Asymmetric Catalysis

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Orthogonal Enantioselectivity Approaches Using Homogeneous and Heterogeneous Catalyst Systems: Friedel–Crafts Alkylation of Indole**

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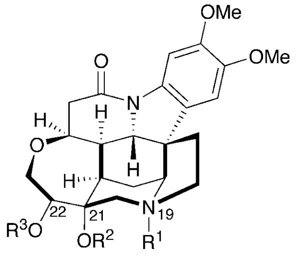
Heterogeneous chiral catalysts have attracted considerable attention from a wide range of scientific disciplines because of their fundamental and practical importance.[1] Recent efforts have focused on the development of more efficient and practical immobilization methods for homogeneous chiral catalysts,[2] and notable success has been achieved by using covalent tethering strategies in asymmetric reactions.[3] Although different conformational preferences between homogeneous and heterogeneous systems are possible, successful orthogonal enantioselectivity using heterogeneous systems—that is, orthogonal to that observed with homogeneous systems—has not yet been achieved.[4] Herein we describe the first example of such selectivity. Our rationale was based on the premise that solid supports, such as zeolites and silicates, would immobilize homogeneous chiral metal complexes, which are generated from rigid multifunctional brucine-derived ligands **1**, through electrostatic interactions.[5] This mode is believed to provide a facile mechanism for inducing conformational changes with immobilized chiral complexes.

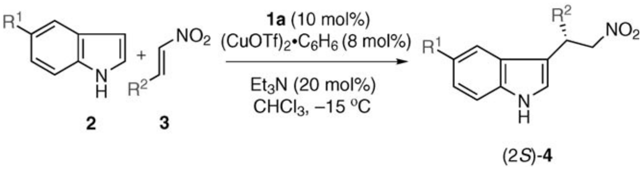


1a: R^1 = lone pair, R^2 = H, R^3 = H
1b: R^1 = Bn, Br^-, R^2 = H, R^3 = H
1c: R^1 = lone pair, R^2 = H, R^3 = Ac
1d: R^1 = lone pair, R^2 = Ac, R^3 = Ac

The asymmetric Friedel–Crafts alkylation of indoles with nitroalkenes has received considerable attention because of the synthetic versatility of chiral indole derivatives in the preparation of biologically active indole alkaloids.[6] Several asymmetric catalyst systems, including organocatalysts[7] and chiral metal complexes,[8] have been developed for this reaction and have utilized dual activation of the nitro group and the indole NH moiety. Encouraged by our previous success[9] in the control of catalyst–substrate arrangements with multiple binding modes of **1** for either metal coordination or hydrogen bonding, we therefore selected the Friedel–Crafts alkylation of indole with nitroalkenes to examine the feasibility of our orthogonal enantioselectivity approach.[10]

We first examined the homogeneous asymmetric Friedel–Crafts alkylation of indole in the presence of 10 mol % of ligand **1** and copper salts (Table 1). Catalytically active chiral copper complexes were generated using 20 mol % of Et_3N in $CHCl_3$ (Table 1, entries 1–3), and $(CuOTf)_2{\cdot}C_6H_6$ was identified as the optimal copper source (Table 1, entry 3) to maximize the enantioselectivity of the formation of (2*S*)-**4**. With the optimal homogeneous reaction conditions in place,

Table 1: Friedel–Crafts alkylation of indoles with the homogeneous catalyst system.[a]



Entry	Metal	R^1	R^2	Yield of (2*S*)-**4** [%][b]	*ee* [%][c]
1	$Cu(OTf)_2$	H	Ph	50	86
2	CuCl	H	Ph	60	92
3	$(CuOTf)_2{\cdot}C_6H_6$	H	Ph	80	93
4	$(CuOTf)_2{\cdot}C_6H_6$	H	4-MeC_6H_4	70	95
5	$(CuOTf)_2{\cdot}C_6H_6$	H	4-ClC_6H_4	71	89
6	$(CuOTf)_2{\cdot}C_6H_6$	H	4-$OMeC_6H_4$	60	82
7	$(CuOTf)_2{\cdot}C_6H_6$	H	1-naphthyl	70	90
8	$(CuOTf)_2{\cdot}C_6H_6$	H	2-naphthyl	65	90
9	$(CuOTf)_2{\cdot}C_6H_6$	H	3-ClC_6H_4	78	91
10	$(CuOTf)_2{\cdot}C_6H_6$	H	*c*-hexyl	55	86
11	$(CuOTf)_2{\cdot}C_6H_6$	Br	Ph	70	95
12	$(CuOTf)_2{\cdot}C_6H_6$	OMe	Ph	82	94

[a] Reaction conditions: indole (0.5 mmol), nitroalkenes (0.5 mmol) in $CHCl_3$ (0.16 M). [b] Yield of isolated products **4** after column chromatography. [c] Determined by HPLC analysis using a chiral stationary phase. The absolute configuration of products **4** were determined by comparison of HPLC data with authentic samples. Tf = trifluoromethanesulfonyl.

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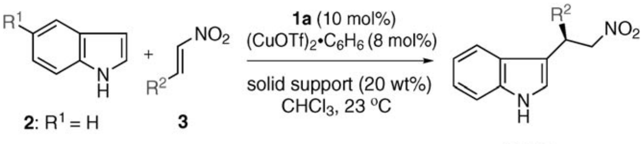
we investigated the reaction scope using various nitroalkenes and indole derivatives (Table 1, entries 4–12). High enantioselectivities were achieved for aromatic nitroalkenes with different electronic (Table 1, entries 4–6) and steric effects (Table 1, entries 7–9). Moreover, aliphatic nitroalkene (Table 1, entry 10) and 5-substituted indoles (Table 1, entries 11 and 12) were well tolerated under our optimized homogeneous conditions, thus demonstrating the high level of enantiocontrol that is possible with this asymmetric catalyst–substrate arrangement.

We then turned our attention to the corresponding heterogeneous catalyst system. Thus, solid supports were incorporated by mixing with $(CuOTf)_2{\cdot}C_6H_6$ and ligand **1** in $CHCl_3$ for 4 hours at 0 °C. Indeed, using such a simple method of immobilization[11] the preparation of (2*R*)-**4** was possible; and here we postulate the potential ionic interactions between trifluoromethanesulfonate and the OH groups of the solid supports as well as our ligand. Next, we examined various solid supports to further optimize the stereoselectivity of the reaction (Table 2). The use of silica gel (32–63 μm) and Celite generally provided < 20 % conversion at 0 °C with 20–30 % *ee*.[12] Although a modest yield of (2*R*)-**4** was observed even at ambient temperature (Table 2, entry 1), use of other readily available solid supports significantly enhanced the reactivity (Table 2, entries 2–10). Among the powdered zeolite solid supports screened,[13] 4 Å molecular sieve (M.S.), 13X M.S., and Na-Y zeolite provided (2*R*)-**4** in 62–68 % ee (Table 2, entries 3, 5, and 7). In addition, the use of neutral alumina as a solid support delivered good levels of reactivity and enantioselectivity (Table 2, entry 10). Our preliminary investigation into the substrate scope of the heterogeneous catalyst system revealed that highly orthogonal catalyst–substrate arrangements are possible with various aromatic nitroalkenes to give the Friedel–Crafts alkylation products, (2*R*)-**4**—which has the opposite configuration to that observed in the homogeneous system—in good yields and enantioselectivities (Table 2, entries 11–15).[14]

Table 2: Friedel–Crafts alkylation of indole with the heterogeneous catalyst system.



2: $R^1 = H$ **3** (2*R*)-**4**

Entry	Solid support	R^2	Yield of (2*R*)-**4** [%][b]	*ee* [%][c]
1	SiO_2	Ph	50	24
2	3 Å M.S.	Ph	80	30
3	4 Å M.S.	Ph	95 (67)[d]	68 (98)[d]
4	5 Å M.S.	Ph	80	20
5	13X M.S.	Ph	75	63
6	NH_4-Y zeolite	Ph	60	42
7	Na-Y zeolite	Ph	75	62
8	Al_2O_3, basic	Ph	80	40
9	Al_2O_3, acidic	Ph	80	40
10	Al_2O_3, neutral	Ph	85	63
11	4 Å M.S.	4-MeC_6H_4	88	78
12	4 Å M.S.	4-ClC_6H_4	90	82
13	4 Å M.S.	4-$OMeC_6H_4$	72	84
14	4 Å M.S.	1-naphthyl	88	84
15	4 Å M.S.	2-naphthyl	81	82

[a] Reaction conditions: indole (0.5 mmol), nitroalkenes (0.75 mmol) in $CHCl_3$ (0.16 M). [b] Yield of isolated products **4** after column chromatography. [c] Determined by HPLC analysis using a chiral stationary phase. The absolute configuration of products **4** were determined by comparison of HPLC data with authentic samples. [d] After a single recrystallization.

While further investigation is needed to formulate the precise relationship of the chiral outcome between our homogeneous and heterogeneous catalyst systems, our results are consistent with the catalyst–substrate orientations shown in Figure 1 a (the homogeneous system) and Figure 1 b (the heterogeneous system), respectively. Consistent with this proposal is our observation of the absence of hydrogen-bonding interactions in the homogeneous system and the presence of such effects in the heterogeneous case. Thus, in the presence of 20 mol % *i*PrOH the homogeneous catalyst system gave the Friedel–Crafts product (2*S*)-**4** ($R^2 = Ph$) in 60 % yield and 87 % *ee*, while the corresponding heterogeneous system gave (2*R*)-**4** ($R^2 = Ph$) in 50 % yield and 20 % *ee*. The heterogeneity of our catalysts was confirmed by successful asymmetric reactions using isolated solid catalysts: the in situ generated heterogeneous catalysts were filtered, washed with excess of $CHCl_3$, and dried under high vacuum. Upon use of such isolated heterogeneous catalysts, the Friedel–Crafts product (2*R*)-**4** ($R^2 = Ph$) was obtained in 80 % yield, but with a diminished enantioselectivity in 40 % *ee*. Meanwhile, the in situ generated heterogeneous catalysts gave (2*R*)-**4a** ($R^2 = Ph$) in 80–90 % yield and 63–68 % *ee*. We reasoned the lower enantioselectivities by the

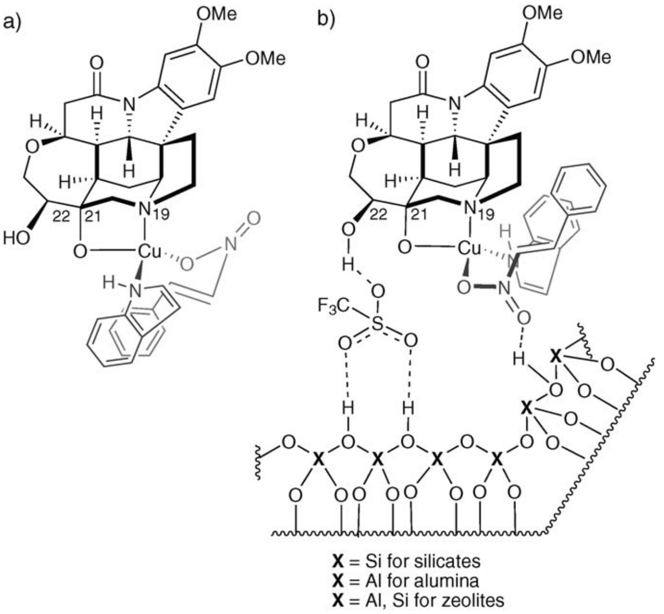


Figure 1. Proposed stereochemical models for a) homogeneous, and b) heterogeneous systems.

isolated heterogeneous catalysts might result from the possible leaching of metal, triflate, and ligand upon washing and drying. Further insight into our proposed stereochemical model in Figure 1 b was also obtained upon the use of catalysts derived from CuCl or Cu(OTf)$_2$ that were supported on 4 Å M.S., where product (2*S*)-**4** was obtained in 30 % yield and 2 % *ee*, and (2*R*)-**4** in 85 % yield and 35 % *ee*, respectively. Our preliminary studies into the potential roles of the C21–OH and C22–OH in our ligand **1 a** reveal that both alcohol moieties are critical for the generation of catalytically active species. Thus, use of the modified ligands **1 b–d** (having either the nitrogen atom or the C21–OH/C22–OH group protected), significantly lower enantioselectivities were observed.

In summary, we have developed a system that gives complementary enantioselectivities under homogeneous and heterogeneous conditions, respectively for the catalytic asymmetric Friedel–Crafts alkylation of indole. We note that the heterogeneous system is easily achieved by the addition of a suitable solid support to the reaction mixture. The study of the scope of this reaction and the extension of this approach to other carbon–carbon bond-forming reactions is currently underway and our results will be reported in due course.

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[12] The reactions carried out at −15 °C have been investigated in the presence of various solid supports including 4 Å M.S. and neutral alumina. The results were generally identical to the reactions at 0 °C; $<$ 50 % yields with 10–30 % *ee*, however on occasions less than 10 % *ee* were observed for the products (2*R*)-**4**. Presently, we reason that the inconsistent enantioselectivity of reactions at −15 °C represents the typical biphasic nature of reactions with our heterogeneous catalyst system. We thank one of the referees for pointing out the role of temperature on the heterogeneous system.

[13] The use of beads/pellet solid supports resulted in catalysts with significantly lower enantioselectivities.

[14] No difference in reactivity and enantioselectivity was observed in reactions involving 4 Å M.S. and neutral alumina as the solid supports. Other aryl, alkyl nitroalkenes, and indole derivatives provided (2*R*)-**4** in 60–90 % yields and 50–60 % *ee*. A full account will be published elsewhere.