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Rate acceleration and diastereoselectivity in chelation-controlled indium-promoted Barbier allylation of pyridine-2- and quinoline-2-imines in aqueous solvents

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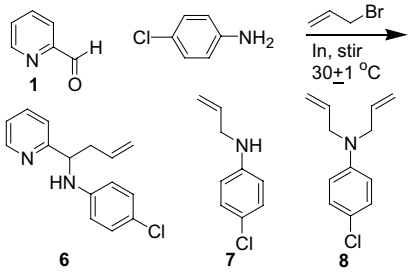
Abstract—The imines generated in situ from 2-pyridinecarboxaldehyde/2-quinolinecarboxaldehyde and aryl amines undergo indium-mediated Barbier allylation in aqueous media to provide homoallylic amines. Crotyl and cinnamyl bromides lead to diastereoselective allylation with d.r. up to 98:2.

Indium-promoted allyl addition reactions continue to be regarded amongst the premier methods for carbon–carbon bond formation under aqueous conditions.[1] Significant efforts have been made to elucidate the impact of proximal groups on the π-facial selectivity. In the cases of α- and β-hydroxy,[2] amino,[3] carboxy,[4] amido[5] etc., substituted aldehydes and ketones, the excellent to moderate diastereocontrol during allylation leads to *syn*-α-substituted/*anti*-β-substituted homoallylic alcohols. The influence of aqueous solvents in achieving high diastereoselectivities is significant. In all these reactions, the involvement of a chelated transition state has been proposed and its participation is supported by the accelerated reaction rates.

Due to the ease of hydrolysis of imines under aqueous conditions, allylation of imines in water has met with limited success, and only water-stable and presynthesized activated imine analogs such as aryl/sulfonyl hydrazones, sulphimines[6] and oxime ethers[7] have been employed in aqueous indium-mediated allylations. In the course of our investigations to develop new indium-mediated allylation reactions of imines in water, we have found that imines generated from 2-pyridinecarboxaldehyde **1** and 2-quinolinecarboxaldehyde **2** and aryl amines undergo efficient Barbier-type allylation in aqueous solvents. The reactions of 3-pyridinecarboxaldehyde **3**, *p*-anisaldehyde **4** and *p*-chlorobenzaldehyde **5** have been studied to evaluate the role of co-ordination of the pyridine and quinoline nitrogen.

The reaction of **1**, *p*-chloroaniline, indium metal and allyl bromide was chosen as a model reaction (Scheme 1).

On performing the reaction in water, *p*-chloroaniline was converted to *N*-allyl-*p*-chloroaniline **7** and *N*,*N*-diallyl-*p*-chloroaniline **8** and the homoallylic amine **6** was not formed. For the reactions carried at 30±1 °C in THF–H_2O,[8] a stirred solution of **1** and *p*-chloroaniline in THF was diluted with the appropriate amount of water and stirring continued for 30–60 min. During this period, the solid/liquid imine separated out.[8] Indium metal and allyl bromide were then added and stirring was continued. On using the H_2O–THF (1:1) solvent system, the desired homoallylic amine **6** was isolated in



Scheme 1.

Keywords: Indium; Imines; Aqueous solvent; Allylation; Diastereoselective.

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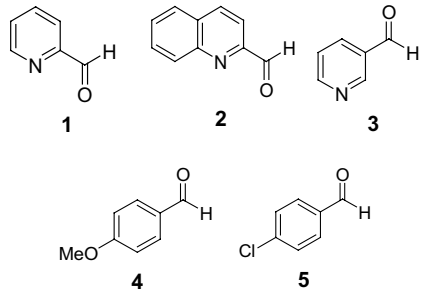
81% yield along with compounds **7** and **8** (15%). On increasing the H_2O–THF ratio to 2:1 and 4:1, the yield of homoallylic amine **6** was increased to 82% and 89%, respectively. Significantly, in the case of the H_2O–THF 4:1 system, only traces of **7** and **8** were formed. On increasing the ratio of H_2O–THF to 6:1 or 8:1, only a mixture of **7** and **8** could be isolated. Therefore, H_2O–THF (4:1) was the optimal solvent system for the synthesis of homoallylic amine **6** from **1**, *p*-chloroaniline, allyl bromide and indium.

In these reactions, the increase in the water–THF ratio resulted in an increase in reactivity of the allyl indium reagent[3b,7,9] and a decrease in the hydrolysis of water insoluble imines. The co-ordination of the pyridine nitrogen with indium increased the electron deficiency on the imine and thus increased reactivity towards the allyl indium. Therefore, the combination of the increase in the reactivity of the allyl indium and imine due to co-ordination and a decrease in the hydrolysis of imine leads to more efficient allylation. The lack of allylation of the presynthesized imine (from **1** and *p*-chloroaniline) in water showed that a small amount of THF is necessary for the allylation (Table 1).



The reactions of **1** with other arylamines in H_2O–THF 4:1 provided homoallylic amines in 75–86% yield (Table 2, entries 2–6) (Scheme 2). Contrary to reported homoallylic amine synthesis from *o*- and *p*-chloro- and *o*-nitroanilines[10] and presynthesized allyl stannanes[11] in water, here the nature and position of the substituent on the aniline appears to have little effect on the reaction. Similarly, the in situ generated imine from **2** and *p*-chloroaniline also underwent allylation to provide homoallylic amine in 78% yield along with a homoallylic alcohol (8%) (Table 2, entry 7).

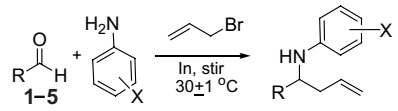
Table 1. Effect of the solvent system on homoallylic amine formation

Entry	Solvent	Time (h)	**6** (%)	**7**+**8** (%)
1	H_2O	14	—	80
2	H_2O–THF (1:1)	4	81	15
3	H_2O–THF (2:1)	4	82	10
4	H_2O–THF (4:1)	4	89	Traces
5	H_2O–THF (6:1)	20	—	90
6	H_2O–THF (8:1)	20	—	90
7	H_2O[a]	No reaction		

[a] Presynthesized imine.

Table 2. Synthesis of homoallylic amines using allyl bromide

Entry	Aldehydes	X	Time (h)	Yield (%)
1	**1**	*p*-Cl	4–5	89
2	**1**	*o*-Cl	4–5	86
3	**1**	*p*-Me	4–5	85
4	**1**	*p*-OMe	4–5	80
5	**1**	*o*-CO_2Me	4–5	75
6	**1**	*p*-F	4–5	78
7	**2**	*p*-Cl	4–5	78
8	**3**	*p*-Cl	12–14	0
9	**4**	*p*-OMe	8–10	10
10	**5**	*p*-Cl	8–10	20

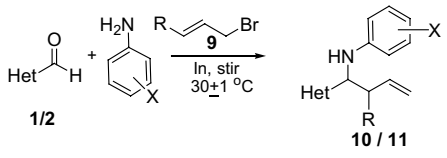


Scheme 2.

In the case of allylation of the in situ generated imine (tlc) from 3-pyridinecarboxaldehyde and *p*-chloroaniline, the reaction proceeds quite slowly[8] (12–14 h). Also, only amine allylated products **7** and **8** could be isolated and formation of the homoallylic amine was not observed. In the case of allylation of the in situ generated imines from *p*-anisaldehyde and *p*-chlorobenzaldehyde, only 10–20% of the homoallylic amine and 80–90% of homoallylic alcohol was formed (Table 2, entries 9 and 10). Probably, in the absence of an appropriately placed additional coordinating site, the allyl transfer reaction is slow and therefore the hydrolysis of the imine to the aldehyde and amine and subsequent allylation of the aldehyde predominates. It seems that the co-ordination of pyridine and quinoline nitrogens with allyl indium is essential for smooth allylation of their imines in water.

In the case of indium-promoted allylation reactions of carboxaldehydes, the rate of acceleration is in general accompanied by high diastereoselectivity.[2a–c] In order to evaluate the role of chelation on the diastereoselectivity, the reactions of imines derived from aldehydes **1** and **2** and aryl amines with substituted allyl halides have been studied.

The reaction of the imine derived from **1** and *p*-chloroaniline with crotyl bromide (**9**, R = CH_3) and indium in THF–H_2O (4:1) provided the homoallylic amine **10a** (63%) along with the amine allylated products (4–7%). (Scheme 3). The ^{1}H NMR spectrum of **10a** showed that it exists as mixture of two diastereomers in a 90:10 ratio. On using the imine derived from *o*-chloroaniline, a



Scheme 3.

Table 3. Diastereoselective synthesis of homoallylic amines

Entry	Aldehyde	R	X	**10/11**	*syn:anti*	Yield (%)
1	**1**	CH_3	*p*-Cl	**10a**	90:10	63
2	**1**	CH_3	*o*-Cl	**10b**	88:12	65
3	**1**	CH_3	*m*-Cl	**10c**	86:14	64
4	**1**	CH_3	*p*-Br	**10d**	90:10	63
5	**1**	CH_3	*p*-CH_3	**10e**	86:14	45
6	**1**	CH_3	*o*-CO_2Me	**10f**	80:20	55
7	**1**	C_6H_5	*p*-Cl	**10g**	98:2	22
8	**1**	C_6H_5	*o*-Cl	**10h**	98:2	25
9	**2**	CH_3	*p*-Cl	**11a**	91:9	69
10	**2**	CH_3	*o*-Cl	**11b**	90:10	60
11	**2**	CH_3	*m*-Cl	**11c**	83:17	66
12	**2**	CH_3	*p*-Br	**11d**	88:12	72
13	**2**	CH_3	*p*-F	**11e**	90:10	61
14	**2**	C_6H_5	*p*-Cl	**11f**	98:2	73
15	**2**	C_6H_5	*o*-Cl	**11g**	98:2	20

diastereomer ratio of 88:12 was achieved and in the case of *m*-chloroaniline the d.r. decreased to 86:14. The presence of an electron donating group (Table 3, entry 5) or an additional co-ordinating group on aniline (Table 3, entry 6) lowered both the diastereoselectivity and the yield of the homoallylic amine. Similarly, imines generated in situ from **2** and aryl amines underwent diastereoselective allylation with crotyl bromide to provide homoallylic amines **11a–e** (60–72%) along with the corresponding homoallylic alcohol (5–8%) (Table 3, entries 9–13).

The reactions of imines derived from **1** or **2** and aryl amines, with cinnamyl bromide (**9**, $R = C_6H_5$) and indium provided the homoallylic amines **10g**, **10h**, **11f** and **11g** with high diastereoselectivities (d.r.>98:2) although the yield of the homoallylic amine was, in general, lower.

In all the homoallylic amines derived from crotyl bromide, the major diastereomer showed an N–CH doublet at a higher δ value. It seems that all these reactions follow the same mechanism for allylation. In order to provide insight into the mechanism, the X-ray crystal structure[12] of **11f** was determined. The formation of the *syn* addition product (Fig. 1) in this reaction confirmed the participation of the quinoline/pyridine nitrogen in the allylation.

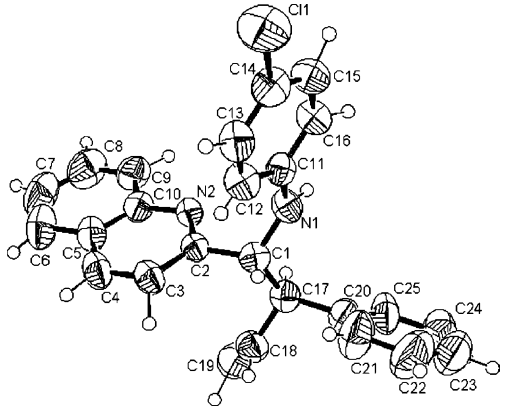


Figure 1. The ORTEP view (50% ellipsoid) of **11f**.

In the case of the recently reported three component allylation of aldimines in an aqueous sodium dodecyl sulfate medium, the reactions proceeded only in the presence of hydrated Lewis acids[10] and required pre-synthesized allylating reagents.[11,13,14] Furthermore, the reactions were limited to the transfer of the unsubstituted allyl moiety only. Therefore, the present results not only provide a relatively simpler approach involving four components in one reaction pot, they lead to increased scope in terms of diastereoselective synthesis. The further participation of other nitrogen-based co-ordinating groups (NH_2, NR_2, NHR, etc.) α- or β- to the imine in diastereoselective allylation reactions is currently being evaluated.

Acknowledgements

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12. The X-ray crystal data was measured by using θ–2θ scan mode. The structure was solved by using direct method SHELX-97. **11f**, $C_{25}H_{21}ClN_2$, monoclinic, space group C/2C, $a = 24.646$, $b = 12.494$, $c = 14.761$ Å; $\beta = 114.78°$; $v = 4126.4$ Å^3; $z = 8$; d.c. $1.239\ mg\ m^{-3}$; MoKα = 0.70930 Å; The structure solution is based on 3777 reflections, which converged to $R = 0.04$. CCDC reference number 231880.
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