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Enantioselective Friedel–Crafts Reaction of Indoles with Carbonyl Compounds Catalyzed by Bifunctional Cinchona Alkaloids

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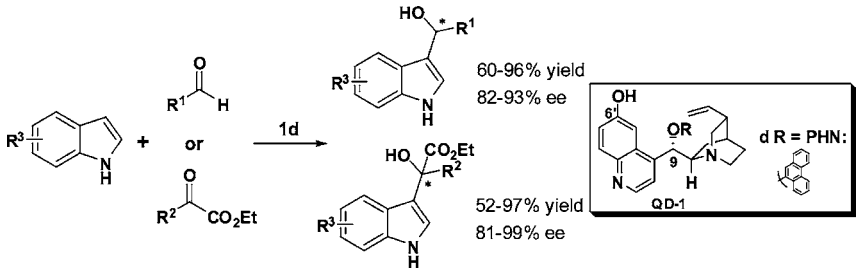
ABSTRACT



In this communication, we report an efficient asymmetric Friedel–Crafts reaction that, unprecedently, is applicable to a wide range of both indoles and carbonyls. The use of a readily accessible catalyst in combination with a high enantioselectivity that is insensitive to reaction concentration, temperature, air, and moisture should allow this reaction to provide useful enantioselective access to new chiral indole derivatives.

The preparation and functionalization of indoles continues to be a fascinating subject in organic synthesis due to the frequent appearance of indoles in biologically interesting natural and unnatural compounds.[1] The development of catalytic enantioselective methods for the facile synthesis of optically active indole derivatives has recently attracted significant attention.[2−7] The electron-rich nature of the indole ring renders enantioselective Friedel−Crafts reactions of indoles with readily available prochiral electrophilic starting materials a strategically important approach to access enantiomerically enriched indole derivatives.[4−7]

Several highly enantioselective conjugate additions of indoles to various Michael acceptors have been developed using either chiral metallic[4] or organic[5] catalysts. These studies established a considerable substrate scope with respect

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to both the indoles and the Michael acceptors. In contrast, a catalytic enantioselective 1,2-nucleophilic addition that is broadly applicable to both indoles and carbonyl compounds is lacking, although such a reaction represents another direct and versatile means to synthesize enantiomerically enriched chiral indole derivatives. Although high enantioselectivity has been achieved with chiral metal and organic catalysts, respectively, these catalysts are only effective toward ethyl 3,3,3-trifluoropyruvate.[6] To fully realize the potential of this important strategy for generating chiral indole derivatives, more generally effective chiral catalysts must be developed.[7] We wish to report here a highly enantioselective Friedel−Crafts reaction that is applicable to a wide range of both indoles and carbonyl compounds with bifunctional cinchona alkaloids.

In their recent report of the cinchonine- or cinchonidine-catalyzed addition of indoles to ethyl 3,3,3-trifluoropyruvate, Török, Prakash, and co-workers demonstrated that blocking either the quinuclidine or the 9-OH led to dramatically reduced enantioselectivity by the natural cinchona alkaloids.[6b] Thus, cinchonine was postulated to function as a base−acid bifunctional catalyst to simultaneously activate both the indoles and ethyl 3,3,3-trifluoropyruvate via the quinuclidine and the 9-OH moiety, respectively, to achieve synthetically useful enantioselectivity. Recent studies by us and others establish that cooperative hydrogen-bonding catalysis with 6′-OH and 9-thiourea cinchona alkaloids (**1**, Figure 1) as

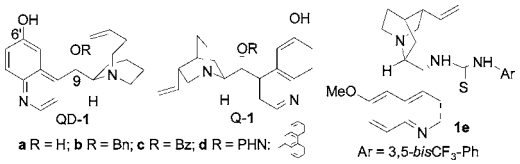
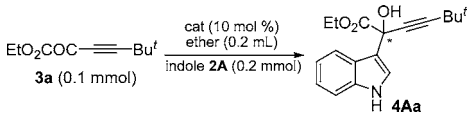


Figure 1. 6′-OH cinchona alkaloid derivatives.

base−acid bifunctional catalysts provides a useful platform for the development of a wide range of highly enantioselective C−C bond forming reactions.[7c,8,9] The high efficiency of bifunctional cinchona alkaloid catalysts **1** in the promotion of mechanistically unrelated C−C bond formations led us to envision that they might function as efficient catalysts for enantioselective Friedel−Crafts reactions of indoles with carbonyl compounds with broad scope.

To verify this assumption, we investigated the cinchona alkaloid-catalyzed reaction of indole (**2A**) with an alkynyl α-ketoester **3a**. As summarized in Table 1, 6′-OH cinchona

Table 1. Asymmetric Friedel−Crafts Reaction of Indole **2A** to α-Ketoester **3a**



entry	catalyst	temp/°C	time/h	conversion/%[a]	ee/%[b]
1	quinidine	23	20	68	−72
2	cinchonine	23	20	<10	7
3	QD-**1a**	23	20	82	83
4	QD-**1b**	23	20	54	88
5	QD-**1c**	23	20	<10	85
6	QD-**1d**	23	20	74	89
7	Q-**1d**	23	20	78	−87
8	**1e**	23	20	<5	11

[a] Determined by ^{1}H NMR analysis. [b] Enantiomeric excess was determined by HPLC.

alkaloids **1** were found to afford better activity and enantioselectivity than that by quinidine or cinchonine, and the highest enantioselectivity was obtained with QD-**1d**. Importantly, a complete reaction could be accomplished with QD-**1d** to produce the corresponding Friedel−Crafts adduct in 96% yield and 88% ee (entry 1, Table 2). In stark contrast, the same reaction in the presence of 9-thiourea cinchona alkaloid **1e**, a highly efficient catalyst for the enantioselective Friedel−Crafts addition of indoles to imines,[7c] proceeded in less than 5% conversion and afforded the Friedel−Crafts adduct in only 11% ee (entry 8, Table 1).

Further studies revealed that catalyst **1d** tolerates structural alterations of either the indoles or the alkynyl α-ketoesters (entries 1−3, Table 2). Moreover, the scope of the reaction could be readily extended to aryl α-ketoesters (entries 4−17, Table 2). With aryl α-ketoesters bearing a strong electron-

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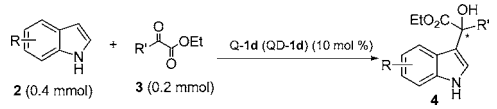
Table 2. Highly Enantioselective Friedel−Crafts Addition of Indoles **2** to α-Ketoesters **3** with Q-**1d** and QD-**1d** (in Parentheses)[a]



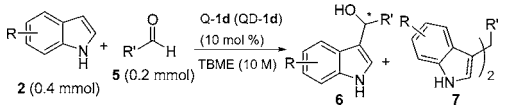
entry	R		R′		temp/ °C	time/h	yield/%[b]	ee/%[c]
1	H	**2A**	Bu^t	**3a**	23	63(62)	89(96)	87(88)
2	6-MeO	**2B**	Bu^t	**3a**	23	40(40)	86(79)	84(88)
3	H	**2A**	Ph	**3b**	23	44(43)	79(80)	88(90)
4	H	**2A**	4-CN−Ph−	**3c**	23	56(55)	88(77)	97(97)
5	4-MeO	**2C**	4-CN−Ph−	**3c**	23	64(64)	79(79)	99(99)
6	5-Cl	**2D**	4-CN−Ph−	**3c**	23	71(70)	85(96)	96(94[h])
7	6-MeO	**2B**	4-CN−Ph−	**3c**	23	58(59)	97(97)	97(96)
8	6-Br	**2E**	4-CN−Ph−	**3c**	23	61(61)	67(80)	95(95)
9	7-Me	**2F**	4-CN−Ph−	**3c**	23	66(66)	96(85)	97(97)
10	H	**2A**	4-NO_2−Ph−	**3d**	23	72(71)	88(95)	98(95)
11	H	**2A**	4-Cl−Ph−	**3e**	23	(24)	(13[g])	(95)
12[d]	H	**2A**	4-Cl−Ph−	**3e**	23	72(88)	95(93)	95(95)
13[e]	H	**2A**	4-Cl−Ph−	**3e**	70	24(24)	97(96)	89(86)
14[d]	H	**2A**	Ph−	**3f**	23	88(88)	63(71)	94(93)
15[e]	H	**2A**	Ph−	**3f**	70	36(36)	92(91)	86(86)
16[f]	6-MeO	**2B**	Ph−	**3f**	70	28(29)	92(72)	84(82)
17[e]	6-Cl	**2G**	Ph−	**3f**	70	51(51)	96(87)	84(81)
18[e]	H	**2A**	4-MeO−Ph−	**3g**	70	56	52	83

[a] Unless noted, reactions were carried out with 0.2 mmol of **3** and 0.4 mmol of **2** in 0.4 mL of Et_2O with 10 mol % of Q-**1d**. The results in parentheses were obtained with QD-**1d** to give the opposite enantiomer; see Supporting Information for details. [b] Isolated yield. [c] Determined by HPLC analysis. [d] The reactions were carried out in ether (10 M). [e] The reactions were carried out in TBME (10 M). [f] The reactions were carried out in TBME (4 M). [g] Conversion was determined by ^{1}H NMR analysis. [h] The absolute configuration was determined to be *S* by X-ray analysis (see Supporting Information for details).

withdrawing substituent, the enantioselectivity could be sustained at a very high level for additions of a wide variety of indoles substituted with electron-donating or -withdrawing groups at the 4−7 positions (entries 4−10, Table 2). As expected, aryl α-ketoesters bearing a less electron-withdrawing group such as ketoester **3e** are much less reactive. The reaction proceeded in only 13% conversion after 24 h, albeit still in high enantioselectivity (entry 11, Table 2). We found, however, that the enantioselectivity of **1d** is insensitive to reaction concentration. Consequently, by carrying out the **1d**-catalyzed reaction at 10.0 M concentration, **3e** could be converted into the desired product in high yield and excellent enantioselectivity (entry 12, Table 2). Interestingly, the enantioselectivity of the reaction remained high even at elevated temperature (entry 13 vs 12, Table 2). Thus, synthetically useful enantioselectivities and yields could be obtained even for aryl α-ketoesters bearing an electron-donating group (**3g**) when the reaction was performed at 10.0 M and 70 °C (entry 18, Table 2).

Catalyst **1d** was also found to be effective for Friedel−Crafts reactions of indoles with aldehydes (Table 3).

Table 3. Asymmetric Friedel−Crafts Addition of Indoles **2** to Aldehydes **5** with Q-**1d** and QD-**1d** (in Parentheses)



entry	R		R′		temp/ °C	time/ h	6/7[a]	yield/ %[b]	ee/%[c]
1	H	**2A**	EtO_2C−	**5a**[d]	rt	6	>95:5	95(85)	93(93)
2	6-Br	**2E**	EtO_2C−	**5a**[d]	rt	4	>95:5	96(95)	90(90)
3	6-OMe	**2B**	EtO_2C−	**5a**[d]	rt	4	>95:5	94(93)	90(82)
4	H	**2A**	2-NO_2−Ph−	**5b**	rt	72	>95:5	96(95)	90(89)
5	H	**2A**	4-NO_2−Ph−	**5c**	rt	72	>95:5	90(90)	88(83)
6	H	**2A**	4-CF_3−Ph−	**5d**	rt	72	>95:5	85(83)	88(88)
7	H	**2A**	4-Cl−Ph-	**5e**	70	40	7:1	75	83
8	H	**2A**	Ph-	**5f**	70	48	2:1	60	82

[a] The ratio was determined by ^{1}H NMR analysis of the crude product. [b] Isolated yield. [c] Determined by HPLC analysis. [d] ∼50 wt % in toluene.

Although reactions with glyoxalate **5a** proceeded most rapidly and afforded the best enantioselectivity (entries 1−3, Table 3), it is particularly noteworthy that the addition of indole to various simple aromatic aldehydes proceeded in good enantioselectivity and useful yield (entries 4−8, Table 3). To our knowledge, these results provide the first documentation of a highly enantioselective catalytic Friedel−Crafts reaction with a simple aldehyde.[10]

In conclusion, we established that 6′-OH cinchona alkaloids are able to promote highly enantioselective Friedel−Crafts reactions of indoles with carbonyl compounds. This reaction is applicable not only to a wide variety of indoles but also to a substantial range of α-ketoesters and aldehydes. This new asymmetric reaction thus expands considerably the range of optically active indole derivatives that can be directly generated from readily available prochiral precursors. The use of a readily accessible catalyst in combination with a high enantioselectivity that is insensitive to reaction concentration, temperature, air, and moisture should further enhance the utility of this reaction in asymmetric synthesis of chiral indole derivatives.

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Supporting Information Available: Experimental details and spectroscopic data for synthetic intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

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