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Ter-pyridine catalyzed allylation of aldehydes and ketones under metal-free condition

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ABSTRACT

Ter-pyridine derivatives were found to be potential catalyst for homoallylation of carbonyl groups. High yields of the products with short reaction times of ~2 h were observed in several cases. These new catalysts work efficiently with the simple reagent such as allyl magnesium bromide and hence can avoid the use of other sensitive or toxic reagents. It was found that the presence of polar groups on the catalysts made them extremely efficient without the presence of any metal salts.

Introduction

The synthesis of homoallylic alcohols by allylation of different aldehydes and ketones has been an active topic of research for many years as homoallylic alcohols are important building blocks for the composition synthesis of biologically active compounds.[1,2] They have also been used as important precursors for a series of organic transformations such as cyclization reactions,[3] epoxidations, and aziridinations.[3–5]

Homoallylic alcohols can be formed by nucleophilic addition of different allyl reagents to ketones and aldehydes in the presence of variety of catalysts/additives.[6–8] However, the catalytic systems that are most commonly used for the homoallylation suffer with some limitations. For example, the most widely used reagents such as allyl tin complexes are not very suitable due to their high toxicities.[9,10] Also, the commonly used catalysts for these reactions involve various boron or transition metal-based lewis acids, tin and aluminum, which are extremely moisture sensitive in nature.[11] There are few reports where different metal salts such as $GdCl_3$, $CeCl_3$, and $ZrOCl_2$[12] have been used for carrying out these reactions. However, many of these reagents are expensive, corrosive or toxic, and hence highly unsuitable to be used for large-scale synthesis.

Another approach that has widely been used for the synthesis of homoallylic alcohols is the addition of various ligands/additives such as pyridine and bipyridyl derivatives to expedite these reactions.[10–12] However, the use of substituted ter-pyridine derivatives for similar role has not been much explored yet. In one of the reports by Kobayashi et al. the ter-pyridine was used as an additive in a CdF_2 catalyzed homoallylation reaction.[11d,11f,11g] This system also has limitations due to the high toxicity of CdF_2. Hence due to the limitations associated with various transition metals and Lewis/Bronsted acid catalyst used in homoallylation reactions, we were encouraged to generate a metal-free methodology to carry out such reactions.

In our continuing efforts toward achieving that goal, an efficient synthesis of homoallylic alcohols was done using a simpler Grignard reagent, allylmagnesium bromide, in the presence of different ter-pyridine derivatives as catalysts. No metal salts or free metals were used as co-catalysts during the course of the reaction. In the present study, different derivatives of ter-pyridine were used to carry out the reaction. The nitrogen of the pyridine rings act as the ligand toward the magnesium while the polar groups on the catalyst form a hydrogen bond, which help in the activation of the carbonyl group toward addition reaction. This allows for the formation of C—C bonds, resulting in good yields of homoallylic alcohols with improved reaction times.

Results and discussion

In our initial attempt, the reaction between benzaldehyde and allyl magnesium bromide (1 mmol, 1.0 M solution in hexane) in THF was carried out in a dry vial in the presence of di-(2-picolyl) amine (20 mol %). The reaction mixture was allowed to stir at room temperature for several hours. During this time, the reaction was

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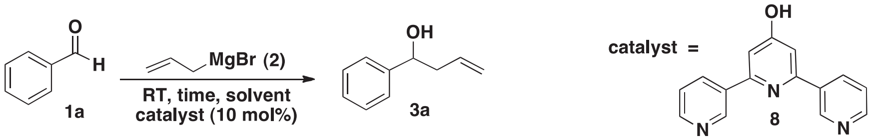
monitored by TLC (8:2/hexane/EtOAc) at every hour and after 10 h the reaction was quenched using saturated solution of ammonium chloride. The reaction mixture was then extracted with ethylacetate and ^{1}H NMR for the crude product **3a** was used to estimate the percent conversion of the reaction. The NMR showed 40% conversion after 10 h. Although no side product was formed, a large percentage of the aldehyde remained unreacted even after 10 h. We then tried the same reaction conditions with catalyst **8** and got very promising results.

We next investigated the effects of different solvent systems and reaction times on the reaction rate in the presence of catalyst **8**. The reaction was carried out at room temperature (RT) with 10 mol % of catalyst loading. It was found that, solvent has not much influence on the rate of the reaction however longer reaction period shows a better reaction conversion.

We then moved forward with the study and started screening different transition metal salts such as $CdCl_3$ and $SnCl_3$, in the presence of the dipyridyl ligand. And while performing one of the controlled reactions, it was accidentally found that one of the derivatives of ter-pyridine was behaving as a promising catalyst without the presence of any metal salt as lewis acid/base catalyst. Excited to get these results, we decided to pursue the testing of some more pyridine and ter-pyridine based derivatives as catalysts. These derivatives include dipyridyl, di-(2-picolyl)amine, ter-pyridine, 4′-chloro-2.2′:6,2″-terpyridine, 4′-hydroxy-2,2′:6,2″ terpyridine, and 4′-thio-2,2′:6′,2″-terpyridine (Table 1).

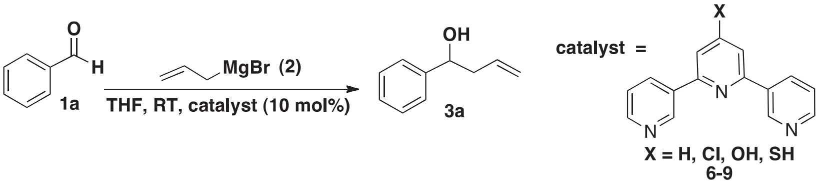
As summarized in Table 2, the use of pyridyl derivatives alone was not enough to catalyze the reaction. When the ^{1}H NMR of the reaction catalyzed by pyridyl derivatives was tested, poor yields were obtained even with very long reaction times. No product formation was obtained with dipyridyl (**4**, entry 1, Table 2) and with di-(2-picolyl)amine (**5**, entry 2, Table 2), only 40% conversion was seen after 10 h. The crude products were used to run the ^{1}H NMR to get the more precise conversion rates. The crude ^{1}H NMR for the reaction showed an ample amount of unreacted aldehyde but no side product formation was indicated. We then started screening the ter-pyridine derivatives starting with 4′-chloro-2,2′:6′,2″-terpyridine (**7**, entry 4, Table 2, entry 4). Surprisingly, 4′-chloro-2,2′:6′,2″-terpyridine (**7**) did not give a good reaction profile and reaction was never completed even after running overnight. However, when we use the commercially available 4′-hydroxy-2,2′:6′,2″-terpyridine (**8**, entry 5, Table 2), the percent conversion was very high as well as the reaction time was reduced to 2 h. With this motivation, we searched for different ter-pyridine related catalysts and found that the 4′-thio-2,2′:6′,2″-terpyridine (**9**, entry 5, Table 2) was a very effective catalyst too with almost the same efficiency as that of **8**. Also, with 3 mol % of catalyst **8**, only 40% reaction conversion was observed after 3 h. However,

Table 1
Effect of solvent and reaction time on the reaction



S. No.	Solvent	Reaction time (h)	Yield (%)
1	Tetrahydrofuran	1	42
		2	83
		3	96
2	Dichloromethane	1	23
		2	30
		3	38
3	Acetonitrile	2	26
		7	36
4	1,4-Dioxane	8	26

Table 2
Effect of various catalysts on the allylation of carbonyl compounds[a,b]



S. No.	Catalyst	Time (h)	Yield (%)
1	Dipyridyl (**4**)	12	No reaction
2	Di-(2-picolyl)amine (**5**)	10	40
3	Ter-pyridine (**6**)	Overnight	21
4	4′-Chloro-2,2′:6′,2″-terpyridine (**7**)	14	28
5	4′-Hydroxy-2,2′:6′,2″-terpyridine (**8**)	2.5	94
6	4′-Thio-2,2′:6′,2″-terpyridine (**9**)	2.5	91
7	No catalyst	Overnight	28

[a] All reactions were carried out at −30 °C–rt in THF.
[b] Percent conversion has been determined using ^{1}H NMR of crude products.

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