focused on the functionalization of the more nucleophilic pyrrole moiety of the indole core nucleus; studies on the asymmetric substitution at the less reactive benzene positions are scarce, especially the direct functionalization of the C7-position because of the poor reactivity of this carbon center. Nevertheless, a handful of examples have been reported using transition-metal-catalyzed C–H functionalization strategies, which undoubtedly give the corresponding products in nonenantioselective manners.

Indoles bearing chiral side chains on the C7-position occurred in many biologically active natural products (Figure 1), such as streptide, (+)-asperazine, (−)-lyngbyatoxin A, cytoblastin, and teleocidin B. The common strategies for the synthesis of this structure motif include de novo ring syntheses and substrate-controlled coupling reactions of C7 halogenated indoles. Some indirect catalytic enantioselective protocols have also been developed by using C7-preactivated indole derivatives as intermediates. For example, the copper(II)–bioxazoline complex catalyzed oligomerization of C7 iodonium salt of indoles and the chiral phosphoric acid promoted cascade reaction of 7-vinylindoles. Taking advantage of the ortho-position activating/directing ability of the hydroxyl group, hydroxyindoles react similarly to naphthols in organocatalysis. Using this strategy, Pedro developed a general protocol for the asymmetric functionalization of the indole benzene ring including the C7-substitution of 6-hydroxyindole. Our research group also reported the enantioselective Friedel–Crafts alkylation/lactonization of hydroxyindoles with 3-methyleneoxindoles for the synthesis of pyrroldihydrocoumarins. However, even with these advancements, only limited types of electrophiles are applicable in this strategy. The more nucleophilic C3-position is still the dominant reaction site in most cases. Therefore, the development of new strategies for the highly regio and enantioselective Friedel–Crafts alkylation at the C7-position of the indole ring remains one of the most challenging topics in indole chemistry.

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Figure 1. Biologically active natural products containing C7-functionalized indole skeletons.
Very recently, we reported an example of chiral phosphoric acid promoted asymmetric Friedel–Crafts alkylation of \( \beta,\gamma \)-unsaturated \( \alpha \)-ketimino esters with indoles at the C3-position, and the enantioselectivities of the corresponding products were significantly improved through the introduction of a hydrogen-bonding donor at the C4-position of the indole ring. As a continuation of our research interest in asymmetric Friedel–Crafts alkylation of indoles, we envisaged that the alkylation might switch to the C7-position in the presence of a para-directing group at the C4-position of the indole ring. The amine moiety is a well-known para-directing group in asymmetric catalysis, and the C7 halogenation and formylation of 4-aminindole derivatives became common practices for the syntheses of C7-substituted indolactam alkaloids; however, no catalytic asymmetric protocol has been reported to date. Herein, we present our recent research progress in this field.

To verify our hypothesis, the reaction of phenyl \( \beta,\gamma \)-unsaturated \( \alpha \)-ketimino ester 2a with N-benzyl-1H-indol-4-amine (3a) was chosen as a model reaction. The catalytic efficiency of various BINOL-derived chiral phosphoric acids was examined in dichloromethane at room temperature. As shown in Table 1, the expected C7-functionalized compound 4aa was formed as the only product in high yields, and catalyst 1g gave the best stereocontrol (Table 1, entry 7), while toluene was formed as the only product in high yields, and catalyst 1g gave the best stereocontrol (Table 1, entry 7), while toluene proved to be the optimal reaction solvent in terms of enantioselectivity of 4aa (Table 1, entry 11). The ee value was slightly increased to 92% with the use of more sterically hindered 3b as nucleophile, and the best result was obtained when this reaction was performed at 10 °C with the addition of 4 Å molecular sieves as additive to afford the corresponding product 4ab in 96% yield with 96% ee (Table 1, entry 14).

With the optimal reaction conditions determined, we subsequently studied the scope of this regio- and enantioselective C7 Friedel–Crafts alkylation with respect to various substituted \( \beta,\gamma \)-unsaturated \( \alpha \)-ketimino ester 2 with 3b (Scheme 1). In general, aromatic substrates produced the corresponding adducts in high yields (88–97%) with excellent enantioselectivities (94–99% ee), regardless of the electronic nature and substitution patterns of the functional groups on the aromatic ring of 2. On the other hand, aliphatic substrates were also tolerated in this transformation to give the corresponding products in high yields but with modest stereoselectivities (39–81% ee). For example, the use of cyclopropyl \( \beta,\gamma \)-unsaturated \( \alpha \)-ketimino ester 2s gave 4sb in 82% yield and 81% ee, while only 52% ee of 4rb was obtained when cyclohexyl substrate 2r was examined. Interestingly, when phenyl \( \beta,\gamma \)-unsaturated \( \alpha \)-keto ester 2w was tested, a cyclization product 4wa was formed in 38% yield with 39% ee and 3:2:1 dr. The absolute configuration of 4eb, which was produced using (R)-1g as catalyst, was determined to be S by X-ray crystallographic analysis.

Scheme 1. Substrate Scope with Respect to \( \beta,\gamma \)-Unsaturated \( \alpha \)-Ketimino Ester 2a

![Scheme 1](image)

Table 1. Optimization of the Reaction Conditions

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4Reactions were performed on a 0.1 mmol scale in 0.5 mL of solvent at 25 °C unless otherwise noted. 5Isolated yields are given. 6Enantionic excess was determined by HPLC on a chiral stationary phase. 7With 4 Å molecular sieves (60 mg) as additive. 8Performed at 10 °C.
Accordingly, most products obtained using (S)-1g as catalyst have R configurations.

The substrate scope with respect to different substituted 4-aminoindoles was also investigated. The results are presented in Scheme 2. First, the effect of substituents on the amine moiety was studied, and the results indicated that substituted alkyl groups significantly influenced the enantiomeric outcome of this reaction. A slightly decreased ee value of 92% of the product 4aa was observed with the use of N-benzyl substrate 3a, while N-isobutyl substrate 3c furnished 4ac in 81% ee. The presence of a chiral alkyl substituent on amine moiety had almost no impact on the stereocontrol of this reaction. This was exemplified by the reaction of 3e with 2a, which produced the corresponding products 4ae or 4aer both in 90% yield with 84% ee and 10:1 dr when promoted by (S)-1g or (R)-1g, respectively. Surprisingly, simple 4-aminoindole (3d) reacted smoothly with 2a, and the corresponding C7-functionalized product 4ad was formed in 90% yield with 58% ee. Next, we evaluated 4-aminoindoles with alkyl-substituted pyrrole rings. Interestingly, N-benzyl-2-methyl-4-aminoindole furnished the product with relatively lower enantioselectivity compared with that of 2-methyl-4-aminoindole (65% ee for 4af vs 87% ee for 4ag). Other substrates with a bare amine moiety such as 3-isopropyl and 2,3-dimethyl-4-aminoindoles were also examined, and the corresponding products were obtained with high enantioselectivities (94% ee for 4ah and 81% ee for 4ai).

Finally, the utility of this asymmetric C7-position Friedel–Crafts alkylation was investigated. Compound 4ab was prepared on a gram scale with the high yield and enantioselectivity maintained. Taking advantage of the synthetic diversity of the α-ketimino ester moiety, the corresponding products could be further transformed into some interesting chiral indole derivatives. For example, reduction of 4ab by Hantzsch ester in toluene with (RS)-1a as catalyst gave an unnatural α-amino acid derivative S in 92% yield with 98% ee and 5:1 dr. Promoted by LiOH, 4ab underwent hydrolysis in THF/H2O to form an indole N1- and C7-fused tricycle 6. Treatment of 6 with SOCl2 in methanol gave its corresponding ester 7 (an analogue of 4wa) in 36% overall yield with 98% ee and 4.3:1 dr (Scheme 3).

In conclusion, we have developed a method for the regio- and enantioselective C7-position Friedel–Crafts alkylation of indoles. A variety of substituted βγ-unsaturated α-ketimino esters and 4-aminoindoles were tolerated to afford the corresponding C7 functionalized products in high yields (up to 97%) with moderate to excellent enantioselectivities (39–99% ee). Scale-up reaction and representative transformations of one product were also carried out to investigate the usefulness of this protocol in organic synthesis. More importantly, this strategy can be potentially used for the synthesis of pharmaceutically important C7 functionalized (−)-indolactam V analogues for biological evaluations.19e,21 We are currently examining the applications of other electrophiles in the catalytic asymmetric C7 functionalization of indole derivatives.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.7b03703.

Typical experimental procedure and characterization for all products (PDF)

Accession Codes
CCDC 1584381 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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**REFERENCES**
