Squaramide-catalyzed enantioselective Friedel–Crafts reaction of indoles with imines†

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Chiral squaramides are highly enantioselective catalysts for Friedel–Crafts reaction of indoles with *N*-tosyl imines, affording 3-indolyl methanamine products in 85–96% yields and 84–96% ees.

Hydrogen bond catalysis is playing an increasingly important role in the development of enantioselective reactions.[1] Compared to many metal-based catalysts, hydrogen bond catalysts are readily prepared, stable to moisture and oxygen, and easily isolated and reused. The pioneering work of Jacobsen[2] and Takemoto[3] on thiourea based chiral hydrogen bond donors has inspired a myriad of related thiourea catalysts as well as the development of numerous enantioselective transformations, many of which had eluded traditional, metal-based catalysis. We have been interested in uncovering new platforms for hydrogen bond catalysis, particularly those capable of providing dual hydrogen bond activation. In this regard, we recently reported on the development of chiral squaramides as a new class of hydrogen bond donor catalysts, with distinctly different structural parameters than thioureas.[4] In initial studies we showed that a chiral squaramide nicely catalyzes the Michael addition reactions of various 1,3-dicarbonyl compounds to a range of nitroalkenes at very low catalyst loadings.[4] More recently, we have found a related chiral squaramide to be broadly effective for the highly enantioselective conjugate addtion reaction of diphenyl phosphite to assorted nitroalkenes.[5] We now report the first highly efficient squaramide-catalyzed enantioselective Friedel–Crafts reaction of indoles with imines.

The Friedel–Crafts reaction represents the main thoroughfare by which C–C bonds are introduced on the indole framework. As such, this process has been investigated extensively, and many hydrogen-bonding promoted Friedel–Crafts reactions of indoles have been reported over the past few years.[6–9] Specifically, for the enantioselective Friedel–Crafts reaction of indoles with imines, two families of highly efficient organocatalysts have been shown to be effective.[6] In 2006, Deng and coworkers showed that cinchona alkaloid-based thiourea catalysts, at 10% loading, gave the aryl imine addition products in 83–97% enantioselectivities.[6a] The following year, You and coworkers reported chiral phosphoric acids to be superb catalysts for analogous addition reactions, with enantioselectivities of >99% having been observed in several instances.[6b,9] Other chiral phosphoric acids have also been reported to promote such reactions, with excellent results.[7,8]

A small library of squaramide-based catalysts (Fig. 1) was prepared and their capacity to promote Friedel–Crafts

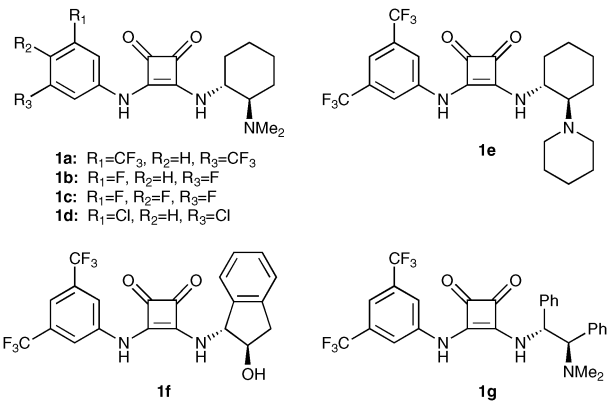
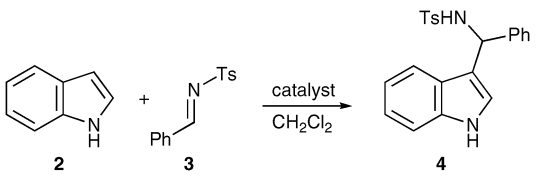


Fig. 1 Structures of squaramide-based H-bonding catalysts.

Table 1 Survey of reaction temperature and catalyst loading



Entry[a]	Catalyst (mol%)	T/°C	Yield (%)[b]	ee (%)[c]
1	2.5	0	32	94
2	2.5	rt	52	93
3	2.5	50	80	92
4	2.5	75	76	85
5	1	50	31	88
6	5	50	81	91
7	10	50	90	91

[a] Reaction conditions: 3 equiv. of imine, 1 M indole in CH_2Cl_2, 48 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis (Chiralcel OD-H column).

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reactions of indoles was evaluated. The catalysts are easily synthesized by sequential addition–elimination reactions of two amines with commercially available dimethyl squarate (3,4-dimethoxy-3-cyclobutene-1,2-dione).

The initial studies were carried out using the reaction of indole (**2**) and *N*-tosylimine **3** as substrates and squaramide **1a** as the catalyst. When the reaction was carried out at room temperature using 2.5 mol% of the catalyst, the addition product (**4**) was formed in 93% ee, albeit in 52% yield (Table 1, entry 2). Interestingly, at 50 °C the product was obtained in higher yield, with only a slight decrease in enantioselectivity (92%, entry 3). Increasing the catalyst loading offered no particular advantage (entries 6, 7). A brief survey of solvents showed CH_2Cl_2 and tetrahydrofuran (THF) to provide comparable results (Table 2). Since the best results were obtained in THF—95% ee and 88% yield—it was selected for further studies of this Friedel–Crafts reaction. Early studies with imines of aliphatic aldehydes gave promising results, but lower enantioselectivities (*vide infra*).

Table 2 Survey of the reaction solvent

Entry	Solvent	Yield (%)	ee (%)
1	Toluene	75	92
2	CH_2Cl_2	85	94
3	$CHCl_3$	83	94
4	THF	88	95
5	EtOAc	70	93

Table 3 Survey of the squaramide catalysts

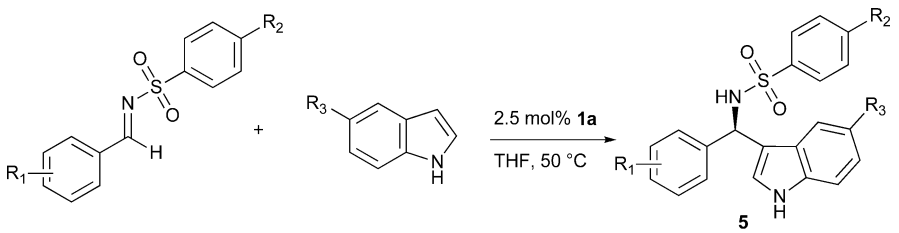
Entry[a]	Catalyst	Yield (%)[b]	ee (%)[c]
1	**1a**	80	94
2	**1b**	48	84
3	**1c**	49	85
4	**1d**	50	86
5	**1e**	24	4
6	**1f**	90	0
7	**1g**	81	92

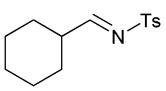
[a] Reaction conditions: 2.5 mol% catalyst, 3 equiv. of imine, 1 M indole in CH_2Cl_2 at 50 °C, 24 h. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralcel OD-H).

The optimized conditions were then used to assess the effectiveness of several related chiral squaramides (Table 3). Three catalysts having the core structure of **1a** but differing in the substituents on the aryl ring were examined, and all were found to provide inferior results (entries 2–4). Three catalysts having a different chiral amine component were also evaluated. Interestingly, catalyst **1e**, which provided excellent enantioselectivity in our recently reported Michael addition of diphenyl phosphite to nitroalkenes, was a poor catalyst for the present reaction, giving a nearly racemic product.[5] Likewise, the 1-amino-2-indanol containing squaramide (**1f**), while it afforded the product in excellent yield, provided no enantioselectivity. On the other hand, the 1,2-diphenylethylenediamine derived catalyst (**1g**) was quite effective and gave the addition product in 81% yield and 92% ee. This survey showed catalyst **1a** to afford the best yield and enantioselectivity.

The scope of chiral squaramide catalyzed enantioselective Friedel–Crafts reactions of a diverse range of indole and imine substrates was evaluated next. The reactions were carried out using catalyst **1a**, under the optimized conditions noted above

Table 4 Squaramide-catalyzed enantioselective Friedel–Crafts reaction of indoles with *N*-tosyl imines



Entry[a]	Product	R_1	R_2	R_3	Time/h	Yield (%)[b]	ee (%)[c]
1	**5a**	4-Cl	4-Me	H	24	94	95.5
2	**5b**	2-Cl	4-Me	H	18	91	94
3	**5c**	4-Br	4-Me	H	72	92	96
4	**5d**	2-Br	4-Me	H	48	92	93
5	**5e**	4-F	4-Me	H	72	90	92
6	**5f**	4-H	4-Me	H	72	88	95
7	**5g**	4-Me	4-Me	H	26	86	91
8	**5h**	4-OMe	4-Me	H	48	89	93
9	**5i**	4-isopropyl	4-Me	H	72	87	94
10	**5j**	4-H	4-Me	5-Me	72	92	91
11	**5k**	4-H	4-Me	5-OMe	72	96	93
12	**5l**	4-H	4-Cl	H	36	85	84
13	**5m**	4-H	2-Me	H	72	88	90
14	**5n**			H	92	75	81

[a] Reaction conditions: 2.5 mol% catalyst, 4 equiv. of imine, 1 M indole in THF at 50 °C. [b] Isolated yield. [c] Determined by chiral HPLC analysis (Chiralcel OD-H).

(Table 4). All reactions proceeded in good to excellent yields and, generally, excellent enantioselectivities. Importantly, the Friedel–Crafts reaction of an aliphatic aldehyde derived imine was also examined and afforded the expected product in good yield and enantioselectivity (75% yield, 81% ee, 92 h, 5 mol% catalyst loading, entry 14). Current efforts are focused on the optimization of catalyst and conditions for aliphatic imine substrates, and the results will be reported in due course.

The results above show that the chiral squaramide family of hydrogen bond donors are highly effective catalysts for the enantioselective Friedel–Crafts reaction of indoles with imines. The ease of preparation combined with their modular nature allows for convenient tuning of the chiral environment and the pK_a of the donor hydrogens of squaramides.

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