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Highly Enantioselective Friedel–Crafts–type Alkylation Reactions of Indoles with Chalcone Derivatives using a Chiral Barium Catalyst

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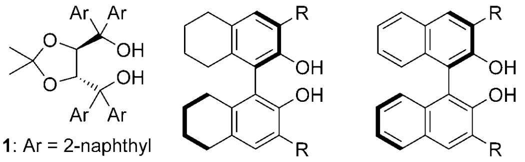
Alkaline earth metals are abundant, nontoxic and inexpensive, and have high coordination numbers. Their salts have both Brønsted basicity and Lewis acidity. Despite these characteristic features, only recently have successful examples using alkaline earth metal compounds as catalysts in organic synthesis been reported.[1–5] We have developed anionic chiral calcium catalysts prepared from calcium alkoxides or amides and chiral bisoxazoline (box) ligands[4] and strontium catalysts prepared from strontium alkoxides or amides and chiral sulfonamides.[2] These catalysts worked well as Brønsted bases for several catalytic asymmetric carbon–carbon bond-forming reactions. We also found that a chiral coordinative ligand (pybox)[5] was applicable for asymmetric 1,4-addition and Mannich-type reactions using a calcium catalyst. Herein, we report that chiral barium complexes prepared from barium amides and chiral ligands work well as efficient catalysts for asymmetric Friedel–Crafts–type alkylation reactions of indoles with chalcone derivatives.

Enantioselective Friedel–Crafts–type alkylation reactions of indoles provide versatile methods for the preparation of optically active indole derivatives. As catalytic asymmetric reactions are ideal from a viewpoint of efficiency, some catalysts for these reactions have been developed recently; however, most are chiral Lewis acids[6a–g, 7a–d] or organocatalysts.[6h–k, 7e] To the best of our knowledge there are no examples of Brønsted base catalyzed asymmetric Friedel–Crafts–type reactions of indoles with enones.[8] Moreover, in spite of their versatile synthetic utilities, the use of chalcone derivatives as enones has been limited.[6g]

We considered that alkaline earth metal complexes might function as chiral Brønsted base catalysts in the Friedel–Crafts–type reactions of indoles. The reaction of indole **8a** with chalcone **9a** was selected as a model reaction, and several combinations of alkaline earth amides[9] with chiral ligands were tested. First, we examined the combination of alkaline earth metal amides with taddols (α,α,α′,α′-tetraaryl-1,3-dioxolan-4,5-dimethanoles) **1**[10] in the model reaction (Figure 1). When barium amide (barium bis(hexamethyldisilazide), [Ba(hmds)$_2$]) and **1** were combined, the desired adduct was obtained in good yield with low enantioselectivity (Table 1, entry 1). We then proceeded to use other alkaline earth metal amides, [Sr(hmds)$_2$] and [Ca(hmds)$_2$]. It was interesting to find that [Sr(hmds)$_2$] gave a racemic product. The desired alkylated indole was obtained in good yield and with high enantioselectivity when using [Ca(hmds)$_2$] (Table 1, entries 3–6). Furthermore, the opposite enantiomers were obtained when using [Ba(hmds)$_2$] and [Ca(hmds)$_2$] with the same ligand **1**. We further optimized the reaction conditions using [Ca(hmds)$_2$] with **1**. As the enantioselectivity decreased in diethyl ether, we elected to use ether-free [Ca(hmds)$_2$] instead of [Ca(hmds)$_2$]·1.3 Et$_2$O and, as expected, the enantioselectivity increased to 94 %



1: Ar = 2-naphthyl

2: R = SiPh$_2$Me
3: R = H
4: R = SiPh$_3$
5: R = Si*i*Pr$_3$
7: R = SiPhMe$_2$

6: R = SiPh$_3$

Figure 1. Chiral ligands combined with alkaline earth metal compounds.

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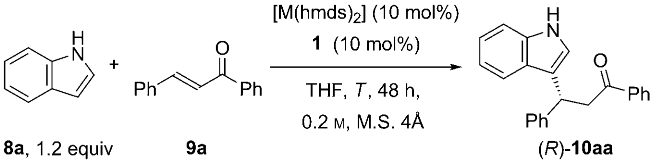
Table 1. Alkaline earth metal amide/taddol-catalyzed Friedel–Crafts-type reaction.



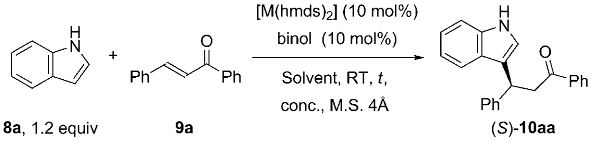
Entry	M	Conditions	Yield [%]	*ee* [%]
1	Ba	RT, MS 4 Å	85	42[a]
2	Sr	RT, MS 4 Å	82	2[a]
3	Ca[b]	RT, MS 4 Å	70	84
4	Ca[b]	RT	69	89
5	Ca[b]	20 °C	61	91
6	Ca	20 °C	61	94

[a] The opposite enantiomer (*S*)-**10aa** was obtained. [b] [Ca-$(hmds)_2$]·1.3 Et_2O.

(Table 1, entry 6). We then investigated several other substrates under the optimized conditions. Low yields were recorded, even after relatively long reaction times (>48 h), with low enantioselectivities in most cases. We further tried to optimize the reaction conditions by including additives such as metal Brønsted bases, Lewis acids, and organobases, and so forth, but no improvement was obtained.

Next, we examined other chiral ligands combined with alkaline earth metal amides (Table 2). As our preliminary work on direct-type amide aldol reactions showed that a combination of barium compounds with H_8-binol ligands such as **2** provided promising results,[1b] we first tested the model reaction of indole **8a** with chalcone **9a** in the presence of 10 mol% each of [Ba$(hmds)_2$] and H_8-binol **3**. The reaction proceeded in moderate yield, but, disappointingly, the product was racemic. However, to our delight, when [Ba$(hmds)_2$] was combined with 3,3-substituted H_8-Binol **4**,[11] the reaction proceeded smoothly to afford the desired adduct in 96% yield with 72% *ee* (Table 2, entry 2). We also examined other alkaline earth metal amides ([Sr$(hmds)_2$] and [Ca$(hmds)_2$]); however, lower yields and enantioselectivities were obtained (Table 2, entries 3 and 4). We then further optimized the reaction conditions using [Ba$(hmds)_2$] and **4** in order to improve the enantioselectivity. The choice of solvent was found to be crucial for the selectivity. The desired product (*S*)-**10aa** was obtained in 86% yield with 95% *ee* when *t*BuOMe/THF (9:1) was used as the solvent (Table 2, entry 14).

Table 2. Optimization of reaction conditions.

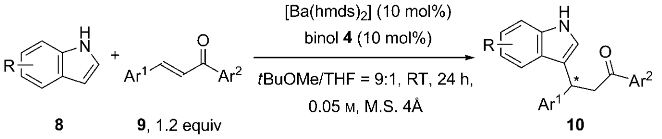


Entry	M	Binol	Conditions	Yield [%]	*ee* [%]
1	Ba	**3**	THF, 48 h, 0.2 M	58	1
2	Ba	**4**	THF, 48 h, 0.2 M	96	72
3	Sr	**4**	THF, 48 h, 0.2 M	28	18[a]
4	Ca	**4**	THF, 48 h, 0.2 M	13	32[a]
5	Ba	**2**	THF, 48 h, 0.2 M	quant.	67
6	Ba	**5**	THF, 48 h, 0.2 M	80	20
7	Ba	**6**	THF, 48 h, 0.2 M	81	46
8	Ba	**4**	Et_2O, 48 h, 0.2 M	77	80
9	Ba	**4**	*t*BuOMe, 48 h, 0.2 M	71	86
10	Ba	**4**	Solvent[b], 24 h, 0.2 M	86	81
11	Ba	**4**	Solvent[b], 24 h, 0.1 M	91	90
12[c]	Ba	**4**	Solvent[b], 24 h, 0.1 M	99	89
13[c]	Ba	**4**	Solvent[b], 24 h, 0.05 M	90	91
14[c]	Ba	**4**	Solvent[d], 24 h, 0.05 M	86	95

[a] The opposite enantiomer (*R*)-**10aa** was obtained. [b] *t*BuOMe/THF = 2:1. [c] Indole (1.0 equiv) and chalcone (1.2 equiv) were used. [d] *t*BuOMe/THF = 9:1.

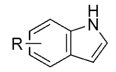
We then investigated the substrate scope under optimized conditions (Table 3). For chalcone derivatives, substrates bearing both electron-withdrawing and electron-donating groups in the benzene ring afforded high yields and enantioselectivities (Table 3, entries 1–7). As for the effects of the positions of substituents on the aromatic rings on yield and enantioselectivity, the *para*-substituted substrates afforded the highest enantioselectivity compared with other substrates, whilst *meta*-substituted substrates afforded lower

Table 3. Substrate scope for indole derivatives.

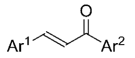


Entry	8	9	Product	Yield [%]	*ee* [%]
1	**8a**	**9a**	**10aa**	86	95
2[a]	**8a**	**9b**	**10ab**	quant.	93
3	**8a**	**9c**	**10ac**	97	91
4	**8a**	**9d**	**10ad**	92	93
5	**8a**	**9e**	**10ae**	89	96
6	**8a**	**9f**	**10af**	68(80[b])	95(92[b])
7[a]	**8a**	**9g**	**10ag**	80	95
8	**8a**	**9h**	**10ah**	87	95
9	**8a**	**9i**	**10ai**	81	85
10	**8a**	**9j**	**10aj**	78	89
11[a]	**8a**	**9k**	**10ak**	92	94
12	**8b**	**9a**	**10ba**	90	85
13	**8c**	**9a**	**10ca**	96	93
14	**8d**	**9a**	**10da**	67	96
15[a]	**8e**	**9a**	**10ea**	88	95
16[a,c]	**8f**	**9a**	**10fa**	84	70

[a] 60 h. [b] *t*BuOMe/THF = 2:1. [c] Ligand **7** was used.



8a: R = H
8b: R = 5-Cl
8c: R = 5-MeO
8d: R = 4-MeO
8e: R = 5-Me
8f: R = 2-Me



9a: Ar^1 = Ph, Ar^2 = Ph
9b: Ar^1 = *p*-ClC_6H_4, Ar^2 = Ph
9c: Ar^1 = *o*-ClC_6H_4, Ar^2 = Ph
9d: Ar^1 = Ph, Ar^2 = *p*-ClC_6H_4
9e: Ar^1 = *p*-FC_6H_4, Ar^2 = Ph
9f: Ar^1 = *p*-$MeOC_6H_4$, Ar^2 = Ph
9g: Ar^1 = Ph, Ar^2 = *p*-$MeOC_6H_4$
9h: Ar^1 = *p*-MeC_6H_4, Ar^2 = Ph
9i: Ar^1 = *m*-MeC_6H_4, Ar^2 = Ph
9j: Ar^1 = *o*-MeC_6H_4, Ar^2 = Ph
9k: Ar^1 = *p*-$MeOC_6H_4$, Ar^2 = *p*-FC_6H_4

enantioselectivity, while maintaining high enantioselectivity (Table 3, entries 8–10). We also examined several indole derivatives (Table 3, entries 12–16). When 5-chloroindole was used, the enantioselectivity decreased slightly but the yield remained high (Table 3, entry 12). In the cases of indoles with electron-donating groups at the 5-positions, the reactions proceeded smoothly to afford the corresponding adducts in high yields and with high enantioselectivities (Table 3, entries 13 and 15). When 4-methoxyindole was used, the yield decreased slightly, but the enantioselectivity was still high (Table 3, entry 14). We then conducted the reaction of 2-methylindole, and found that the reaction proceeded slowly and the enatioselectivity decreased, presumably because of steric hindrance at the 2-position (Table 3, entry 16).

As for the catalyst structure, we assumed the formation of barium phenoxide from barium amide and H_8-binol, based on NMR analyses.[12] A plausible catalytic cycle of this reaction is shown in Figure 2.[13] First, the barium phenoxide deprotonates[14] the nitrogen proton of an indole derivative to afford a chiral barium–indole complex.[15] The complex then reacts with a chalcone derivative enantioselectively to afford an initial Friedel–Crafts adduct. The barium moiety then moves from the oxygen to the nitrogen of the adduct to form a barium amide again. Finally, this species deprotonates the indole to afford the product, along with regeneration of the chiral indole.

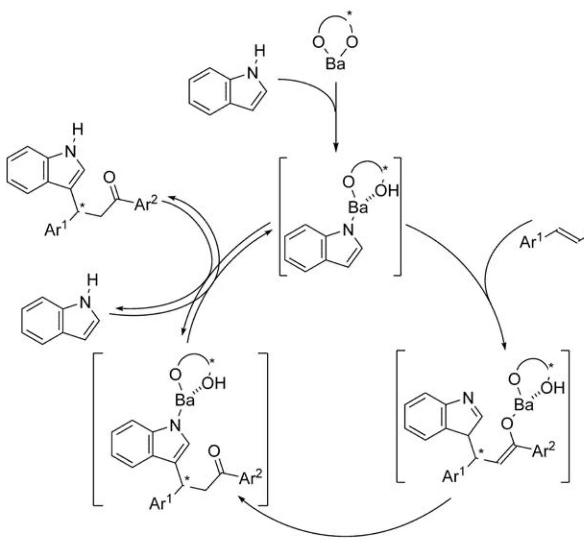


Figure 2. A plausible catalytic cycle.

In conclusion, we have developed novel barium/binol catalysts prepared from a barium amide and a chiral ligand (binol). These catalysts effectively promote the asymmetric Friedel–Crafts–type alkylation reactions of indoles with chalcone derivatives. To the best of our knowledge, this is the first example of Brønsted base catalyzed asymmetric Friedel–Crafts–type reactions of indoles with enones. Further investigations to clarify the precise mechanism of this reaction and the catalyst structure, and to develop other reactions using alkaline earth metal compounds as catalysts, are underway.

Experimental Section

A typical experimental procedure: $[Ba(hmds)_2]$ (0.015 mmol), 3,3′-$(Ph_3Si)_2$-H_8-Binol **4** (0.015 mmol), and M.S. 4 Å (50 mg) were added to a 10 mL flame-dried vial with screw cap under an argon atmosphere. THF (0.25 mL) was then added and the mixture was stirred for 2 h at room temperature. Solutions of indole (**8a**, 0.15 mmol) in *t*BuOMe (1.4 mL) and chalcone (**9a**, 0.18 mmol) in a mixture of THF (0.050 mL) and *t*BuOMe (1.3 mL) were then added successively. The mixture was stirred for 24 h at room temperature and then sat. NH_4Cl (aq.) was added to quench the reaction. After the addition of CH_2Cl_2 (10 mL), the organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2 (15 mL × 2). The organic layers were combined and dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was purified by preparative TLC (cyclohexane/ether = 2:1) to afford the desired product.

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Keywords: alkaline earth metals · alkylation · asymmetric catalysis · barium · calcium

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