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Construction of an Asymmetric Quaternary Carbon Center *via* Allylation of Hydrazones

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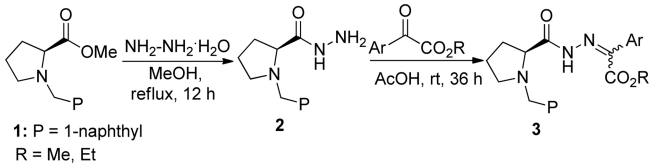
There has been great interest in developing methods for asymmetric nucleophilic allylic addition of organometallic reagents to imine derivatives.[1] The resulting homoallylic amines are valuable compounds which are used as building blocks for preparing biologically active molecules and pharmaceutically important compounds.[2] However, due to the low reactivity of C=N bonds to nucleophiles, strong organometallic reagents are required, causing deprotonation of enolizable imines instead of addition. Among the various allylic metal reagents, allylindium reagents are suitable for allylation of imines. Allylindium reagents have several advantages including low basicity, selective nucleophilicity, low toxicity, and stability to moisture and air.[3]

Asymmetric indium-mediated allylation of imine derivatives bearing a chiral auxiliary is a reliable strategy for the synthesis of chiral homoallylic amines. Various techniques for indium-mediated stereoselective allylation of imines bearing a chiral auxiliary have been reported. In 1997 Loh and co-workers reported indium-mediated allylation with imines derived from *L*-valine methyl ester.[4] Since then, many forms of indium-mediated allylation bearing a chiral auxiliary have been reported, including imines derived from (*S*)-valinol,[5] (*R*)-phenylglycinol,[6] uracil,[7] (*R*)-phenylglycinol methyl ester,[8] *N*-*tert*-butanesufinamide,[9] and (1*R*,2*S*)-1-amino-2-indanol.[10] However, the synthesis of chiral auxiliaries often involves a laborious multi-step synthesis with expensive reagents. Therefore, the development of readily accessible chiral auxiliaries for asymmetric indium-mediated allylation is in high demand.

Herein we describe stereoselective indium-mediated allylation to hydarzones bearing *L*-proline, which affords α,α-disubstituted α-amino acid derivatives with controlled quaternary carbon stereogenic centers. Many biologically active compounds and drugs contain quaternary carbon centers;[11] nonetheless, controlling the stereochemistry of quaternary carbon centers in these compounds is very difficult. The reactions for asymmetric construction of quaternary carbon centers *via* indium-mediated allylation are very rare.[12]

Chiral hydrazones **3** were prepared by a condensation reaction of compound **2** with α-ketoesters in AcOH (Scheme 1). Aromatic α-ketoesters afforded *Z*-diastereomers as major products with the hydrogen bonding between the carbonyl of the ester group and N-H moiety, proved by the appearance of a peak around 12.5 ppm in ^{1}H NMR.

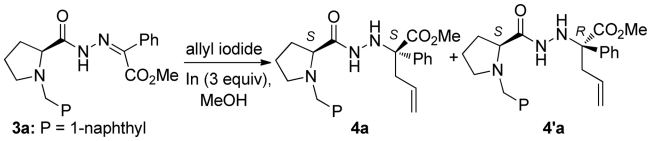


Scheme 1

3a as a single diastereomer was chosen as a model compound. The allylation of chiral hydrazone **3a** with indium (3 equiv) and allyl iodide (6 equiv) proceeded well in MeOH at room temperature. The desired homoallylic amine derivative was obtained in 96% yield with 63:37 dr (Table 1, entry 1). As the reaction temperature lowered, improved stereoselectivities were obtained (entries 2 and 3). With 3 equiv of In and 3 equiv of allyl iodide, the reaction did not proceed at −20 °C (entry 4). The reaction did not proceed in toluene, THF and CH_2Cl_2 at −20 °C.

To evaluate the generality and scope of the reaction, a range of hydrazones were subjected to optimal conditions. The results are presented in Table 2. Aromatic hydrazones with electron-donating as well as electron-withdrawing groups gave high yields and good diastereoselectivities. Interestingly, regardless of geometry of the hydrazones, the allylation afforded the same diastereomer as major allylated products (entry 1 *vs* 2, 3 *vs* 4 and 6 *vs* 7). When the allylation was performed with a mixture of stereoisomers, the obtained

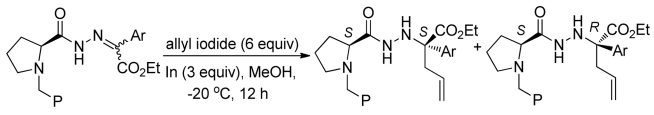
Table 1. Optimization of the reaction conditions



Entry	Allyl-I (equiv)	Temp (°C)	Time (h)	Yield (%)[a]	Dr (**4a**: **4'a**)[c]
1	6	rt	1	96	63:37
2	6	0	2	93	71:29
3	6	-20	12	94	80:20
4	3	-20	24	NR[b]	-

[a]Isolated yields. [b]Starting material was recovered. [c]Diastereomeric ratio was determined by ^{1}H NMR spectroscopy, comparing the integral ratio of methyl group.

Table 2. Allylation of hydrazones



3: P =1-naphthyl **4** **4'**

Entry	Ar	Product	Yield (%)[a]	Dr (**4**:**4'**)[c]
1	(*Z*)-C_6H_5, **3b**	**4b**	92	75:25
2	(*E*)-C_6H_5, **3b**	**4b**	91	75:25
3	(*Z*)-*p*-Me-C_6H_4, **3c**	**4c**	83	75:25
4	(*E*)-*p*-Me-C_6H_4, **3c**	**4c**	85	77:23
5	(*Z*)-*p*-Et-C_6H_4, **3d**	**4d**	91	74:26
6	(*Z*)-*p*-MeO-C_6H_4, **3e**	**4e**	96	77:23
7	(*E*)-*p*-MeO-C_6H_4, **3e**	**4e**	91	75:25
8	(*Z*)-*p*-Me_2N-C_6H_4, **3f**	**4f**	83	88:12
9	(*Z*)-*p*-F-C_6H_4, **3g**	**4g**	86	76:24
10	*p*-F-C_6H_4, **3g**[b]	**4g**	85	75:25

[a]Isolated yields. [b]A mixture of *E* and *Z* isomers (50:50) was used. [c]Diastereomeric ratio was determined by ^{1}H NMR spectroscopy, comparing the integral ratio of hydrogen in amide moiety.

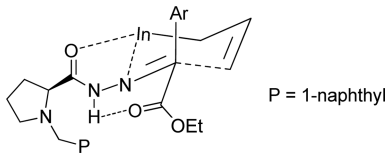


Figure 1. Plausible transition state.

diastereomeric ratio (75:25 dr) exceeded the *E*:*Z* isomeric ratio (50:50) (entry 10). It seems that the hydrazones having *E*-geometry are converted into the more stable *Z*-diastereomers due to the hydrogen bonding between N-H and the carbonyl of the ester group under the reaction conditions. We assume that the allylation of the hydrazones occurs through a six-membered cyclic transition state as depicted in Figure 1. The nucleophile attacks the *Si*-face of the hydrazones, affording compound **4** as the major diastereomers. The configuration of new stereogenic center of the major diastereomer **4** was assigned to be *S* as an analogy of the previous report.[13] In summary, a method for the asymmetric synthesis of chiral quaternary carbon centers with hydrazones has been developed.

Typical Reaction Procedure for 4b: Allyl iodide (0.69 mmol, 0.06 mL) was added to a stirred solution of hydrazone (0.12 mmol, 50 mg) and indium powder (0.35 mmol, 40 mg) in methanol (5 mL) at –20 °C and the contents were stirred for 12 h. After completion of the reaction (confirmed by TLC), the solvent was evaporated, quenched with 1 M HCl and extracted into CH_2Cl_2. The organic phase was separated, dried and further purified by flash column chromatography over silica gel (*n*-hexane/EtOAc, 6:4) to provide the desired addition products: syrup; $[\alpha]_D^{20} = -59.2$ (c 0.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.15 (t, *J* = 6.8 Hz, 3H), 1.58-1.81 (m, 3H), 2.09-2.20 (m, 1H), 2.22-2.31 (m, 1H), 2.65-2.79 (m, 2H), 2.96-3.04 (m, 1H), 3.17-3.24 (m, 1H), 3.77 (d, *J* = 14 Hz, 1H), 3.87 (d, *J* = 14 Hz, 1H), 4.09-4.19 (m, 2H), 5.03-5.10 (m, 2H), 5.17 (d, *J* = 6.8 Hz, 1H), 5.65-5.78 (m, 1H), 6.96-7.03 (m, 2H), 7.03-7.13 (m, 3H), 7.34-7.42 (m, 2H), 7.45-7.54 (m, 2H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.82-7.93 (m, 2H), 8.60 (d, *J* = 6.2 Hz, 1H). ^{13}C NMR ($CDCl_3$): 14.0, 24.1, 30.4, 41.3, 54.2, 56.9, 61.5, 67.3, 70.8, 119.5, 123.3, 125.4, 125.6, 126.0, 126.1, 126.6, 127.8, 128.0, 128.1, 128.8, 131.6, 132.4, 133.7, 134.2, 138.5, 171.6, 172.8.

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