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Asymmetric Friedel-Crafts Reaction of Indoles with Imines by an Organic Catalyst

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Abstract

In this communication, we report an asymmetric Friedel-Crafts reaction of indoles with imines catalyzed by a bifunctional cinchona alkaloid catalyst. This is the first efficient organocatalytic asymmetric Friedel-Crafts reaction of indoles with imines. This reaction is operationally simple and, unprecedentedly, affords high enantioselectivity for a wide range of indoles and both aryl and alkyl imines. This establishes a direct, convergent and versatile approach to optically active 3-indolyl-methanamines, a structural motif embedded in numerous indole alkaloids and synthetic indole derivatives.

The 3-indolyl-methanamine structural motif **3** is embedded in numerous indole alkaloids and synthetic indole derivatives.¹ An efficient catalytic asymmetric Friedel-Crafts reaction of indoles **1** with imines **2** will provide a direct, convergent and versatile method for the enantioselective construction of **3** from readily accessible achiral precursors (Scheme 1).^{2–7} If realized with a readily accessible chiral catalyst and in broad scope for both the indole **1** and the imine **2**, especially including alkyl imines, this reaction could enable the development of new strategies for asymmetric synthesis of chiral indole compounds.

Despite considerable efforts, to date,^{7–8} only two highly enantioselective catalytic Friedel-Crafts reactions of indoles and imines have been reported, and both utilize chiral Cu-complexes as catalysts.⁷ While these chiral Cu-complexes effectively promote enantioselective Friedel-Crafts reactions of indoles with aryl imines^{7a} and α -imino esters^{7b}, respectively, they have not yet been shown to be effective for any unactivated alkyl imines. Moreover, their efficiency also depends on the electronic properties of the indoles.^{7a} For example, although the addition of 5-methoxyindole to *N*-(4-nitrobenzylidene)-benzenesulfonamide with a chiral Cu-bisoxazoline complex took place in 92% ee, the addition of 5-bromoindole proceeded in only 77% ee.^{7a} Herein, we wish to report the first highly enantioselective Friedel-Crafts reaction of indoles with imines with a chiral organic catalyst. Unprecedentedly, the high enantioselectivity of this organocatalytic reaction is sustainable not only for indoles of various electronic properties but also for both aryl and alkyl imines.

The association of 3-indolyl-methanamines **3** with an acid is well known to trigger its reaction with indoles to form bisindole compounds **4**.^{2a,7,8} Furthermore, alkyl imines readily tautomerize to the corresponding enamine. Thus, the development of an efficient catalytic enantioselective Friedel-Crafts reaction of indoles **1** and imines **2** requires a chiral catalyst that is effective in activating the weakly electrophilic imines **2** yet is still compatible with the acid-sensitive 3-indolyl-methanamines **3** and imines **2**.

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Supporting Information Available: Experimental procedures and characterization of the products; X-ray analysis data for (–)-(S)-**3Af**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

We and others have reported readily accessible and tunable 6'-OH^{9,10} and 9-thiourea¹¹ cinchona alkaloids as bifunctional catalysts for asymmetric C-C bond forming reactions. Mechanistic studies of cinchona alkaloids^{9b,12} and chiral thioureas¹³⁻¹⁴ indicate that these newly emerging bifunctional chiral organic catalysts promote asymmetric reactions through a network of hydrogen bonding interactions with the reacting nucleophiles and electrophiles. We envisaged that such traits, achieving efficient catalysis via multiple and mild activating interactions simultaneously with the two reacting substrates, might render these bifunctional chiral organic catalysts particularly suitable to address several challenging problems in the development of enantioselective Friedel-Crafts reaction of indoles with imines as described above.¹⁵

We therefore investigated 6'-OH and 9-thiourea cinchona alkaloids (**4-6**) for their ability to promote the Friedel-Crafts reaction of indole **1A** to *N*-Bs phenyl imines **2a** (Table 1). At room temperature in THF, the reactions with **4-6** proceeded in less than 20% conversion after 48 hours (entries 1-6). However, the reaction was found to proceed in very high enantioselectivity with the 9-thiourea cinchona alkaloids (entries 5-6). Remarkably, the enantioselectivity remained very high even at 50 °C, at which the reaction was much faster (entries 11-12, Table 1). After further optimizations, we established that the reaction with 10 mol% of quinidine-derived 9-thiourea cinchona alkaloid **6** in ethyl acetate at 50 °C proceeded to completion after 24 hours to afford **3Aa** in 92% ee (entry 13). The corresponding quinine-derived catalyst **7** afforded the same enantioselectivity for the other enantiomer of **3Aa** (entry 14). Notably, under the same condition, *N*-Me indole was found to be inactive. This experimental result is consistent with the notion that 9-thiourea cinchona alkaloids activate the indole (**1A**) and the imine through hydrogen bonding interactions.

We then examined the scope of the reaction. The enantioselectivity of the Friedel-Crafts alkylation of various indoles with imine **2a** was found to be insensitive to the electronic property of the indole ring (entries 1, 3-7, Table 2), in contrast to that by the chiral Cu-complex. The enantioselectivity did not change when the protecting group in **2** was changed from *N*-Bs to *N*-Ts.¹⁶ We were pleased to find that this reaction is very general with respect to the imines **2**. Aryl imines of various electronic properties (**2a-h**) could be readily converted into the desired adducts in 89-97% ee and 83-99% yield. The ability of catalysts **6** and **7** to afford high enantioselectivity at elevated temperature allows the reaction of even relatively electron-deficient indole **1C** with an electron-rich aryl imine **2d** to proceed in useful enantioselectivity (entry 14, Table 2). Most significantly, excellent enantioselectivity could be achieved with various *N*-Ts alkyl imines including those bearing no α -substituent (**2i-m**, Table 3). Finally, the removal of the *N*-Ts in **3** could be readily accomplished in excellent yield without compromising the integrity of the stereocenter (Scheme 2).¹⁷

In summary, we have developed the first highly enantioselective Friedel-Crafts reaction of indoles with imines using a chiral organic catalyst. With unprecedented scope for both indoles and imines and utilizing practical chiral catalysts, this reaction provides a direct and broadly useful catalytic enantioselective approach toward 3-indolyl-methanamines **3**, which should facilitate the asymmetric synthesis of biologically interesting indole compounds. Its unique applicability to alkyl imines in particular should open new possibilities in the total synthesis of indole alkaloids and their analogues.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
A General Approach toward 3-Indolyl Methanamines **3** via Enantioselective Friedel-Crafts Reaction

Scheme 2.
Conversion of *N*-Ts to *N*-CBz 3-indoly-methanamine **8**

Table 1

Enantioselective Friedel-Crafts Reaction with Cinchona Alkaloids^a

Entry	Cat.	T /°C	Conv/% ^b	ee/% ^c	Entry	Cat.	T /°C	Conv/%	ee/%
1	quinidine	23	<5	-	8	QD-4a	50	9	8
2	QD-4a	23	<5	-	9	QD-4b	50	41	4
3	QD-4b	23	<5	-	10	QD-4c	50	6	0
4	QD-4c	23	<5	-	11	5	50	35	94
5	5	23	12	96	12	6	50	86	89
6	6	23	20	96	13 ^d	6	50	100	92
7	quinidine	50	74	0	14 ^e	7	50	100	92

^aUnless noted, reactions were carried with **2a**(0.10 mmol) and **1A**(0.20 mmol) in 0.10 mL solvent for 48 h.

^bDetermined by NMR analysis.

^cDetermined by HPLC analysis.

^dThe reaction was carried out in EtOAc(0.050 mL) for 24 h.

^eReaction was carried with 0.30 mmol of **2a**(0.30 mmol) and **1A**(0.60 mmol) in EtOAc (0.15 mL) for 36 h.

Table 2

Cinchona Alkaloid-Catalyzed Friedel-Crafts Reactions of Indoles with Aryl Imines^a

Entry	1	2	Time/h	Yield/% ^b	ee/% ^c
1	1A: R=H	2a: R=H, P=Bs	36(36)	87(96)	94(92)
2	1A: R=H	2b: R=H, P=Ts	60(60)	96(96)	94(94)
3	1B: R=6-Cl	2a	72(72)	86(88)	90(95)
4	1C: R=6-Br	2a	60(72)	86(88)	95(95)
5	1D: R=6-OMe	2a	36(36)	89(90)	92(91)
6	1E: R=5-Me	2a	48(36)	98(94)	89(90)
7	1F: R=4-OMe	2a	72(72)	88(94)	91(89)
8	1A	2c: R=4-Cl, P=Ts	28(28)	98(98)	94(93)
9	1A	2d: R=3-OMe, P=Ts	72(72)	94(95)	92(90)
10	1A	2e: R=2-Br, P=Ts	18(18)	98(98)	93(93)
11	1A	2f: R=4-CF ₃ , P=Ts	8(8)	97(97)	96 ^d (97)
12	1A	2g: R=4-Me, P=Bs	46(46)	93(96)	92(94)
13	1A		12(12)	88(89)	96(94)
14	1D	2f	36(36)	92(99)	95(94)
15 ^e	1C	2d	72(72)	86(83)	86(83)

^a Unless noted, reactions were carried with 0.3 mmol of **2**, 0.6 mmol of **1** in 0.15 mL EtOAc with 10 mol% **7**, the results in parentheses were obtained with **6** to give opposite enantiomer, see Supporting Information.

^b Isolated yield.

^c Determined by HPLC analysis.

^d The absolute configuration was determined to be S, see Supporting Information

^e Reaction at 70 °C.

Table 3

Enantioselective Friedel-Crafts Reactions of Indoles with Alkyl Imines^a

entry	2	T/°C	Time/hr	Yield /% ^b	ee /% ^c
1	2i	50	48(48)	86(88)	94(92)
2	2j	50	48(48)	85(84)	94(94) ^d
3	2k	50	12(12)	85(85)	95(96)
4	2l	50	12(12)	53(55)	96(97)
5 ^e	2m	-25	10(10)	65(65)	96(96)

^a Unless noted, reactions were carried with **2** (0.3 mmol) and **1A** (0.6 mmol) in EtOAc (0.15 mL), the results in parentheses were obtained with **6** to give opposite enantiomer, see Supporting Information;

^b Isolated yield;

^c Determined by HPLC analysis.

^d The absolute configuration was determined to be *R*; see Supporting Information.

^e The reaction in toluene.