Asymmetric Allylations

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Indium-Mediated Asymmetric Allylation of Acylhydrazones Using a Chiral Urea Catalyst**

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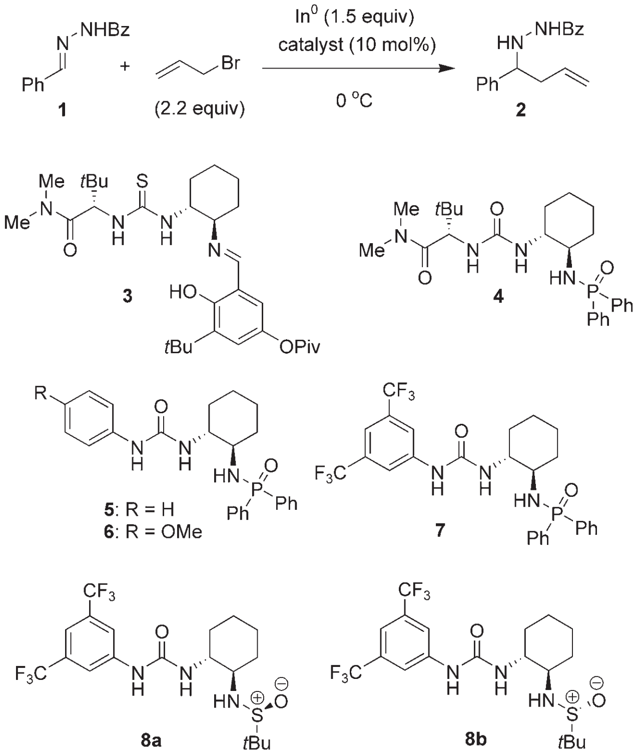
Imine allylation represents a powerful strategy for the synthesis of enantioenriched homoallylic amines, and considerable effort has been devoted to devising enantioselective versions of this transformation.[1–3] In situ generated allylindium reagents are attractive candidates as nucleophilic partners in C=N allylation reactions because of their mildness, functional group tolerance, and low toxicity.[4] While several chiral-auxiliary-based methods for stereoselective allylindium addition to C–N double bonds have been developed,[5] only a single catalytic asymmetric variant has been identified thus far.[6] In that example, an organic catalyst derived from binol was shown to catalyze hydrazone allylation in moderate yield and enantioselectivitiy (≈70–85% *ee*), with improved results attainable when stoichiometric quantities of the binol derivative were employed (84–97% *ee*).

Chiral urea and thiourea derivatives have proven extraordinarily useful as catalysts for the enantioselective activation of imine and carbonyl derivatives toward nucleophilic addition.[7] However, despite the extensive application of these organic catalysts in asymmetric synthesis, their use in conjunction with organometallic reagents has yet to be developed. We sought to take advantage of the modular nature of these catalysts by incorporating a Lewis basic group in proximity to the urea moiety in order to promote the addition of organometallic reagents to C=N bonds through dual activation.[8,9] We report here the successful evolution of this strategy, with the discovery of a new sulfinamide-urea catalyst that promotes the indium-mediated allylation of acylhydrazones with high levels of enantioselectivity and yield.

The first-generation thiourea catalyst **3** (Scheme 1) was found to mediate the addition of allylindium reagent to *N*-acylhydrazone **1** in 79% yield but with only 38% *ee* (Table 1). Replacement of the imine portion of catalyst **3** with a phosphinic amide (**4**) yielded almost racemic product; however, when the *tert*-leucine portion of the catalyst was replaced by a phenyl group (**5**), moderate enantioselectivity was restored. We were intrigued by the promising results attained with such a simple bifunctional catalyst, so we pursued further optimization of this scaffold. The presence of an electron-donating group on the aromatic ring of the catalyst (**6**) resulted in a decrease in enantioselectivity to 24% *ee*. In contrast, improving the hydrogen-bond-donor ability of the catalyst by introducing electron-withdrawing groups on the aromatic ring, as in **7**, led to significant improvements in enantioselectivity. Replacing the phosphinic amide with a *tert*-



Scheme 1. Model allylation reaction and representative catalysts. Bz: benzoyl; Piv: pivaloyl.

Table 1: Catalyst optimization studies for the enantioselective allylation of **1**.

Catalyst	Yield [%][a]	*ee* [%]
3	79	38
4	52	−2
5	91	30
6	82	24
7	90	52
8a	75	26
8b	87	91

[a] Determined by HPLC by integration against an internal standard.

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butyl sulfinamide functionality had a dramatic impact on catalyst performance.[10] The diastereomeric sulfinamides **8a** and **8b** promoted the allylation of **1** with 26% and 91% *ee*, respectively. Crystallographic analysis of **8b** revealed an intramolecular hydrogen bond between the NH group of the sulfinamide and the C=O function of the urea in the solid-state structure (Figure 1). This hydrogen bond may serve to increase the Lewis acidity of the urea functionality and/or to rigidify the catalyst structure.

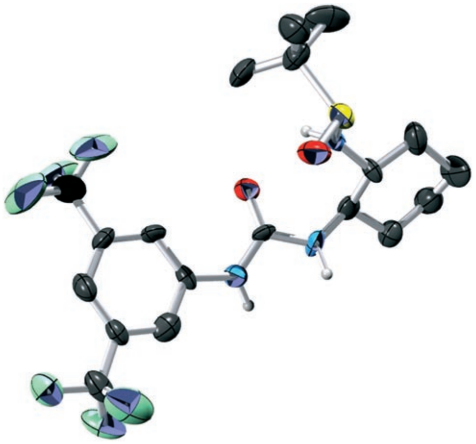


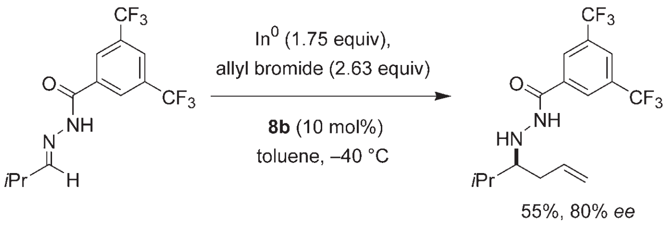
Figure 1. ORTEP view (50% probability level) of the solid-state structure of catalyst **8b** (O red, S yellow, F green, N blue, C gray).

The scope of the indium-mediated allylation was developed with optimized catalyst **8b** (Table 2). Acylhydrazones derived from aromatic or heteroaromatic aldehydes were found to undergo the allylation with both high *ee* and yield.[11] Substrates bearing *ortho* substituents on the aromatic ring were particularly effective, with enantioselectivities between 93–95% *ee* observed (Table 2, entries 6–8). Aryl halides were compatible with the reaction conditions (Table 2, entries 2 and 6). Acylhydrazones derived from aliphatic aldehydes underwent allylation with substantially lower *ee* values (generally less than 50% *ee*); however, measurable improvements were attained with substrates bearing electron-deficient *N*-acyl groups (Scheme 2).

Table 2: Asymmetric allylation of acylhydrazones catalyzed by **8b**.

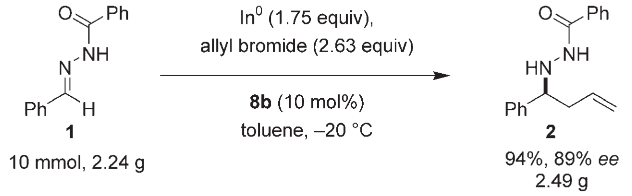
Entry	R	Yield [%]	*ee* [%]
1	C_6H_5[a]	87	92
2	*p*-ClC_6H_4[b]	83	92
3	2-furyl[a]	90	87
4	2-thienyl[a]	82 (93)[c]	93 (87)[c]
5	*p*-$(CO_2CH_3)C_6H_4$[a]	92	76
6	*o*-BrC_6H_4[a]	78 (89)[c]	93 (90)[c]
7	*o*-$CH_3C_6H_4$[a]	89 (98)[c]	95 (94)[c]
8	1-naphthyl[a]	89 (99)[c]	95 (92)[c]
9	*p*-$(CH_3O)C_6H_4$[b]	79	93

[a] Conditions: **8b** (10 mol%), −20°C, toluene, indium powder (1.75 equiv), allyl bromide (2.63 equiv). [b] Conditions: **8b** (10 mol%), −20°C, toluene, indium powder (1.35 equiv), allyl bromide (2.00 equiv). [c] Yields and *ee* values in parentheses correspond to results obtained using higher stir rates (see Supporting Information for experimental details).



Scheme 2. Allylation of an aliphatic acylhydrazone catalyzed by **8b**.

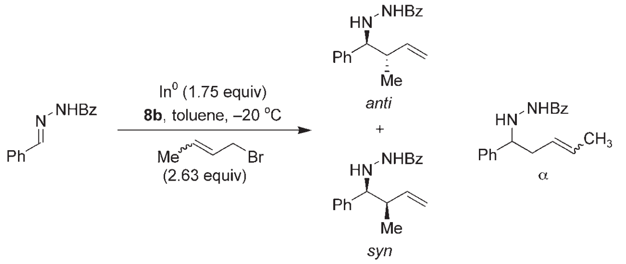
During the course of these studies, we observed that the generation of the allylindium species was dependent on both the batch of indium and the rate of stirring. When the stir rate was high, the formation of the allylindium was rapid, resulting in complete consumption of the indium metal. In these cases, slightly lower enantioselectivities but increased yields were obtained in acylhydrazone allylations (Table 2, entries 4 and 6–8; values in parentheses). To address whether this phenomenon might lead to problems upon reaction scale-up, the allylation was performed on 10 mmol of **1**. This reaction was found to proceed with 89% *ee* and 94% yield, only a minor deviation from the aforementioned results of 87% yield and 92% *ee* obtained on a 1-mmol scale (Scheme 3 vs entry 1, Table 2).



Scheme 3. Gram-scale allylation of hydrazone **1**.

Enantioselective crotylation reactions were also examined using catalyst **8b** (Table 3). The *syn* and *anti* diastereomeric products were generated with high *ee* values but with

Table 3: Asymmetric crotylation of acylhydrazone catalyzed by **8b**.



Substrate	Yield [%]	Product ratio *anti*	*syn*	α
(*E*)-crotyl bromide	70	1.10 (90% *ee*)	1.00 (85% *ee*)	0.40 (>90% *ee*)
(*Z*)-crotyl bromide	71	1.57 (95% *ee*)	1.00 (86% *ee*)	0.38 (90% *ee*)

very poor diastereoselectivities. It is likely that the allylindium reagent is not geometrically stable,[12] as the reactions of both (*Z*)- and (*E*)-crotyl bromide afforded similar product mixtures.

The discovery of catalyst **8b**, which bears both a urea and sulfinamide functionality, has led to the first application of urea catalysis for highly enantioselective additions of organometallic reagents. The bifunctional nature of the catalyst, in which a hydrogen-bond donor and a Lewis base are positioned properly and in close proximity, was found to be crucial for the attainment of high *ee* values. The utility of **8b** and related urea derivatives in other synthetically interesting nucleophile–electrophile reactions is under current investigation.

Experimental Section

General procedure for the allylation of acylhydrazones catalyzed by **8b**: Benzoic acid *N'*-[1-(2-bromo-phenyl)-but-3-enyl]-hydrazide (Table 2, entry 6). 2-bromobenzoic acid benzylidene hydrazide (303 mg, 1.00 mmol), indium powder (200 mg, 1.74 mmol), and **8b** (47 mg, 0.10 mmol) were added to a 20-mL scintillation vial. The vial was purged with N_2 for approximately 20 min, and then toluene (10 mL) was added. The reaction mixture was cooled to −78 °C, and then allyl bromide was added (228 μL, 2.63 mmol; purified through an alumina plug immediately prior to use). The reaction mixture was stirred vigorously at −20 °C for 19 h, then removed from the cold bath, and immediately quenched with 1 N HCl (4 mL) at room temperature. The reaction mixture was diluted with ethyl acetate (25 mL) and 0.67 N NaOH (60 mL). The aqueous layer was extracted with ethyl acetate (2 × 25 mL), and the organic layer was dried with Na_2SO_4, filtered, and concentrated. The resulting residue was purified by chromatography on silica gel (20 % ethyl acetate/hexanes) to afford a white solid (270 mg, 0.78 mmol, 78 % yield). The enantiomeric excess was determined to be 93 % by SFC using a commercial chiral stationary phase (Chiralpak OD-H, 15 % methanol/CO_2, 4 mL min^{-1-1}, 30 °C, 254 nm; t_r(minor): 2.42 min, t_r(major): 2.77 min; $[\alpha] = -78$ deg cm^3 g^{-1} dm^{-1} ($c = 0.730$ g cm^{-3}, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.67$ (dd, $J = 1.8$, 7.7, 1 H), 7.62–7.58 (m, 2 H), 7.54 (dd, $J = 1.1$, 7.7, 1 H), 7.50–7.40 (m, 2 H), 7.39–7.31 (m, 3 H), 7.13 (dt, 1 H, $J = 1.8$, 8.1), 5.97–5.88 (m, 1 H), 5.31 (dd, $J = 2.6$, 7.0, 1 H), 5.21 (dd, $J = 2.1$, 17.2, 1 H), 5.17 (d, $J = 10.6$, 1 H), 5.8–5.6 (m, 1 H), 2.6–2.5 (m, 1 H), 2.40 ppm (app dt, $J = 8.4$, 14.3, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 167.2$, 140.7, 134.0, 133.0, 132.8, 131.8, 128.8, 128.6, 128.3, 127.7, 126.8, 124.5, 118.4, 62.1, 39.3 ppm. IR (NaCl): $\tilde{\nu} =$ 3282.7 (br), 3064.7, 1638.4 9 (s), 1467.7 cm^{-1}. ESI *m/z* [M+1]: 345.1 and 347.1.

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[10] Catalyst **8b** was synthesized using commercially available racemic *tert*-butyl sulfinyl chloride (Aldrich). The thiourea variant of **8b** promoted the model reaction with decreased enantioselectivity, presumably owing to competitive coordination of the thiourea functionality to the allylindium species.

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