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A One-Pot Asymmetric Synthesis of Homoallylic Amines *via* Indium-Mediated Allylation of Hydrazones

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Homoallylic amines are an important structural element of natural products and valuable synthetic building blocks in organic syntheses.[1] The nucleophilic addition of organometallic reagents to the C=N bond is a straightforward method for the synthesis of homoallylic amines.[2] However, due to the low reactivity of imines toward nucleophiles, more reactive nucleophiles are required for the addition reaction. Thus, there are some drawbacks to such methods including aza-enolization[3] and competitive formation of side products.[4] Some organometallic reagents such as allylsilanes[5] and allylboronates[6] have been successfully employed for the formation of homoallylic amines. Employing allylindium reagents for the synthesis of homoallylic amines is attractive as indium reagents have low toxicity and low basicity and are stable to moisture and air.

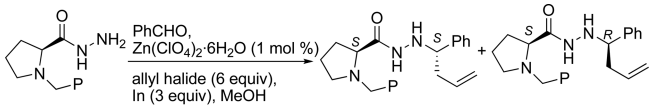
Recently, various methodologies for the enantioselective allylation of imines in the presence of chiral ligands have been developed.[7] However, the synthesis of chiral ligands is frequently difficult and requires multi-step synthesis. Diastereoselective allylation of imines bearing a chiral auxiliary is a reliable and efficient method for the synthesis of optically pure homoallylic amines. Several chiral imines have been developed for indium-mediated allylations. Since Loh and co-workers' report,[8] chiral *N*-aliphatic imines, which are derived from amino acid derivatives such as (*S*)-valinol[9] and (*R*)-phenylglycinol,[10] have been used for diastereoselective allylations. Yus and co-workers developed a method for the synthesis of optically pure homoallylic amines *via* chiral *N*-sulfinyl imines.[11] Chiral imines have also been widely employed. Among the chiral imine derivatives, chiral hydrazones are the choice of chiral auxiliary due to advantages that include ease of preparation, high reactivity, and high selectivity. Although (*S*)-1-amino-2-methoxymethylpyrrolidine[12] and (*S*)-4-phenylmethyl-oxazolidin-2-one-derived hydrazones[13] have been employed for indium-mediated diastereoselective allylations, these auxiliaries have some drawbacks such as the use of expensive and toxic reagents and multiple steps for their synthesis.

Herein, we wish to report a one-pot stereoselective allylation of aldimines bearing an *L*-proline moiety to afford chiral homoallylic amine derivatives in a highly stereoselective manner. A one-pot asymmetric reaction that involves aldehydes, chiral hydrazides, and an allyindium species is attractive since the reaction is simple and easy to perform as well as being both eco-friendly and rapid.[14]

Benzaldehyde was chosen as a model substrate, and $Zn(ClO_4)_2{\cdot}6H_2O$ was chosen as the catalyst since it is known to be an efficient promoter for the formation of hydrazones.[15] We examined the one-pot allylation with benzaldehyde, a chiral *L*-proline-derived hydrazide, allyl bromide and indium in the presence of 1 mol % $Zn(ClO_4)_2$ in methanol at room temperature. The reaction proceeded smoothly and was complete in 2 h affording 87% of the allylated product with a 60:40 dr (Table 1, entry 1). The reaction rate was much faster than that of the reaction performed without a catalyst (15 h).[15] This result suggests that $Zn(ClO_4)_2{\cdot}6H_2O$ promotes the formation of hydrazone as well as assists in the allylation of the resulting hydrazone. The same reaction performed using allyl iodide instead of allyl bromide at room temperature gave an 85% chemical yield of the product with no stereoselectivity (entry 3). However, the reaction time was shortened. As the reaction temperature was lowered, the stereoselectivity increased. When performed at –20 °C, the reaction was complete in 10 h with high diastereoselectivity (entry 5). Upon changing from methanol, a polar solvent, to nonpolar solvents such as toluene, dichloromethane, or chloroform, the reaction did not proceed at –20 °C.

With optimized reaction conditions in hand, we investigated the scope of the reaction with various aldehydes. The results are presented in Table 2. The reaction with aromatic aldehydes that were substituted with an electron-donating

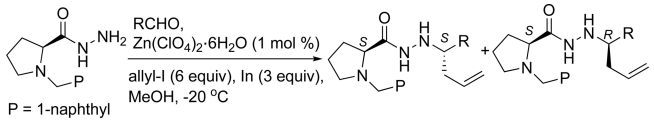
Table 1. Screening the reaction conditions



Entry	Allyl-X	Temp (°C)	Time (h)[a]	Yield (%)[b]	Dr (*S*,*S*: *S*,*R*)[c]
1	Br	rt	2	87	60:40
2	Br	0	4	82	65:35
3	I	rt	0.5	85	53:47
4	I	0	1	85	60:40
5	I	-20	10	85	91:9

[a]Reaction time for the allylation. [b]Isolated yields. [c]Diastereomeric ratio was determined by ^{1}H NMR spectroscopy.

Table 2. Synthesis of homoallylic amine derivatives from various aldehydes



Entry	R	Time (h)[a]	Yield (%)[b]	Dr (*S*,*S*:*S*,*R*)[c]
1	Ph	10	85	91:9
2	4-MeO-C_6H_4	10	82	72:28
3	2,3,4-Tri-MeO-C_6H_2	6	80	73:17
4	2,3,4-Tri-MeO-C_6H_2	72	80	81:19[d]
5	2-Me-C_6H_4	10	86	83:17
6	4-O_2N-C_6H_4	10	80	85:15
7	4-Cl-C_6H_4	10	86	72:28
8	2-Br-C_6H_4	24	85	75:25[d]
9	2-F-C_6H_4	48	86	76:24[d]
10	^{t}Bu	3	89	55:45

[a]Reaction time for the allylation. [b]Isolated yield. [c]Diastereomeric ratio was determined by ^{1}H NMR spectroscopy. [d]The reaction was performed at −30 °C.

group afforded the desired products in high yields and high diastereoselectivities (entries 2-5). Aromatic aldehydes with electron-withdrawing groups also gave the desired products in high yields and moderate to high diasteroselectivities (entries 6-9). The reaction with aromatic aldehydes with a substituent at the sterically hindered *ortho* position produced the corresponding allylated product in high yields and high diastereoselectivities (entries 5, 8 and 9). Sterically hindered *tert*-butyl aldehyde gave the desired product in a high yield and poor diastereoselectivity (entry 10). A reaction with allylindium reagents prepared at room temperature was performed, showing no difference from the Barbier type reaction. The configurations of the allylated products were confirmed by comparing optical rotations with literature values after cleavage of the auxiliary *N*-*N* bond with SmI_2.[13]

In summary, a diastereoselective, one-pot indium-mediated addition reaction to *L*-proline-derived hydrazones in the presence of $Zn(ClO_4)_2{\cdot}6H_2O$ has been developed. The method affords an efficient reaction for the synthesis of optically pure homoallylic amines in high yields and diastereomeric ratios up to 91:9.

General Procedure for *o*-Toylaldehyde. A solution of aldehyde (75 μL, 0.65 mmol), chiral hydrazone (200 mg, 0.65 mmol), and $Zn(ClO_4)_2{\cdot}6H_2O$ (4 mg, 1.0×10^{-2} mmol) in methanol (5 mL) was stirred at room temperature. After completion of the reaction (confirmed by TLC), to the above solution were added indium powder (225 mg, 1.95 mmol) and allyl iodide (0.36 mL, 3.90 mmol) at −20 °C. The reaction was quenched with 1 M HCl and extracted with ethyl acetate. The organic phase was separated, dried, and further purified by flash column chromatography over silica gel (*n*-hexane/EtOAc, 7:3) to afford the desired addition products. Syrup; $[\alpha]_D^{20} = -9.4$ (c 0.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.50-1.75 (m, 3H), 1.75-1.90 (m, 1H), 2.12 (s, 3H), 2.20-2.40 (m, 3H), 2.68-2.90 (m, 1H), 3.32 (dd, 1H, J = 5.0, 10.0 Hz), 3.80-3.95 (m, 2H), 4.12-4.24 (m, 1H), 4.74 (brs, 1H), 4.99-5.15 (m, 2H), 5.55-5.75 (m, 1H), 6.74 (d, 1H, J = 7.6 Hz), 6.78-6.89 (m, 1H), 6.95-7.17 (m, 2H), 7.21-7.31 (m, 1H), 7.32-7.41 (m, 2H), 7.43-7.50 (m, 1H), 7.71 (d, 1H, J = 8.4 Hz), 7.83 (d, 1H, J = 8.4 Hz), 7.87 (d, 1H, J = 8.4 Hz), 8.19 (brs, 1H); ^{13}C NMR ($CDCl_3$) δ 19.3, 23.9, 30.3, 39.5, 53.9, 56.6, 59.0, 67.1, 117.7, 122.9, 125.4, 126.0, 126.2, 126.9, 127.7, 128.7, 130.2, 131.6, 133.5, 134.4, 135.8, 139.0, 172.8. Anal. Calcd for $C_{27}H_{31}N_3O$: C, 78.42; H, 7.56; N, 10.16. Found: C, 78.44; H, 7.53; N, 10.16.

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