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Catalytic Enantioselective Indium-Mediated Allylation of Hydrazones

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

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

gregory.cook@ndsu.edu

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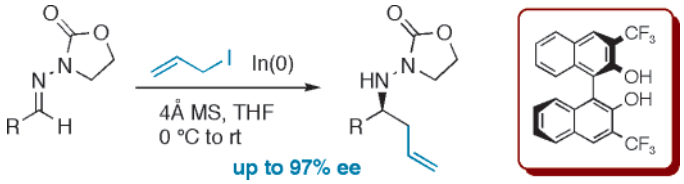
ABSTRACT



A facile and highly selective indium-mediated allylation of hydrazones utilizing BINOL ligands is described. Chiral (*R*)-3,3′-bistrifluoromethylBINOL afforded homoallylic amines in up to 97% ee with stoichiometric ligand. Employing only 10 mol % ligand afforded selectivity of up to 92% ee.

Over the past decade, allylindium complexes have emerged as mild and effective reagents for the allylation of carbonyl compounds.[1] The application of chiral ligands to indium-mediated allylations has been an arduous challenge due to the low heterophilicity of the organoindium reagents. Enantioselective allylation of aldehydes utilizing allylindium was reported by Loh and produced homoallylic alcohols in moderate to good enantioselectivity using an excess of cinchona alkaloids as chiral additives.[2] Use of 2 equiv of a cerium−pybox Lewis acid afforded ee up to 92% in one example. Very recently, Singaram has reported the enantioselective allylation of aldehydes using excess chiral amino alcohol additives with ee up to 93%.[3] Herein, we report the first *enantioselective* indium-mediated allylation of hydrazones affording homoallylic amines in high selectivity employing a *catalytic* amount of chiral additive.

A direct method for the preparation of chiral amines is the addition of carbon nucleophiles to C═N bonds. However, relative to carbonyls, imine derivatives are generally less reactive, and the use of very strong organometallic reagents is usually required for nucleophilic addition.[4] Thus, enamine formation and functional group tolerance are common impediments in these processes. Several examples of indium-mediated allylation of C═N bonds have been reported,[5] affording an alternative to highly basic nucleophiles. Asymmetric variants have utilized chiral auxiliaries to effect a diastereoselective addition. For example, chiral sulfinimine derivatives,[6] imines derived from amino acids[7] and α-keto

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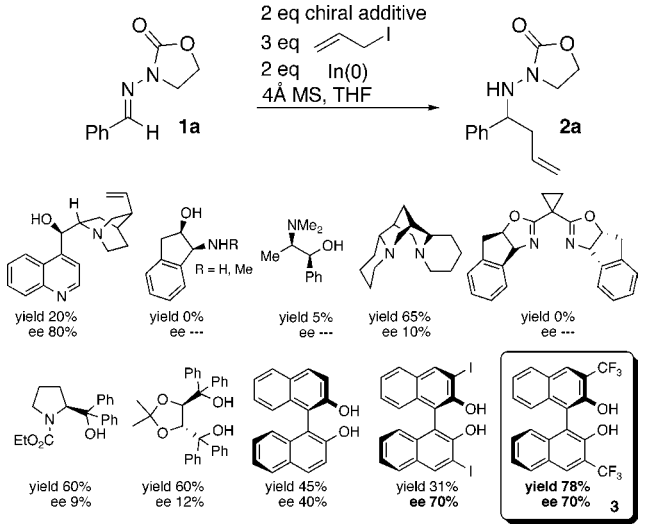
chiral sultams,[8] have afforded relatively good diastereoselectivity and yield. Recently, we reported[9] the highly diastereoselective allylation of chiral hydrazones bearing an oxazolidinone auxiliary introduced by Friestad.[10] This offered advantages in diastereoselectivity and reaction rate over the fluoride-promoted allylsilane addition to chiral hydrazones reported by Friestad, particularly for aliphatic aldehyde-derived hydrazones. To date, allylsilanes have been most successful for stereoselective allylation of acylhydrazone derivatives. Using CuCl and chiral ligands with allyltrimethoxysilane, Friestad has observed measurable but low (9.7% ee) selectivity.[11] The enantioselective allyation of acylhydrazones using chirally modified allyl silanes has been reported by Leighton,[12] and high selectivity (~85−97% ee) was obtained in most cases. Chiral sulfoxide-promoted allylation of hydrazones with allyltrichlorosilane has been reported using an excess of the promoter in up to 93% ee.[13] In addition, Kobayashi has demonstrated that chiral BINAP oxides could promote this reaction using substoichiometric amounts (20 mol %, 56% ee; 40 mol %, 69% ee).[14] Chiral bis-allylpalladium catalysts have also been employed in enantioselective allylation of imines with allylsilanes and allylstannanes with good to high ee (up to 94%).[15]

So far, the utility of allylindium in enantioselective allylations has been very limited. Considering the excellent success obtained in the addition of allylindium reagents toward chiral hydrazones,[9] we sought to develop the enantioselective variation of this reaction. We began by surveying several chiral additives (Scheme 1) such as bisoxazoline ligands, chiral amino alcohols, chiral diamine derivatives, etc. with the benzaldehyde-derived achiral hydrazone **1a**. The reaction was carried out with 2 equiv of the chiral additive, 2 equiv of indium metal, and 3 equiv of allyl iodide. Most resulted in very low selectivity or sluggish reactions. However, similar to Loh's report, the use of 2 equiv of (−)-cinchonidine afforded good enantioselectivity (80% ee). Unfortunately, the yield was very poor. Addition of $In(OTf)_3$

Scheme 1



Lewis acid improved the reaction to 85% yield; however, this was detrimental to the selectivity (29% ee). Chiral diols, particularly (*R*)-BINOL, afforded modest yield and selectivity.[16] This prompted us to investigate other BINOL derivatives to optimize the reaction. The 3,3′-diiodoBINOL resulted in an improvement in selectivity, and the 3,3′-bistrifluoromethyl-BINOL[17] (**3**) derivative performed the best, affording a 72% yield of **2a** in 70% ee. THF was the best solvent examined; very low yields and selectivities were observed in CH_2Cl_2 (20% yield, 7% ee), and no reaction was observed in CH_3CN. This may be attributed to the lack of generation of the active allylindium reagent as evidenced by remaining unreacted In(0). Water appeared to be detrimental to the enantioselectivity, and optimal results were obtained with the addition of 4 Å molecular sieves (45% ee without 4 Å MS). The concentration was also critical for success of the reaction and was optimal at 0.17 M in substrate. When the reaction was either diluted or concentrated by a factor of 2, lower enantioselectivity was obtained (45 and 67% ee, respectively). This is difficult to rationalize, but may be due to varying disproportionation between organoindium species of different oxidation states.[12]

After successful reactivity and selectivity were established for the allylation of hydrazone **1a** using excess ligand, the stoichiometry of the chiral additive and the substrate scope of the reaction were investigated. Results are summarized in Table 1. We were gratified to find that the reaction of **1a** could be carried out with good selectivity employing only 10 mol % of the ligand, 1.1 equiv of In(0), and 1.5 equiv of allyl iodide, giving **2a** in 70% ee and 77% yield. Additionally, the stoichiometric reaction improved under these conditions as well (84% ee). Para-substituted derivatives performed even better, as demonstrated by substrates **1b**−**d**. The π-donor substituents, Cl and OMe, afforded greater

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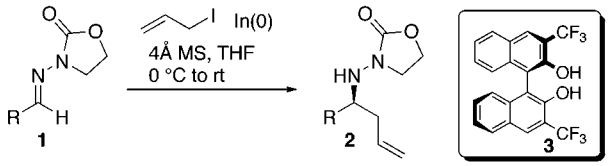
Table 1. Enantioselective Allylation of Hydrazones



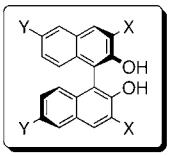
hydrazone	R	10 mol% **3** yield %	10 mol% **3** ee %	100 mol% **3** yield %	100 mol% **3** ee %	(recryst)
a		77	70	72	84	
b		60	70	60	87	
c		74 [b] 70	77 82	68 67	**92** **91**	(>99) (>99)
d		78	82	61	**93**	(>99)
e		76	85	63	**97**	
f		67	**91**	50	**97**	
g		40	**92**	0	---	
h		65	70	53	**94**	
i		70	70	65	**91**	
j		79 [c] 60	34 70	76 63	**90** 86	(>99)
k		73	34	61	**92**	
l		73	10	59	**91**	

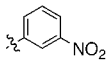
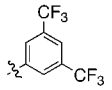
[a] Allylindium/ligand complex was preformed at room temperature, and reactions were carried out starting at 0 °C and warming to room temperature. See Supporting Information for details. Ee was determined by HPLC. Yield and selectivities reported are averages of at least two experiments. [b] (*S*)-3,3′-BistrifluoromethylIBINOL was used, affording the enantiomer. [c] $T = -78$ °C to room temperature.

than 90% ee using 1 equiv of the chiral additives. Ortho-substituted substrates offered the highest enantioselectivity, with the *o*-bromobenzaldehyde-derived **1e** giving the best overall yields and selectivity in both catalytic (85% ee) and stoichiometric (97% ee) reactions. The *o*-Cl substrate **1f** gave an even higher level of enantioselectivity in the catalytic reaction (91% ee), while the *o*-tolyl substrate **1g** provided 92% ee with 10 mol % BINOL derivative. Surprisingly, this substrate would not react with 100 mol % ligand, and the starting material was recovered intact. Furthermore, *o*-trifluoromethyl- and 2,6-dimethyl-substituted substrates failed to react under any conditions. Generally, isolated yields were higher using a catalytic chiral additive. Even aliphatic and cinnamyl derivatives **1j**−**l** reacted to form the chiral homoallylic hydrazines in greater than 90% ee with 100 mol % ligand. This was very rewarding considering that these substrates suffer from competing achiral background reactions, as evidenced by the lower selectivity obtained with catalytic ligand. However, in the case of **1j**, starting the reaction at a lower temperature significantly improved the ee from 34 to 70%, suggesting that opportunity remains for further optimization of the reaction conditions. As many of the oxazolidinone-derived hydrazines were crystalline solids, their optical purity could be increased by simple recrystallization. As demonstrated for **2c**−**e** and **2j**, a single recrystallization conveniently afforded enantiopure product. The absolute configuration of **2a** was determined by benzoylation of the nitrogen and reductive cleavage of the hydrazine bond to afford the known homoallylic benzamide.[9]

To gain more insight into the role of the BINOL ligands, we examined several other analogues, and the results are described in Table 2. It is apparent that electronic effects

Table 2. BINOL Derivatives for Enantioselective Allylation of Hydrazone **1a**[a]



entry	X	Y	yield %	ee %
1	H	H	45	45
2	I	H	31	**70**
3	CF_3	H	78	**70**
4	Me	H	55	28
5	TMS	H	96	2
6	H	Br	85	**70**
7		H	55	44
8		H	64	65

[a] Reactions carried out with 2 equiv of chiral additive, 2 equiv of In(0), and 3 equiv of allyliodide. Ee was determined by HPLC.

rather than steric effects were most important for selectivity. Changing the 3 and 3′ substituents from CF_3 to Me to TMS (entries 3−5) resulted in a marked decrease in the enantioselectivity, while placing a Br in the 6 and 6′ positions (entry 6) led to high selectivity. Larger substituents with electron-withdrawing groups in the 3 and 3′ positions also did not improve the selectivity. Generally, electron-efficient BINOL derivatives performed better than those that were electron-rich, suggesting that the acidity of the BINOL was important. Presently, the nature of the BINOL−indium complex is unknown. Preliminary NMR evidence suggests that one of the BINOL protons may be deprotonated upon interaction with allylindium,[18] as evidenced by upfield shifts of all the BINOL resonances (see Supporting Information). It is not clear whether a chiral allylindium complex is generated in the reaction or whether a chiral indium Lewis acid is responsible for the catalytic reaction, and work is currently underway to further characterize these intermediates.

In conclusion, we have demonstrated a facile and highly enantioselective allylation of hydrazones utilizing BINOL ligands. This represents the first successful example of the use of catalytic amounts of a chiral additive in an addition reaction with allylindium.[19] Efforts are currently underway

(18) In(III) and In(I) allyls have been observed by NMR in the formation of allylindium reagents. Chan, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228.

(19) Chiral In(III) Lewis acids with allylstannanes may involve transmetalation to form allylindium in situ. Lu, J.; Hong, M.-L.; Ji, S.-J.; Loh, T.-P. *Chem. Commun.* **2005**, 1010.

to further optimize the process and understand the role of the BINOL in the reaction.

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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.

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