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Design and Applications of *N-tert*-Butyl Sulfinyl Squaramide Catalysts

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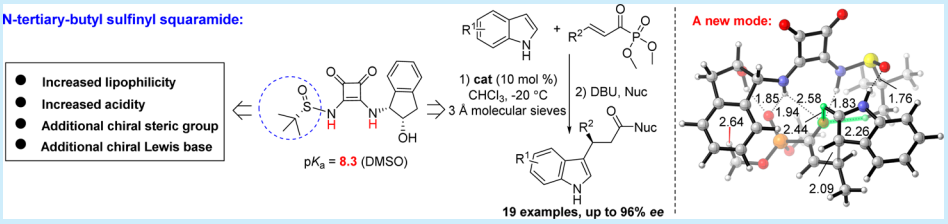
Supporting Information



ABSTRACT: A new chiral HBD system, *N-tert*-butyl sulfinyl squaramide, was designed and synthesized. The core *N-tert*-butyl sulfinyl squaramide with an 1-aminoindan-2-ol skeleton was found to be an efficient catalyst in the enantioselective Friedel–Crafts alkylation of indoles and acyl phosphonates.

Inspired by the mechanistic studies of enzyme catalysis where hydrogen bonding serves a key role in substrate activation, single or dual HBD motifs have been a prominent feature in organocatalysts.[1] In 1994, Curran and Kuo demonstrated for the first time that urea derivatives are competent organic catalysts in the allylation of cyclic sulfinyl radicals with allyltributylstannane.[2] Pioneered by Jacobsen, Schreiner, and Takemoto, thiourea derivatives have become a frequent core of hydrogen-bonding type organocatalysts over the years.[3] In 2008, Rawal applied a chiral squaramide-based organocatalyst in a Michael addition of 1,3-dicarbonyl compounds to nitro olefins and observed excellent chemical efficiency and stereocontrol.[4] Looking back at the process of development of hydrogen-bond catalysts, acidity is a key element to the design and optimization of a new catalyst.[5] Acidity influences the proton-donating ability of the catalyst and is generally consistent with hydrogen-bond strengthening. This is also consistent with the development of the order of the catalyst discovery from urea to thiourea, and then to the squaramide. Among the three skeletons, squaramides often show better catalytic efficiencies than the corresponding (thio)ureas. Although a broad range of important asymmetric transformations has been realized by chiral squaramide catalysis,[6] some drawbacks, such as strong self-aggregation and poor solubility in nonpolar solvent, still limit the application of squaramides in organocatalysis. To date, only one example was reported. Through squaramide-based metal–organic framework (MOF) derivatives, detrimental self-association of the catalyst is prevented, and the biorelevant Friedel–Crafts reaction between indole and β-nitrostyrene is accelerated dramatically.[7] Furthermore, the relatively lower acidity of squaramide hinders the development of squaramide-type catalysts. As a result, novel strategies for the development of highly efficient chiral HBD catalysts that can overcome these shortcomings are highly desirable.

Recently, Ellman and co-workers have developed a new class of urea catalysts that contain the *N*-sulfinyl group, which serves as a chiral controlling element and an acidifying center.[8] Comparing the acidities between *N-tert*-butylsulfinyl substituted (thio)urea and 3,5-bis(trifluoromethyl)phenyl substituted (thio)urea, we found that the *N-tert*-butylsulfinyl showed stronger electronic effects than the latter (Figure 1). In addition, the tertiary butyl of the *N*-sulfinyl is a well-known lipid soluble group. Based on these aspects, we envisioned that a new hydrogen bond system that combines squaramide with *N-tert*-butyl sulfinyl group could solve

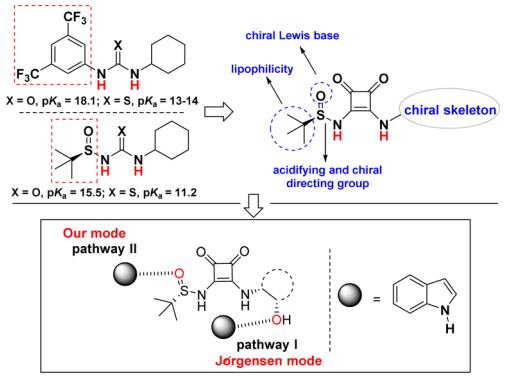


Figure 1. Rational design of *N-tert*-butyl sulfinyl squaramide catalysts.

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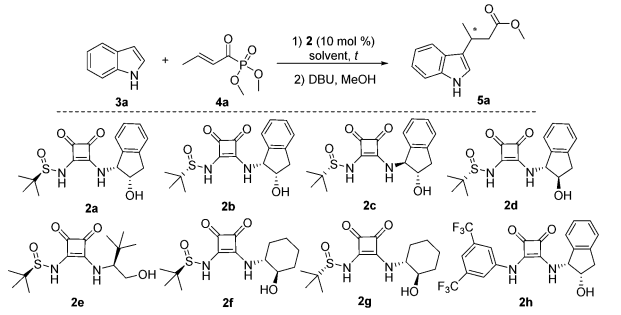
the drawbacks of squaramide catalysts. The *N-tert*-butyl sulfinyl squaramide is proposed to improve the solubility and the acidity of the squaramide catalyst. The presence of a sulfinyl oxygen can serve as a hydrogen-bond accepting site, enabling dual or bifunctional activation modes that enrich the catalytic potential of the *N-tert*-butyl sulfinyl squaramide. Herein, we report the design and synthesis of *N-tert*-butyl sulfinyl squaramides[9] and their application in the asymmetric Friedel−Crafts reaction of indoles with acyl phosphonates.[10,11] The Jørgensen model (I) and our proposed model for catalysis (II) were also investigated (Figure 1).

The reaction of indole **3a** and acyl phosphonate **4a** in CH_2Cl_2 was first investigated. As shown in Table 1, (1*R*,2*S*)-1-aminoindan-2-ol-derived *N*-sulfinyl squaramide **2a** afforded the desired product **5a** in 92% yield but only 3% *ee* (Table 1, entry 1), while the diastereomer **2b** promoted the addition in 93% yield with 76% *ee* (Table 1, entry 2). *trans*-Aminoindanol-derived squaramides **2c** and **2d** resulted in slightly lower yields and poor *ee* values (Table 1, entries 3 and 4). Other amino alcohol-derived *N-tert*-butyl sulfinyl squaramides **2e−g** all resulted in low enantioselectivities (Table 1, entries 5−7). For comparison, conventional squaramide **2h**, which contains the 3,5-bis-(trifluoromethyl)phenyl group, was also investigated in the model reaction in which **5a** was obtained in 50% *ee* (Table 1, entry 8). With the optimal catalyst **2b**, we next screened other conditions. $CHCl_3$ is shown to be a better solvent than CH_2Cl_2 (Table 1, entries 2 and 9). Decreasing the temperature of the reaction along with addition of 3 Å molecular sieves had a positive effect on the enantioselectivity (Table 1, entries 10−12). The optimal condition is shown in entry 12: with 10 mol % **2b** and 3 Å molecular sieves in $CHCl_3$ at −20 °C, the reaction gave **5a** in 85% yield with 94% *ee*.

Table 1. Optimization of Reaction Conditions[a]

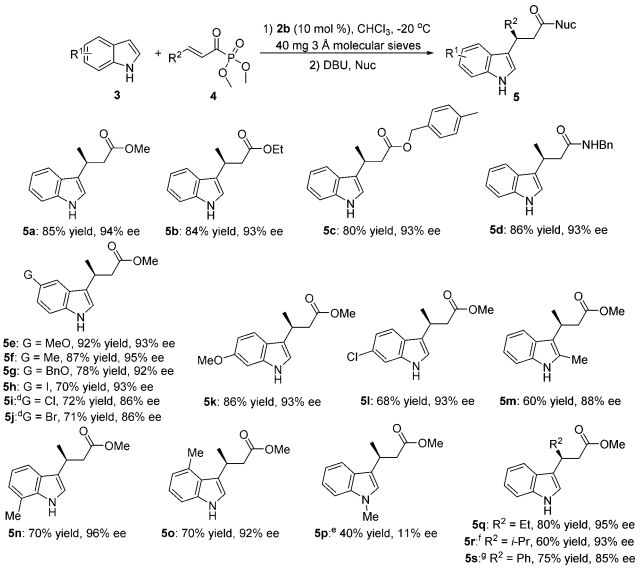


entry	catalyst	solvent	*t* (°C)	yield[b] (%)	*ee*[c] (%)
1	**2a**	CH_2Cl_2	rt	92	3
2	**2b**	CH_2Cl_2	rt	93	76
3	**2c**	CH_2Cl_2	rt	70	3
4	**2d**	CH_2Cl_2	rt	68	4
5	**2e**	CH_2Cl_2	rt	75	−15
6	**2f**	CH_2Cl_2	rt	75	−29
7	**2g**	CH_2Cl_2	rt	70	22
8	**2h**	CH_2Cl_2	rt	70	50
9	**2b**	$CHCl_3$	rt	92	85
10[d]	**2b**	$CHCl_3$	10	93	90
11[d]	**2b**	$CHCl_3$	0	90	92
12[e]	**2b**	$CHCl_3$	−20	85	94

[a]The reactions were performed with 0.1 mmol of **3a**, 0.2 mmol **4a**, and 0.01 mmol of catalyst **2** in 0.5 mL of solvent at the given temperature for 1 d. [b]Isolated yields. [c]Determined by chiral HPLC analysis. [d]The reaction was performed with 40 mg of 3 Å molecular sieves in 2 mL of $CHCl_3$ for 2 d. [e]The reaction was performed with 40 mg of 3 Å molecular sieves in 2 mL of $CHCl_3$ for 3 d.

We next explored the substrate scope. As shown in Scheme 1, using other nucleophiles such as EtOH, $BnNH_2$, or 4-Me-BnOH, the reactivities and enantioselectivities were unaffected (80−86% yields and 93% *ee* for **5b−d**). Five- or 6-position substituted indoles also worked well with this Friedel−Crafts strategy. As a result, the desired products **5e−l** were obtained in good to excellent yields and very good enantioselectivities (68−92% yields and 86−95% *ee*). The reactivity is sensitive to the nature of the substituent on the indole ring: electron-donating substituents enhance the reactivity (**5e-g**, **5k**), and electron-poor indoles require higher temperatures (**5i−j**) to maintain acceptable conversions. Substrates with substituent adjacent to the activation site or attack site on the indole ring were also examined. To our delight, the 7-methylindole transformed to the corresponding methyl ester product **5n** in 70% yield with 96% *ee*. The 2-methylindole and 4-methylindole also gave the Friedel−Crafts products in good yields and *ee* values (**5m** and **5o**). However, only 40% yield and 11% *ee* were obtained for the desired product **5p** in the conversion of methyl protected indole, which indicates that the N−H of the indole is essential for the stereocontrol of the reaction.

Scheme 1. Substrate Scope[a,b,c]



[a]The reactions were performed with 0.1 mmol of **3**, 0.2 mmol of **4**, 0.01 mmol of **2b**, and 40 mg of 3 Å molecular sieves in 2 mL of $CHCl_3$ at −20 °C for 3 d. [b]Isolated yields. [c]Determined by chiral HPLC. [d]At 0 °C. [e]0.1 mmol **3** and 0.1 mmol **4** at rt. [f]In 1 mL of $CHCl_3$ at 0 °C. [g]In 0.5 mL of $CHCl_3$ at 0 °C without 3 Å molecular sieves.

The reaction was also applicable for *β*-ethyl- and *β*-isopropyl-substituted acyl phosphonates, which gave **5q** and **5r** with very good enantioselectivities. For the reaction of indole and *β*-phenyl-substituted acyl phosphonate, the product **5s** was obtained in 75% yield and 85% *ee* under the reoptimizing reaction conditions.[9]

The potential and synthetic application of this catalytic approach was demonstrated by the transformations shown in Figure 2. Using ammonia as the nucleophile, the 1 mmol scale reaction was performed to give amide **6** in good yield and excellent enantioselectivity. Reduction of the amide by $LiAlH_4$ gave the chiral homotryptamine **7**. The enantiomeric excess of **7** was

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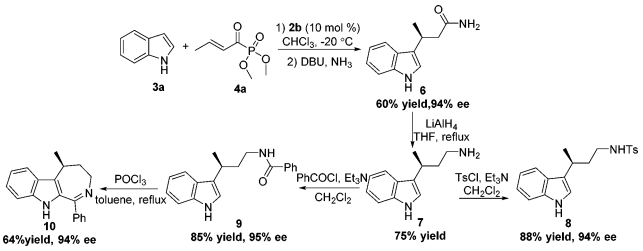

Figure 2. Useful transformations of the product.

determined by analyzing the corresponding sulfonamide derivative **8**, which may serve as an inhibitor of mammalian 15-lipoxygenase.[12] Alternatively, **9** can be obtained by benzoyl protection of **7**. Treating **9** with the traditional Bischler–Napieralski protocols with phosphoryl chloride in toluene gave the 7-endo-trig cyclization product, chiral azepino[3,4-*b*]indole **10**, in 64% yield and 94% *ee*.

To further evaluate the catalytic efficiency of our new catalyst, a kinetic investigation was carried out.[9] The conversion versus time profile for the Friedel–Crafts alkylation of indole **3a** and acyl phosphonate **4a** using 10 mol % **2b** and **2h** was plotted in Figure S1. The new catalyst **2b** exhibited higher reactivity than the conventional squaramide catalyst **2h**. Furthermore, the acidities of catalysts **2b** and **2h** were determined.[9] As shown in Figure S1, the pK_a values of catalysts **2b** and **2h** are 8.30 and 11.87, respectively. This result indicated that the chiral *N*-*tert*-butyl sulfinyl squaramide is more acidic than the corresponding 3,5-bis(trifluoromethyl)phenyl type squaramide. This is consistent with the order of reactivity.

Based on the optimization conditions shown in Table 1, all of the catalysts gave the desired product in moderate to good yields. However, the enantioselectivities differ significantly among them. Previous mechanistic modes (Figure 3, **TS1S** and **TS1R**)[10a] cannot fully explain the experiment results. Since the *tert*-butyl sulfinyl derived organocatalysts have been identified as chiral Lewis base for reduction of imines,[13] a new mechanism was proposed (Figure 3, **TS2S** and **TS2R**) in which the sulfinyl oxygen of *tert*-butyl sulfinyl group as a Lewis base forms a hydrogen bond with the indole N–H moiety, and the enone electrophile is activated by the tridentate squaramide aminoindanol motif.

To determine how the catalyst promotes these reactions, we performed DFT calculations.[9] Extensive explorations of a variety of catalytic arrangements show that the most stable transition state structure is **TS2S**, which involves SO activation of the indole, while **TS1S**, lacking such activation, is 3.7 kcal/mol less stable (Figure 3). **TS2R** is also more stable than **TS1R** by 0.9 kcal/mol (Figure 3). This suggests that the model **2** better describes the transition structures of this Friedel–Crafts reaction. The more stable type **2** TSs can be explained by the stronger hydrogen bond formed between the sulfinyl oxygen of the catalyst and the N–H of indole (1.76 and 1.74 Å), interactions that are not present in the first model. Instead weaker hydrogen bonds are observed between the indole N–H and the hydroxyl oxygen of the catalyst (1.94 and 2.01 Å).

The model **2** TSs also explain the enantioselectivity. **TS2S** is 2.2 kcal/mol more stable than **TS2R**, which is in excellent agreement with the experimental enantioselectivity of 94% *ee*. We explain this result as follows: (1) a favorable electrostatic interaction between the forming enolate oxygen and the electropositive hydrogen alpha to the indole nitrogen at 2.44 Å is observed in **TS2S**;[14] (2) an unconventional C–H···O hydrogen-bonding interaction present in **TS2S** is likely to be crucial to inducing the

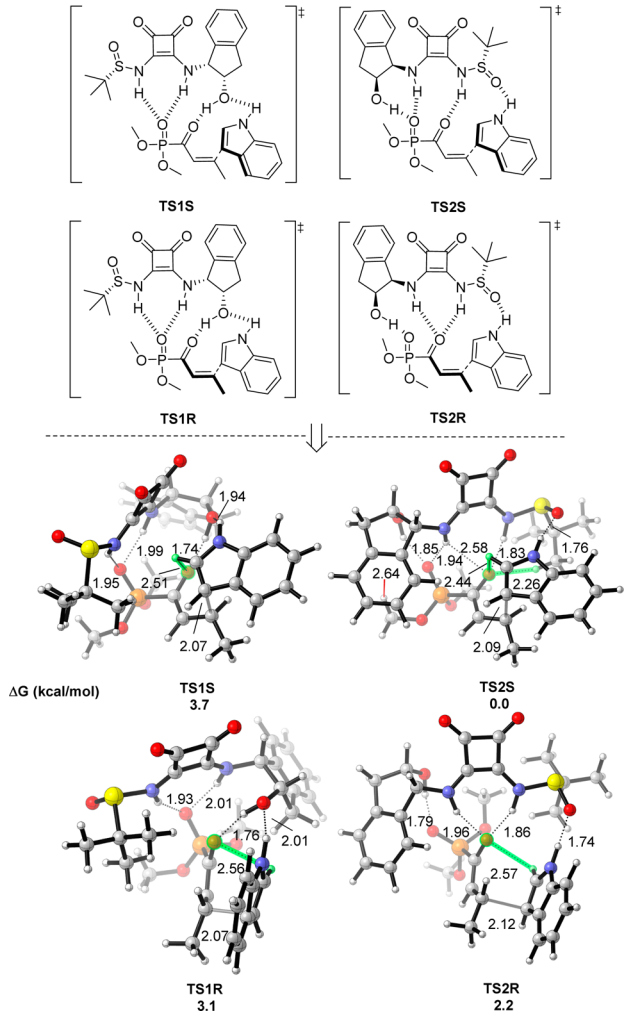

Figure 3. Optimized structures of transition states. The C–H···O interactions are highlighted in green. The red dashed line indicates C–H···π interaction. The bond lengths are in angstroms (Å).

enantioselectivity.[15] Both interactions are labeled in green. In **TS2S**, the distance between the one C–H of *tert*-butyl and the carbonyl oxygen is 2.26 Å, which is shorter than the sum of van der Waals radii of hydrogen and oxygen atoms. The theory of atoms in molecules (AIM) have been used to investigate the interatomic interactions on the basis of the topological properties of electron density.[16] The analysis of electron density at bond critical point (BCP) and its derivatives was used to gain insight into the hydrogen bonding.[17] Topological analysis of the electron density distribution of C–H···O interaction in **TS2S** indicates that this type of interaction is hydrogen-bonding.[18] Using the parameters derived from AIM analysis and the equation reported by Espinosa, the estimated total hydrogen-bonding energies of **TS2S** and **TS2R** are 41.4 and 38.0 kcal/mol (Table S2), respectively.[19,20] The estimated difference in total hydrogen-bonding energies is 3.4 kcal/mol, which is close to the calculated relative free energy difference (2.2 kcal/mol).

This analysis indicates that the difference in free energies is mainly induced by hydrogen-bonding interactions between the catalyst and the substrates. The estimated energies of C–H···O hydrogen-bonding is approximately 3.0 kcal/mol. This interaction makes a key contribution to the stability of **TS2S**. In addition, **TS2S** is also stabilized by a C–H···π interaction between the methyl of phosphonate and the aromatic ring of amino-

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indanol,[21] which is labeled in red. These three stabilizing interactions are not present in **TS2R**. The energy difference between the **TS2S** and **TS2R** arises from the collective favorable electrostatic interactions observed in **TS2S**.

In summary, the design and synthesis of *N-tert*-butyl sulfinyl squaramides is described. The newly designed HBD system demonstrates many advantages over the conventional squaramide catalyst. The investigated *N-tert*-butyl sulfinyl squaramide with a 1-aminoindan-2-ol skeleton successfully catalyzes the enantioselective Friedel–Crafts alkylations of indoles and acyl phosphonate. Moreover, a new mechanism was proposed based on the Lewis base properties of the sulfinyl oxygen. DFT calculation indicated that C–H···O hydrogen-bonding is crucial to induction of the observed enantioselectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00727.

Experimental procedures, characterization data, and computational details (PDF)

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Notes

The authors declare no competing financial interest.

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