CaSH Organocatalysis: Enantioselective Friedel–Crafts Alkylation of Indoles with α,β-Unsaturated Aldehydes

Tian Tian,[a,b] Bao-Jian Pei,[a] Qing-Hua Li,[a] Hao He,[a] Ling-Yan Chen,[a] Xiang Zhou,[b] Wing-Hong Chan,[a] Albert W. M. Lee*[a]

[a] Department of Chemistry, Hong Kong Baptist University, Hong Kong, P. R. of China
Fax +85234117438; E-mail: alee@hkbu.edu.hk

[b] College of Chemistry and Molecular Sciences, Wuhan University, Hubei, P. R. of China

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Abstract: Enantioselective Friedel–Crafts alkylation of indole with α,β-unsaturated aldehyde was catalyzed by camphor sulfonyl hydrazine (CaSH) with good enantioselectivity (81–88%).

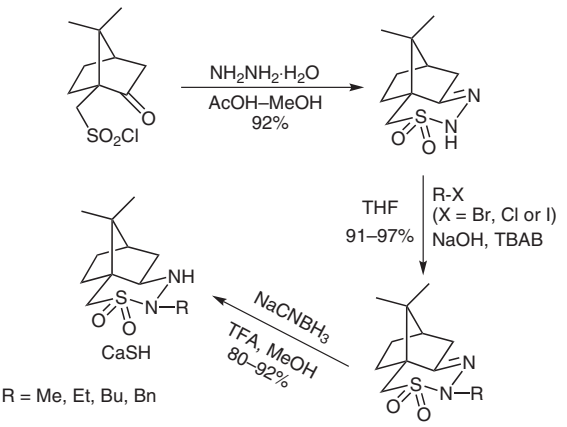
Key words: camphor sulfonyl hydrazine (CaSH), organocatalysis, indole alkylation, α,β-unsaturated aldehydes

Although the term organocatalysis was only coined in 2000,[1] the concept of using small molecules to catalyze asymmetric transformation has appeared in literatures even back in the 1970s. The proline-catalyzed intramolecular aldol reaction by Hajos, Parrish, Eder, Sauer, and Wiechert is an outstanding example.[2] In recent years, we have witnessed an exponential growth in organocatalysis. It has become a highly dynamic and rapidly growing research field. Together with organometallic and enzymatic approaches, organocatalysis has emerged as a new powerful tool for various asymmetric transformations.[3,4] Among numerous asymmetric carbon–carbon forming reactions, the Friedel–Crafts alkylation of aromatic substrates with the α,β-unsaturated carbonyl compounds has received considerable attention.[5] It is not only an important type of reaction in organic synthesis, but also provides important building blocks for the synthesis of many natural products.[6]

Based on the imine formation strategy,[7] MacMillan and co-workers first explored the organocatalytic asymmetric Friedel–Crafts indole alkylation. Employing chiral imidazolidinone salts as organocatalysts, they reported the reactions of indoles, pyrroles, and electron-rich benzenes with α,β-unsaturated aldehydes.[8] The MacMillan-type catalyst has also been used for the indole alkylation with cyclic α,β-unsaturated aldehydes.[9a] Intramolecular Friedel–Crafts-type indole alkylation reactions have also been investigated by other groups.[9b] Further improvements in this type of organocatalytic Friedel–Crafts indole alkylation with α,β-unsaturated ketones by new organocatalysts also appeared recently.[10]

In the reported Lewis base approaches, the key functionalities in these organocatalysts are either primary or secondary amines. We report here that hydrazine functionality is also an effective organocatalyst. It is well established that by attaching a heteroatom to an amine, its nucleophilicity will be greatly enhanced.[11] We envision that if another nitrogen atom is attached to the amino functionality (hydrazine) of an organocatalyst, the so-called α-heteroatom effect could enhance its nucleophilicity.[12] The addition of an electron-withdrawing group such as sulfonyl could further fine tune the extent of the α-effect.

To put these concepts into practice, we have recently prepared a series of camphor sulfonyl hydrazines (CaSH) from camphor sulfonyl chloride by a three-step reaction sequence with good overall yield (70%, Scheme 1). We have demonstrated that CaSH are excellent organocatalysts in asymmetric Diels–Alder reactions and aza-Micheal addition.[13] In this paper, we report the use of CaSH **1** (R = Bn) as organocatalyst in Friedel–Crafts alkylation of indoles with α,β-unsaturated aldehydes.



Scheme 1 Preparation of the camphor sulfonyl hydrazines (CaSH)

Our investigation started with the reaction between indole and (*E*)-crotonaldehyde. We chose trifluoroacetic acid (TFA, 20 mol%) as the additive and toluene as the solvent. CaSH **1** which has very good catalytic effect in asymmetric Diels–Alder reactions was chosen as the organocatalyst. Although indole disappeared after six hours at –40 °C, only trace amount of the desired product **3** was detected (Table 1, entry 1). When electron-withdrawing group such as mesylate, benzoyl, and propyonyl was attached to indole, the reactivities of these N-substituted indoles were decreased to the extent that there were no reactions even at room temperature (Table 1, entries 2–4). To our delight,

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N-methylindole started to show some promising results. Alkylated product **3** was isolated in moderate yield with 60% ee after 9 hours at –40 °C (Table 1, entry 5). For the ease of handling, aldehyde **3**[14] was reduced with $NaBH_4$ directly to alcohol **4**, which is more polar and can be separated easily by flash chromatograph on silica gel. We tried different solvents [Et_2O, CH_2Cl_2, CCl_4, and *i*-PrOH–CH_2Cl_2 (15% v/v)] for this reaction. However, both the yields and the enantioselectivities were poor as compared with using toluene (Table 1, entries 6–9). Finally, we moved to *N*-benzyl indole and found it afforded much better result in terms of yield (60%) and ee (78%, Table 1, entry 10). When the less acidic trichloroacetic acid (TCA) was used as the additive, the result was slightly inferior (Table 1, entry 11). Increased the amount of catalyst and TFA to 30 mol%, the yield and ee were improved to 71% and 81%, respectively (Table 1, entry 12).

With the optimized reaction conditions in hand, we then examined the scope of this CaSH **1** catalyzed alkylation of *N*-benzyl indole with various α,β-unsaturated aldehydes.[15] The results are summarized in Table 2.[16] It was observed that with larger alkyl substituent on the β-position of the unsaturated aldehydes, the reactions were slower with lower yields but higher ee (Table 2, entries 1–4). It is possibly due to the steric effect. For aryl-substituted α,β-unsaturated aldehydes, moderate yields, and up to 88% ee were achieved (Table 2, entries 5–7). When the unsaturated aldehyde was substituted with a strong electron-donating group (OMe), the reaction was very slow even at room temperature (Table 2, entry 8).

In summary, we have demonstrated for the first time that camphor sulfonyl hydrazine (CaSH) is an efficient organocatalyst for enantioselective Friedel–Crafts alkylation of *N*-benzyl indole with α,β-unsaturated aldehydes with good enantioselectivity. The investigation of the other CaSH-catalyzed enantioselective transformations is in progress.

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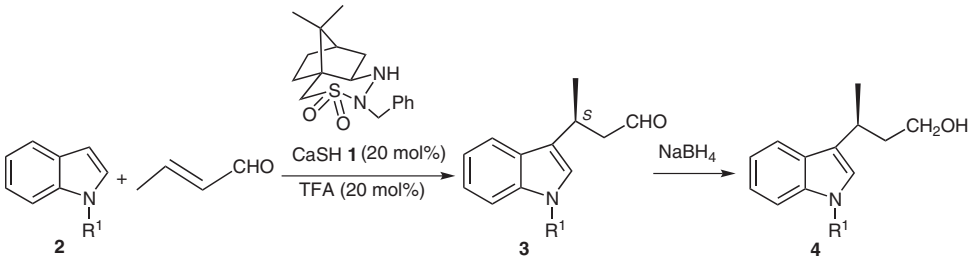
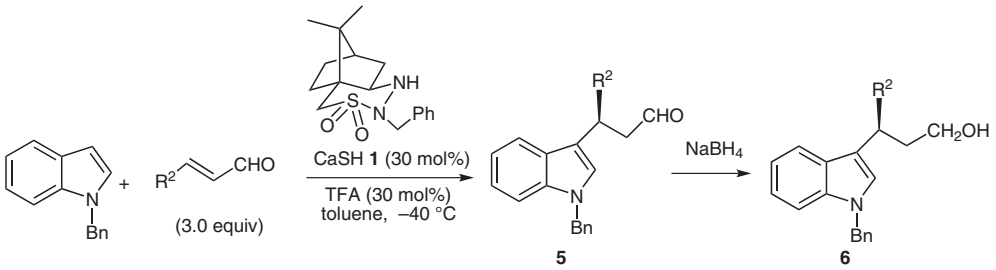
Table 1 Friedel–Crafts Alkylation of Indoles with (*E*)-Crotonaldehyde Catalyzed by CaSH **1**



Entry	R^1	Solvent	Temp (°C)	Time (h)	Yield (%)[a]	ee (%)[b,c]
1	H	toluene	–40	6	<10	–
2	Ms	toluene	–40 to r.t.	72	n.r.	–
3	Bz	toluene	–40 to r.t.	72	n.r.	–
4	propionyl	toluene	–40 to r.t.	48	n.r.	–
5	Me	toluene	–40	9	53	60
6	Me	Et_2O	–40	18	30	40
7	Me	CH_2Cl_2	–40	9	38	43
8	Me	CCl_4	–40	24	34	54
9	Me	*i*-PrOH–CH_2Cl_2	–40	20	49	40
10	Bn	toluene	–40	20	60	78
11[d]	Bn	toluene	–40	30	55	70
12[e]	Bn	toluene	–40	20	71	81

[a] Isolated yield of alcohol **4**.
[b] Determined by chiral HPLC (Chiracel AD-H) of the alcohol **4**.
[c] Absolute configuration was assigned by comparison of the chiral HPLC chromatographs with the literature reported data.[8]
[d] TCA was used instead of TFA.
[e] Conditions: 30 mol% CaSH **1** and 30 mol% TFA.

Table 2 Friedel–Crafts Alkylation of *N*-Benzyl Indole with α,β-Unsaturated Aldehydes Catalyzed by CaSH **1**



Entry	R^2	Time (h)	Yield (%)[a]	ee (%)[b]
1	Me	20	71	81
2	Et	28	67	84
3	Pr	36	63	87
4	Bu	36	46	88
5	Ph	30	50	87
6	4-ClC_6H_4	30	49	88
7	4-BrC_6H_4	20	49	88
8	4-$MeOC_6H_4$	72	<20	–

[a] Isolated yields of the alcohols **6**.
[b] Determined by chiral HPLC analysis of the alcohols **6**.

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(14) Aldehyde **3** (R^1 = Me): ^1H NMR (400 MHz, $CDCl_3$): δ = 9.75 (s, 1 H), 7.63 (d, *J* = 8.0 Hz, 1 H), 7.31 (m, 1 H), 7.26 (m, 1 H), 7.14 (m, 1 H), 6.84 (s, 1 H), 3.75 (s, 3 H), 3.68 (m,

1 H), 2.87 (m, 1 H), 2.71 (m, 1 H), 1.43 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.1, 137.4, 126.8, 125.4, 121.9, 119.3, 119.0, 109.6, 51.2, 32.9, 26.1, 21.9 ppm. Alcohol **4** was obtained by $NaBH_4$ reduction. Alcohol **4** (R^1 = Me): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (dd, *J* = 8.0, 0.8 Hz, 1 H), 7.30 (dd, *J* = 7.2, 0.8 Hz, 1 H), 7.23 (m, 1 H), 7.10 (m, 1 H), 6.85 (s, 1 H), 3.75 (s, 3 H), 3.66 (m, 1 H), 3.22 (m, 1 H), 2.06 (m, 1 H), 1.96 (m, 1 H), 1.40 (d, *J* = 6.8 Hz, 3 H) ppm.

(15) **General Experimental Procedure for CaSH 1 Catalyzed Friedel–Crafts Reaction of Indoles with α,β-Unsaturated Aldehydes**

TFA (0.15 mmol) was added to a solution of CaSH **1** (0.15 mmol) in toluene (1 mL). The solution was stirred for 20 min and then cooled to –40 °C. The α,β-unsaturated aldehyde (1.5 mmol) was then added. After stirring for another 20 min, the N-substituted indole (0.5 mmol) was added. The reaction was stirred until complete consumption of the indoles as determined by TLC. MeOH (2 mL) was added to the reaction mixture followed by $NaBH_4$ (3.0 mmol). The mixture was warmed to 0 °C and stirred for 20 min. The reaction was quenched by H_2O and extracted with EtOAc. The organic solution was dried over anhyd Na_2SO_4. The product **6** was purified by silica gel chromatography (PE–EtOAc, 4:1). The ee was determined by chiral HPLC (Chiracel AD-H) of the alcohol **6** (5% *i*-PrOH in hexane as eluent, 1 mL min^{-1}).

(16) **Spectroscopic Data of Products 6 (Table 2)**

Compound **6** (R^2 = Me): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (dd, *J* = 7.6, 0.8 Hz, 1 H), 7.33 (m, 4 H), 7.21 (m, 4 H), 6.96 (s, 1 H), 5.29 (s, 2 H), 3.30 (m, 2 H), 3.27 (m, 1 H), 2.08 (m, 1 H), 1.95 (m, 1H), 1.44 (d, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.0, 137.1, 129.0, 127.7, 127.6, 126.9, 124.6, 122.0, 121.1, 119.8, 119.1, 110.0, 61.7, 50.1, 40.6, 27.9, 22.1 ppm. HRMS (MALDI-TOF): *m/z* calcd for $C_{19}H_{22}NO$ $[M + H]^+$: 280.1696; found: 280.1695.

Compound **6** (R^2 = Et): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 7.6, Hz, 1 H), 7.25 (m, 4 H), 7.14 (m, 1 H), 7.06 (m, 3 H) 6.88 (s, 1 H), 5.24 (s, 2 H), 3.56 (m, 2 H), 2.93 (m, 1 H), 1.98 (m, 2 H), 1.74 (m, 2H), 0.83 (t, *J* = 7.0 Hz, 3 H) ppm.

Compound **6** (R^2 = Pr): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.0 Hz, 1 H), 7.33–7.24 (m, 4 H), 7.18 (m, 1 H), 7.17–7.06 (m, 3 H) 6.93 (s, 1 H), 5.29 (s, 2 H), 3.62 (m, 2 H), 3.05 (m, 1 H), 2.03 (m, 2 H), 1.18 (m, 2 H), 1.30 (m, 2 H), 0.88 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.0, 137.1, 128.9, 127.8, 127.7, 126.7, 125.6, 121.8, 119.9, 119.0, 118.9, 110.0, 61.9, 50.0, 39.0, 38.9, 33.6, 21.0, 14.4 ppm.

Compound **6** (R^2 = Bu): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, *J* = 7.6 Hz, 1 H), 7.30–7.22 (m, 4 H), 7.14 (t, *J* = 7.6 Hz, 1 H), 7.09–7.03 (m, 3 H), 6.90 (s, 1 H), 5.27 (s, 2 H), 3.59 (m, 2 H), 3.01 (m, 1 H), 2.00 (m, 2 H), 1.78 (m, 2 H), 1.23 (m, 4 H), 0.83 (t, *J* = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.0, 137.1, 128.9, 127.8, 127.7, 126.7, 125.6, 121.8, 119.9, 119.0, 110.0, 61.9, 50.0, 39.0, 36.3, 33.8, 30.2, 23.0, 14.3 ppm.

Compound **6** (R^2 = Ph): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.52 (m, 1 H), 7.38–7.07 (m, 12 H), 7.03 (m, 2 H), 5.30 (s, 2 H), 4.44 (t, *J* = 7.6 Hz, 1 H), 3.68 (m, 2 H), 2.48 (m, 1 H), 2.29 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.1, 138.0, 237.2, 129.0, 128.7, 128.1, 127.9, 127.8, 126.9, 126.4, 125.6, 122.1, 120.0, 119.3, 119.1, 109.9, 61.5, 50.2, 39.4, 39.0 ppm.

Compound **6** (R^2 = 4-ClC_6H_4): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 8.0 Hz, 1 H), 7.33–7.22 (m, 8 H), 7.15 (m, 3 H), 7.01 (m, 2 H), 5.29 (s, 2 H), 4.40 (t, *J* = 7.6 Hz, 1 H), 3.64 (m, 2 H), 2.43 (m, 1 H), 2.22 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.6, 137.8, 137.2, 131.9, 129.4, 129.0, 128.7, 127.8, 127.6, 126.8, 125.5, 122.2, 119.8, 119.4, 118.5, 110.0, 61.2, 50.2, 38.8, 38.7 ppm.

Compound **6** (R^2 = 4-BrC_6H_4): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (m, 3 H), 7.37–7.18 (m, 6 H), 7.15–7.07 (m, 3 H), 6.99 (m, 2 H), 5.28 (s, 2 H), 4.38 (t, *J* = 8.0 Hz, 1 H), 3.62 (m, 2 H), 2.43 (m, 1 H), 2.22 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.1, 137.8, 137.2, 131.7, 129.8, 129.0, 127.8, 127.6, 126.8, 125.5, 122.2, 120.0, 119.8, 119.4, 118.4, 110.0, 61.2, 50.2, 38.8, 38.7 ppm.

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