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

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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 catalytic 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 (Scheme 1).[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**.

We and others have reported readily accessible and tunable 6′-OH[9,10] and 9-thiourea[11] cinchona alkaloids as bifunctional catalysts for asymmetric C−C bond forming reactions. Mechanistic studies of cinchona alkaloids[9b,12] and chiral thioureas[13,14] 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

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

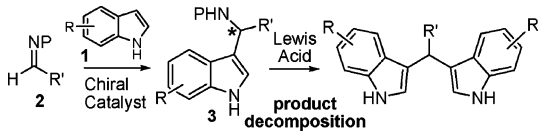
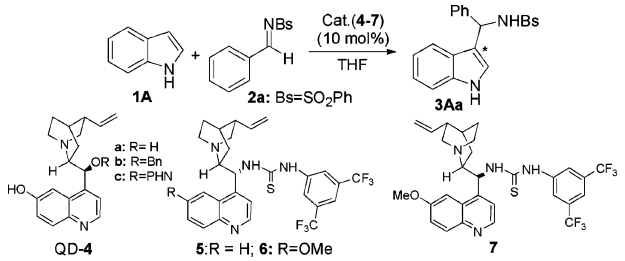


Table 1. Enantioselective Friedel−Crafts Reaction with Cinchona Alkaloids[a]



entry	catalyst	*T*/°C	conv/%[b]	ee/%[c]	entry	catalyst	*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

[a] Unless noted, reactions were carried out with **2a** (0.10 mmol) and **1A** (0.20 mmol) in 0.10 mL of solvent for 48 h. [b] Determined by NMR analysis. [c] Determined by HPLC analysis. [d] The reaction was carried out in EtOAc (0.050 mL) for 24 h. [e] Reaction was carried out with **2a** (0.30 mmol) and **1A** (0.60 mmol) in EtOAc (0.15 mL) for 36 h.

roomtemperature in THF, the reactions with **4**−**6** proceeded in less than 20% conversion after 48 h (entries 1−6). However, the reaction was found to proceed in very high enantioselectivity with the 9-thiourea cinchona alkaloids (entries 5 and 6). Remarkably, the enantioselectivity remained very high even at 50 °C, at which the reaction was much faster (entries 11 and 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 h 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

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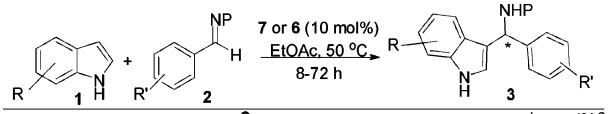
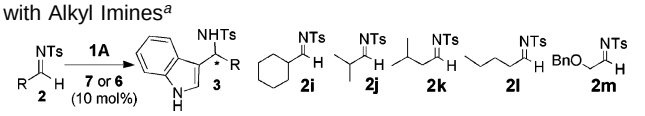
Table 2. Cinchona Alkaloid-Catalyzed Friedel−Crafts Reactions of Indoles with Aryl Imines[a]



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**	 **2h**	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 out with 0.3 mmol of **2**, 0.6 mmol of **1** in 0.15 mL of EtOAc with 10 mol % of **7**, and the results in parentheses were obtained with **6** to give the 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.

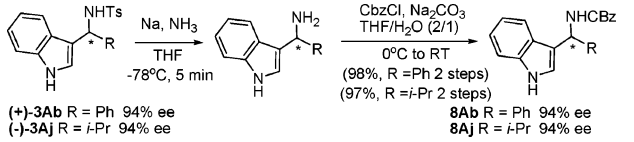
Table 3. Enantioselective Friedel−Crafts Reactions of Indoles with Alkyl Imines[a]



entry	2	*T*/°C	time/h	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 out with **2** (0.3 mmol) and **1A** (0.6 mmol) in EtOAc (0.15 mL), and the results in parentheses were obtained with **6** to give the 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] Reaction in toluene.

Scheme 2. Conversion of *N*-Ts to *N*-Cbz 3-Indolyl Methanamine **8**



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 15, 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.

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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.

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