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Indium mediated Barbier-type allylation of aldimines in alcoholic solvents

Tirayut Vilaivan,[a,]* Chutima Winotapan,[a] Tetsuro Shinada[b] and Yasufumi Ohfune[b]

[a]*Organic Synthesis Research Unit, Department of Chemistry, Faculty of Science, Chulalongkorn University, Phayathai Road, Patumwan, Bangkok 10330, Thailand*

[b]*Department of Material Science, Graduate School of Science, Osaka City University, 3-3-138, Sugimoto, Sumiyoshi-ku, Osaka 558-8585, Japan*

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Abstract—Barbier-type allylation of unactivated aldimines with allyl bromides in the presence of indium powder took place rapidly in alcoholic solvents to give homoallylic amines in fair to good yields. © 2001 Elsevier Science Ltd. All rights reserved.

Carbon–carbon bond formation by nucleophilic addition of carbon nucleophiles to imines is an important tool for synthesizing complex biologically active nitrogen-containing compounds. While addition of a variety of carbon nucleophiles to carbonyl compounds has been extensively investigated and well established, considerably less successful results were obtained in the analogous reactions with imines. The major problem is the relatively low reactivity of unactivated imines towards nucleophilic addition and deprotonation of imines derived from enolizable carbonyl compounds to form enamines.[1–3]

We consider the allyl anion to be a potentially useful nucleophile in such addition reactions since the resulting homoallyic amines can be transformed into several classes of biologically active compounds by a variety of known procedures.[4–6] Among various organometallic species successfully employed in the allylation of C=O and C=N systems,[7] organoindium reagents possess an interesting feature in that they are stable in the presence of water and air, thus, their reactions can be performed without requiring strictly anhydrous conditions nor inert atmosphere.[8–11] A number of indium-mediated allylations of C=N compounds including *N*-sulfonylimines,[12,13] nitrones and hydrazones[14] have been successfully performed in aqueous solvents. However, the analogous aqueous allylation of unactivated imines has not been much studied mainly due to the instability of imines towards hydrolysis.[12,13,15] As a result, all indium-mediated allylations of unactivated imines reported to date have been carried out in aprotic solvents such as DMF or THF under anhydrous conditions.[16–20] We envisioned that the use of alcoholic solvents would not cause the undesired hydrolysis and might provide a driving force for the forward reaction by protonation of the metal amide initially formed. Indeed, dramatic rate acceleration of allylation in the presence of proton sources was previously observed.[21–23] We report herein an efficient entry to homoallylic amines by nucleophilic addition of an allylindium reagent formed in situ from an allyl bromide and indium metal to unactivated aldimines in alcoholic solvents.

Reactions of *N*-benzylidenebenzylamine (**1**) with the allyl indium reagent generated in situ by addition of allyl bromide to the suspension of indium powder were initially attempted in reagent grade THF, but the results were variable and always suffered a long induction period (up to several hours before the indium started to dissolve exothermically). However, the reaction between indium and allyl bromide was instantaneous when anhydrous THF was used as solvent. In both cases, after stirring overnight at room temperature, the desired homoallylic amine (**2**) was obtained in 45% yield which was comparable to that reported in the literature (42%).[16] We next tried to compare different solvents and found that the induction period was shortest (<30 min), and the best yield was obtained, in lower alcoholic solvents including isopropanol, methanol and

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Keywords: allylation; imines; addition reactions; indium and compounds; solvents and solvent effects.

* Corresponding author. Tel.: +66-2-2184961; fax: 66-2-2541309; e-mail: vtirayut@chula.ac.th

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ethanol (Table 1).[24] While the reaction in water was fast, as judged by the disappearance of the indium metal and TLC analysis, the reaction gave 1-phenyl-3-buten-1-ol (**3**) as the major product (85%). The formation of the homoallylic alcohol (**3**) is presumably the result of allylation of the aldehyde derived from indium salt-catalyzed hydrolysis of the imine (**1**). In order to investigate the effect of water on the extent of imine hydrolysis, the reactions were performed in ethanol containing varying amounts of water. It was found that the yield of the homoallylic amine (**2**) dropped from 62 to 7.7 and 3.8% on changing the solvent from absolute ethanol to 95 and 85% ethanol, respectively. In view of the sensitivity of the reaction to water, it is surprising that we obtained reasonably good yields of the desired addition product using commercial absolute alcoholic solvents considering that no attempts to exclude moisture and air were made.[25,26] The reaction appeared to be unique to indium, since treatment of (**1**) with zinc powder/allyl bromide or tin powder/allyl bromide in ethanol under the same conditions gave no allylation product.

Following the successful results with the imine (**1**), the scope of the reaction was explored employing a number of structurally different substituted aldimines (**1a**–**1l**) and allyl bromides (Table 2). In most cases the desired homoallylic amines (**2a**–**2o**) were obtained in yields ranging from fair to good.[27] From Tables 1 and 2, the following trends can be noted: (1) no significant difference in reaction rates and yields was found between methanol, ethanol and isopropanol; (2) the rates of reaction in lower alcohols were faster and the yields were considerably better than the reactions performed in aprotic solvents; (3) imines derived from enolizable aldehydes (entries 6 and 7) gave the desired products albeit in a rather poor yield; (4) the reaction was compatible with a wide variety of potentially reactive functional groups (aryl halide, alkoxy, unprotected alcoholic and phenolic hydroxy, pyridyl), position of substitution (*ortho*, *meta*, *para*) and branching of the *N*-substituents; (5) reactions with substituted allyl bromides (entries 9–11) gave only the γ-adducts; (6) stereoselective addition was possible with imines derived from chiral amines. Although the imine derived from benzaldehyde and (*R*)-α-methylbenzylamine (**1k**) gave poor diastereoselectivity (entry 13), we were pleased to find that the corresponding (*R*)-phenylglycinol-derived imine (**1l**) gave only one diastereomer of the desired allylation products (entries 14 and 15) according to 400 MHz ^{1}H NMR analysis. The scope and application of stereoselective allylations of imines in alcoholic solvents will be the subject of our next investigation.

In conclusion, we have demonstrated that indium-mediated allylation of aldimines in alcoholic medium could provide a convenient access to homoallylic amines and it was possible to extend to a stereoselective version simply by incorporating an optically active amine as the chiral auxiliary.

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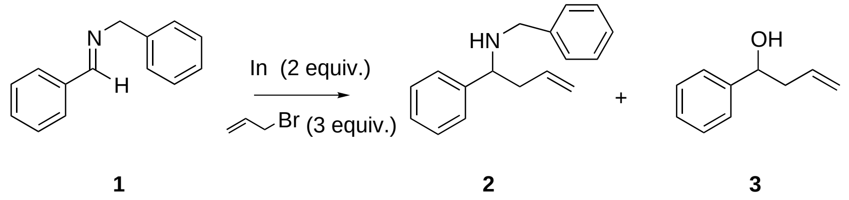
Table 1. Indium mediated allylation of *N*-benzylidenebenzylamine (**1**) in different solvents[a]



Solvent	Product	Yield (%)
THF	**2**	45
^{t}BuOH	–[b]	–[b]
^{i}PrOH	**2**	70
MeOH (absolute)[c]	**2**	72
EtOH (absolute)[c]	**2**	62
H_2O	**3**[d]	85

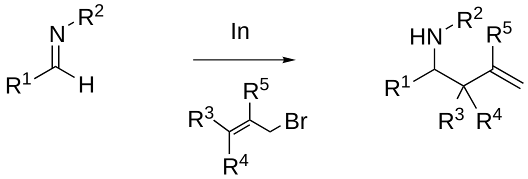
[a] All reactions were performed at 1.0 mmol scale using commercial solvents. No attempts were made to exclude air/moisture.

[b] The indium metal did not completely dissolve even after stirring overnight.

[c] Contains <0.2% water.

[d] Only a trace of (**2**) was formed.

Table 2. Indium mediated allylation of aldimines[a]



1a-1l **2a-2o**

Entry	Imine	Amine	R^1	R^2	R^3 R^4 R^5	Yield (%)[b]	Solvent
1	**1a**	**2a**	3-HOC_6H_4	$PhCH_2$	H H H	66	EtOH
2	**1b**	**2b**	4-ClC_6H_4	$PhCH_2$	H H H	69	EtOH
3	**1c**	**2c**	4-pyridyl	$PhCH_2$	H H H	50	EtOH
4	**1d**	**2d**	2-pyridyl	Ph_2CH	H H H	79	MeOH
5	**1e**	**2e**	2-$MeOC_6H_4$	Ph_2CH	H H H	72	MeOH
6	**1f**	**2f**	^{i}Pr	Ph_2CH	H H H	61	EtOH
7	**1g**	**2g**	$^nC_7H_{15}$	Ph_2CH	H H H	20	MeOH
8	**1h**	**2h**	Ph	Ph_2CH	H H H	40	MeOH
9	**1h**	**2i**	Ph	Ph_2CH	Ph Me H	62[c]	MeOH
10	**1h**	**2j**	Ph	Ph_2CH	Me Me H	30	MeOH
11	**1i**	**2k**	Ph	Ph	Me Me H	55	MeOH
12	**1j**	**2l**	Ph	$(CH_3)_2CHCH_2$	H H H	48	EtOH
13	**1k**	**2m**	Ph	(*R*)-PhCH(Me)	H H H	76[d]	^{i}PrOH
14	**1l**	**2n**	Ph	(*R*)-$PhCH(CH_2OH)$	H H H	74[e]	^{i}PrOH
15	**1l**	**2o**	Ph	(*R*)-$PhCH(CH_2OH)$	H H Me	74[f]	^{i}PrOH

[a] All reactions were performed at 1.0 mmol scale using commercial solvents. No attempts were made to exclude air/moisture.

[b] Yield refers to isolated yield, all products were characterized by ^1H and ^{13}C NMR.

[c] Obtained as ca. 5:1 mixture of diastereoisomers.

[d] d.r. = 2.5:1, cf. Ref 16, yield 25% d.r. = 4:1.

[e] d.r.>9:1, $[\alpha]^{24}_{D}$ −31.4 (c = 1.01, $CHCl_3$).

[f] d.r.>9:1, $[\alpha]^{24}_{D}$ −25.9 (c = 0.96, $CHCl_3$).

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24. Although the reaction was initially stirred overnight before work-up, TLC and ^1H NMR analysis indicated that the reaction was complete as soon as the indium metal had completely dissolved.
25. A trace of the homoallylic alcohol (**3**) (<5%) was also observed in the reaction performed in absolute ethanol (<0.2% water content).
26. A related magnesium-mediated Barbier-type allylation of aldehydes was found to tolerate water up to a threshold level (approximately 7% in THF): Li, C.-J.; Zhang, W.-C. *J. Am. Chem. Soc.* **1998**, *120*, 9102–9103.

27. General procedure for the allylation of imines: To a mixture of the imine (1.0 mmol) and indium powder (228 mg, 2.0 mmol) in an appropriate alcoholic solvent (5 mL) was added allyl bromide (3.0 mmol). The reaction was stirred vigorously at room temperature until all the metal had dissolved (30 min–2 h), at which time, TLC indicated complete reaction. The reaction mixture was diluted with aqueous $NaHCO_3$ and extracted with ethyl acetate. The combined organic extracts were dried, evaporated and the residue purified by flash column chromatography on silica gel using hexane–EtOAc as eluant.