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Indium-Mediated Catalytic Enantioselective Allylation of *N*-Benzoylhydrazones Using a Protonated Chiral Amine

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Abstract: A catalytic enantioselective indium-mediated allylation of *N*-benzoylhydrazones in conjunction with a protonated chiral amine affording enantioenriched homoallylic amines with an extremely high level of enantioselectivity and chemical yield was developed.

Allylation of imine derivatives is an important tool for carbon−carbon bond formation and the introduction of amino groups into carbon skeletons. The resulting homoallylic amine products are highly versatile intermediates, are useful synthetic building blocks, and are biologically active compounds.[1] As such, a great deal of effort has been devoted to developing synthetic methods for their synthesis.[2] Addition of allylic metal nucleophiles to C═N bonds is a straightforward strategy for the synthesis of homoallylic amines. Strong organometallic reagents are required for the nucleophilic addition of imine derivatives due to their low reactivity. The strong basic property of organometallic reagents limits their utility as nucleophilic allylation reagents for base-sensitive imine derivatives. Among the various allylic metal reagents, allylindium reagents are promising for this purpose as they display low basicity, high chemoselectivity, and low toxicity.[3]

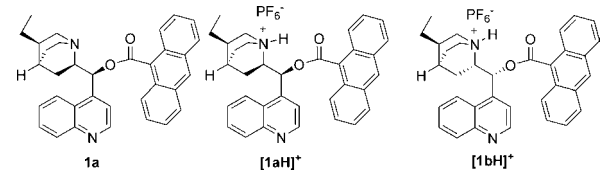
Asymmetric variants of indium-mediated allylation of imine derivatives are problematic since the low heterophilicities of allylindium reagents with a chiral ligand are not able to provide a chiral environment suitable for chiral induction. Asymmetric allylation of imine derivatives with allylindium reagents has mainly relied on chiral auxiliaries in the imine derivatives.[4,5] On the other hand, examples of catalytic asymmetric indium-mediated allylation of imine derivatives are very rare. Cook and Lloyd-Jones[6a,b] as well as Jacobsen[6c] reported indium-mediated enantioselective allylation of *N*-acylhydrazones using binol derivatives and chiral ureas, respectively, with low catalyst loading at low temperature. These reagents gave high enantioselectivity with aryl aldehyde-derived hydrazones bearing an ortho substituent, while aryl aldehyde-derived hydrazones possessing a para substituent afforded lower ee values.

Here, we report a catalytic enantioselective indium-mediated allylation of *N*-benzoylhydrazones in conjunction with a protonated chiral amine that gives rise to enantioenriched homoallylic amines with extremely high levels of enantioselectivity and chemical yield at ambient temperature. To the best of our knowledge, the levels of enantioselectivity and substrate generality reported herein are the highest among those previously reported.

Protonated chiral reagents have proved to be extremely useful as chiral promoters for enantioselective reactions.[7] We assumed that low-basicity indium reagents might permit the use of protonated chiral amines as chiral promoters in indium-mediated allylation of imine derivatives.

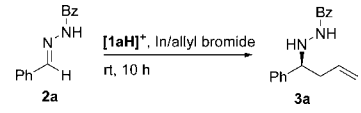
In an initial experiment, the benzaldehyde-derived *N*-benzoylhydrazone **2a** was reacted with allylindium generated *in situ* in MeOH in the presence of 0.1 equiv of the protonated chiral amine **[1aH]**$^+$. The reaction proceeded smoothly at room temperature, affording the addition adduct **3a** in an 89% chemical yield.

Scheme 1



However, the enantioselectivity of the reaction was very poor (Table 1, entry 1). With an increase in the amount of **[1aH]**$^+$ under otherwise identical conditions, the enantioselectivity of the reaction improved dramatically up to 99% ee (entries 2−3). The nonlinear increase in ee values are attributed to deprotonation of some **[1aH]**$^+$ by allyl indium species in competition with catalytic turnover by **[1aH]**$^+$. Further investigation into catalyst loading revealed that the use of as little as 0.3 equiv of **[1aH]**$^+$ was sufficient to attain high levels of enantioselectivity and chemical yield (entry 4). Decreasing amounts of allyl bromide and indium afforded the product in lower yield while attaining high enantioselectivity, suggesting a catalytic turnover (entries 5−6). A control experiment was carried out with the chiral amine **1a**, providing a racemic

Table 1. Enantioselective Allylation of **2a** under Various Conditions



Entry	[1aH]$^+$ (equiv)	Allyl bromide (equiv)	In (equiv)	Solvent	Yield (%)[a]	ee (%)[b]
1	0.1	3	3	MeOH	89	8
2	0.2	3	3	MeOH	90	30
3	0.3	3	3	MeOH	94	99
4	0.5	3	3	MeOH	93	99
5	0.3	2	2	MeOH	84	99
6	0.3	1.5	1.5	MeOH	77	98
7[c]	1.0	3	3	MeOH	83	0
8[d]	0.3	3	3	MeOH	81	0
9	0.3	3	3	THF	38	95
10	0.3	3	3	Toluene	88	38
11	0.3	3	3	CH_3CN	71	47
12	0.3	3	3	CH_2Cl_2	55	69
13	0.3	3	3	$C_2H_4Cl_2$	57	67

[a] Isolated yield. [b] Enantiomeric excess was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA) with hexane−isopropanol as solvent. [c] **1a** was used instead of **[1aH]**$^+$. [d] **1a** and $Et_3N^+HPF_6^-$ were used instead of **[1aH]**$^+$.

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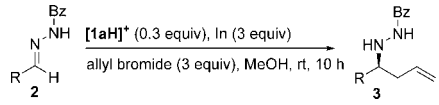
Table 2. Enantioselective Allylation of *N*-Benzoylhydrazones with **[1aH]**$^+$



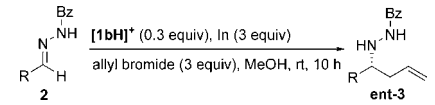
Entry	Substrate	R	Product	Yield (%)[a]	ee (%)[b]
1	**2b**	4-F-Ph-	**3b**	94	99 (*S*)
2	**2c**	4-Cl-Ph-	**3c**	92	98 (*S*)
3	**2d**	4-NO_2-Ph-	**3d**	92	99 (*S*)
4	**2e**	4-MeC(O)-Ph-	**3e**	90	99 (*S*)
5	**2f**	4-MeC(O)NH-Ph-	**3f**	90	99 (*S*)
6	**2g**	4-Et-Ph-	**3g**	88	99 (*S*)
7	**2h**	4-OMe-Ph-	**3h**	90	99 (*S*)
8	**2i**	4-OH-Ph-	**3i**	86	99 (*S*)
9	**2j**	3-Cl-Ph-	**3j**	90	99 (*S*)
10	**2k**	2-Br-Ph-	**3k**	90	99 (*S*)
11	**2l**	2-OMe-Ph-	**3l**	92	99 (S)
12	**2m**	$PhCH_2CH_2$-	**3m**	95	86 (*R*)
13	**2n**	$CH_3(CH_2)_6$-	**3n**	80	80 (*R*)

[a] Isolated yield. [b] Enantiomeric excess was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA) with hexane−isopropanol as the solvent.

mixture in 83% yield (entry 7). A reaction performed in the presence of $Et_3N^+HPF_6^-$ and **1a** afforded a racemic mixture (entry 8). These results and NMR evidence indicate that the promoter **[1aH]**$^+$ might interact with *N*-benzoylhydrazone via hydrogen bonding and $\pi-\pi$ interaction, providing a chiral environment, while the allylindium nucleophile generated *in situ* attacks at the *Si*-face of the C=N bond, resulting in an allylated adduct with high enantioselectivity (see Supporting Information). The addition of allylindium to the *N*-benzoylhydrazone **2a** in THF afforded the product **3a** with a high selectivity of 95% ee, but only in 38% yield (entry 9). Other organic solvents such as toluene, acetonitrile, dichloromethane, and 1,2-dichloroethane compared to methanol were less effective in terms of chemical yield and enantioselectivity (entries 10−13).

We evaluated the scope of the reaction with a wide range of *N*-benzoylhydrazones derived from aldehydes under optimal conditions, and the results are summarized in Table 2. Reactions with aryl aldehyde-derived *N*-benzoylhydrazones with either an ortho substituent or a para/meta substituent proceeded smoothly at ambient temperature in the presence of the protonated chiral amine **[1aH]**$^+$, affording allylated products in high yields with extremely high enantioselectivities, demonstrating the generality of the reaction (entries 1−11). *N*-Benzoylhydrazones derived from aliphatic aldehydes underwent allylation at room temperature with relatively lower ee values and yields (entries 12−13). Functional groups such as chloro, bromo, nitro, ketone, amide, and methoxy were intact under conditions. Interestingly, the labile phenolic functionality did not require protection.

Table 3. Enantioselective Allylation of *N*-Benzoylhydrazones with **[1bH]**$^+$



Entry	Substrate	R	Product	Yield (%)[a]	ee (%)[b]
1	**2a**	Ph	**ent-3a**	92	99 (*R*)
2	**2b**	4-F-Ph-	**ent-3b**	90	99 (*R*)
3	**2d**	4-NO_2-Ph-	**ent-3d**	89	99 (*R*)
4	**2e**	4-MeC(O)-Ph-	**ent-3e**	90	99 (*R*)
5	**2g**	4-Et-Ph-	**ent-3g**	90	96 (*R*)
6	**2h**	4-OMe-Ph-	**ent-3h**	88	99 (*R*)
7	**2n**	$CH_3(CH_2)_6$-	**ent-3n**	81	78 (*S*)

[a] Isolated yield. [b] Enantiomeric excess was determined by HPLC analysis using a chiral column (Daicel Chiralpak IA) with hexane−isopropanol as the solvent.

Enantioselective allylation of *N*-benzoylhydrazones with the chiral promoter **[1bH]**$^+$, the pseudoenantiomer of **[1aH]**$^+$, also underwent the reactions efficiently and provided allylated products with reversed chiralities (Table 3). The allylation of *N*-benzoylhydrazones with **[1bH]**$^+$ was comparable to that of **[1aH]**$^+$ in terms of chemical yield and enantioselectivity. The two promoters **[1aH]**$^+$ and **[1bH]**$^+$, which are salts, were readily recovered after a simple aqueous workup in more than 95% yield. The absolute configuration of **3c** was determined to be *S* by comparing the optical rotation with that reported in the literature.[8] The absolute configurations of all other allylated products were determined in reference to **3c**.

In conclusion, we developed an enantioselective allylation of *N*-benzoylhydrazones in the presence of a protonated chiral amine affording enantioenriched homoallylic amines in high yields, with extremely high enantioselectivities. To the best of our knowledge, this is the first example of employing a protonated chiral amine with organometallic reagents. The method presented here has several features including operational simplicity, generality of substrates, low cost, and reuse of chiral promoters. Further work to expand the scope of the reaction is underway.

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Supporting Information Available: Experimental procedures, compound characterization, NMR spectra, and HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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