

Highly Diastereoselective Indium-Mediated Allylation of Chiral Hydrazones

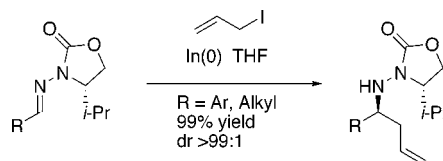
Gregory R. Cook,* Bikash C. Maity, and Robert Kargbo

North Dakota Network in Catalysis, Department of Chemistry and Molecular Biology,
North Dakota State University, Fargo, North Dakota 58105-5516

gregory.cook@ndsu.nodak.edu

Received March 1, 2004

ABSTRACT



The indium-mediated allylation of chiral hydrazones was investigated. Essentially complete diastereoselectivity and quantitative yields were obtained for substrates derived from both aromatic and aliphatic aldehydes.

Chiral amines have found great utility in the preparation of ligands for asymmetric catalysis, and are important building blocks for the synthesis of biologically important compounds. One of the most direct methods for their preparation is the addition of carbon nucleophiles to C=N bonds. However, relative to carbonyls, imine derivatives are generally less reactive, and nucleophilic addition to them usually demands the use of very strong organometallic reagents.¹ Thus, enolization and functional group tolerance are common impediments in these processes.

In the past decade, allylindium has emerged as a mild and effective reagent for the allylation of carbonyl compounds.² Several examples of indium-mediated allylation of C=N bonds have also been reported,³ thus affording an alternative to highly basic nucleophiles. The use of chiral auxiliaries to effect a diastereoselective addition has met with some success. Examples include chiral sulfinimine derivatives⁴ and imines derived from valine.⁵ Imines prepared from α -keto chiral sultams⁶ have provided the best examples to date.

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These methods generally suffer from modest yields, poor diastereoselectivity, auxiliaries that are difficult to cleave, or relatively long reaction times. New methods for the asymmetric indium-mediated allylation of C=N bonds that are procedurally simple, have easily removable auxiliaries, and are general in scope are desirable.

Recently, Friestad reported the allylation of chiral hydrazones utilizing fluoride-induced allylation with allylsilane

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in the presence of a Lewis acid with high selectivity. The hydrazine products were readily cleaved with SmI_2 to afford homoallylic amine derivatives.⁷ Although the chemistry is quite elegant and worked well for most cases, the selectivity with substrates derived from aliphatic aldehydes (~4:1) was lower than that with aromatic substrates. In addition, reaction times were quite long, requiring 2 days to reach completion. To the best of our knowledge, there are no reports of the application of allylindium with chiral hydrazone auxiliaries. We envisioned these reagents would offer improvements in rate, selectivity, and overall ease of the process as compared with allylsilane. Herein we report the results of our investigation of the indium-mediated allylation of Friestad chiral hydrazones.

We first examined the conditions required for the allylation reaction. Interestingly, addition of 1 equiv of indium and 1 equiv of allyl iodide to the substrate in THF was completely unreactive and the starting material was recovered intact. Adding 1.5 equiv of allyl iodide afforded an 86% conversion after 8 h. This could be increased to 95% conversion with 1.5 equiv of $\text{In}(0)$ and 3 equiv of allyl iodide. We found the use of 2 equiv of indium and 3 equiv of allyl iodide in THF was optimal and afforded complete conversion within 3 h. Utilizing more of the reagents gave no additional benefits. The use of less reagent was practical but some starting material always remained after 3 h. The stoichiometry requirements suggest that an allylindium sesquihalide species² was necessary for the reaction to take place.

We next focused our attention on the chiral auxiliary. Thus, we scrutinized several oxazolidinones with the *p*-tolyl hydrazones **1** (Table 1). The phenylglycinol-derived **1a**

Table 1. Allylation of Chiral Hydrazones Auxiliary Screen^a

entry	X_c	yield (%) ^a	dr ^b
1		99	70:30
2		>99	>99:1
3		99	>99:1
4		99	>99:1

^a Conditions: allyl iodide (3 equiv), $\text{In}(0)$ (2 equiv), 100 mg of substrate in 3 mL of THF, rt, 3 h. ^b Isolated yields. ^c Diastereomer ratios determined by careful proton NMR spectroscopy.

reacted in quantitative yield (entry 1); however, the diastereoselectivity was poor. Substrates prepared from phenylalaninol (**1b**), valinol (**1c**), and aminoindanol (**1d**) all proceed with complete diastereoselectivity as indicated by careful proton NMR analysis. The isolated yields in all cases were excellent.

We settled on the smallest auxiliary based on valinol to study the substrate scope of the indium-mediated allylation reaction. Our results are summarized in Table 2. Reaction

Table 2. Allylation of Chiral Hydrazones Substrates^a

entry	R	yield (%) ^a	dr ^b
1	Ph	a 99	>99:1
2		b 99 (95) ^d	92:8 (>99:1) ^d
3		c 95	>99:1
4		d 97 (90) ^d	97:3 (97:3) ^d
5		e 95 (96) ^d	92:8 (92:8) ^d
6		f 50 ^e (95) ^d	>99:1 (>99:1) ^d
7		g 96 (95) ^d	86:14 (>99:1) ^d
8		h 99 (90) ^d	55:45 (97:3) ^d
9		i 99 (92) ^d	66:33 (>95:5) ^d
10		j 99 (90) ^d	66:33 (>95:5) ^d
11		k 95 (90) ^d	78:22 (>95:5) ^d

^a Conditions: allyl iodide (3 equiv), $\text{In}(0)$ (2 equiv), 100 mg of substrate in 3 mL of THF, rt, 3h. ^b Isolated yields. ^c Diastereomer ratios determined by careful proton NMR spectroscopy. ^d $\text{In}(\text{OTf})_3$ (1.3 equiv) added, reaction run for 1 h. ^e Reaction run for 8 h; 48% of the starting material was recovered.

with aromatic aldehyde-derived substrates (entries 1–7) with allyl iodide and indium in THF gave overall excellent yields and excellent diastereoselectivities. There were a couple of exceptions. The *p*-nitro derivative **3f** (entry 6) afforded complete selectivity; however, the reactivity was quite low

and only a 50% yield was obtained (97% based on recovered starting material). The *p*-methoxy substrate **3g** demonstrated good reactivity, but the selectivity dropped to 86:14. Allylation of the cinnamaldehyde hydrazone **3h** (entry 8) proceeded with essentially no selectivity. Aliphatic substrates **3i–k** (entries 9–11) also reacted with poor selectivity. Interestingly, we observed that the selectivity changed for these substrates depending on the scale of the reaction. We determined that excess allylindium reagents in more dilute conditions favored better selectivity. Thus, when 50 mg of **3h** was treated with 4 equiv of In(0) and 6 equiv of allyl indium in 7.5 mL of THF, the selectivity jumped from 55:45 to 98:2. The same increase in selectivity was observed for **3j** giving >95:5 under these conditions. Changing either the concentration or the amount of reagents independently had much less influence on the diastereoselectivity. These observations are difficult to rationalize and we are currently investigating this unusual phenomenon.

The unusual dependence of the diastereoselectivity on the concentration and amount of allylindium reagent suggested that excess In(III) in solution was coordinating the substrate as a Lewis acid.⁸ Thus, we examined the influence of added Lewis acid on the reaction. We were very pleased to see that the addition of 1.3 equiv of In(OTf)₃ to the chiral hydrazones increased both the selectivity and the rate of the reaction. In all cases, the reaction was complete within 1 h. Even the sluggish *p*-nitro substrate afforded **4f** in 95% isolated yield. As shown in entries 7–11, diastereoselectivity was nearly complete in the presence of In(OTf)₃ for the substrates that were previously problematic. Presumably, the Lewis acid coordinates the hydrazone in a chelating fashion to both activate the substrate as well as restrict the conformational mobility allowing for greater reactivity and selectivity.⁹

The use of allylic bromides proved to be problematic. While the simple allyl bromide performed equally well as allyl iodide upon reaction with **3a**, it would only do so in the presence of added In(OTf)₃ (90% yield, >99:1 dr). Surprisingly, cinnamyl bromide, crotyl bromide, prenyl bromide, 3-bromocyclohexene, and propargyl bromide all

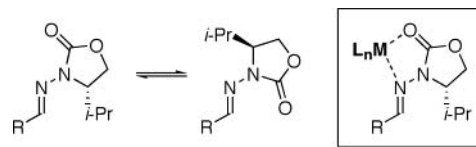
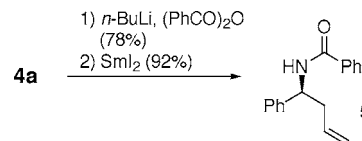


Figure 1. Hydrazone rotamers.

failed to react with hydrazone substrates. We are currently exploring the scope of allylic systems that can be incorporated into this reaction and our results will be reported in due course.

The chiral auxiliary was readily cleaved as reported by Friestad.⁷ As shown below in Scheme 1, **4a** was acylated with benzoic anhydride and the hydrazine was cleaved via reduction with SmI₂.

Scheme 1. Removal of the Chiral Auxiliary



In summary, we have demonstrated the highly diastereoselective indium-mediated allylation of chiral hydrazones. Reactions were operationally simple and reaction times were short. With the employment of In(OTf)₃ Lewis acid diastereoselectivity was controlled for both aromatic and aliphatic substrates. The enantioselective variant of this allylation reaction is currently being pursued.

Acknowledgment. We are grateful to the National Science Foundation (NSF-CHM-0316618) and the ND-EPSCoR Network in Catalysis program (NSF-EPS-0132289) for financial support.

Supporting Information Available: Experimental procedures and characterization data for all compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL0496172

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