Ligand-Accelerated Cadmium-catalyzed Allylation of Aldehydes and Ketones in Aqueous Media

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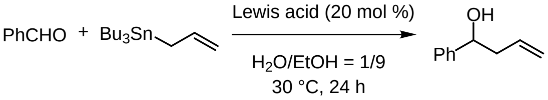
Abstract: Cadmium perchlorate was found to catalyze allylation reactions using allyltributyltin in aqueous media very efficiently. These cadmium-catalyzed allylation reactions are accelerated by ligands such as *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine or 2,9-dimethylphenanthroline. This accelerated catalytic system gave allylation products of various aldehydes and ketones in high yields.

Key words: cadmium, allylation, allyltin, ligand acceleration, aqueous media

Allylation reactions of carbonyl compounds, which afford synthetically useful homoallylic alcohols, have been a subject of extensive investigation.[1] On the other hand, the development of allylation reactions in aqueous media has attracted great attention because of the easy handling, water-tolerance, and unique reactivity of the methodology.[2] Although several kinds of Lewis acid- or Brønsted acid-catalyzed allylation reactions in aqueous media with allyltributyltin have been reported,[3] it is necessary to develop more active and efficient catalysts. In the course of our investigations to exploit new synthetic reactions in aqueous media,[4] we have demonstrated scandium triflate-catalyzed allylation reactions of carbonyl compounds with tetraallyltin in aqueous media.[5] To expand the utility and applicability of the allylation reactions, we have investigated further to develop more efficient catalytic systems. Herein, we report cadmium-catalyzed allylation reactions with allyltributyltin in aqueous media. In this catalytic system, remarkable acceleration by ligands was observed, and not only aldehydes but also ketones reacted with allyltributyltin to afford the corresponding allylated adducts in high yields.

First, we screened several Lewis acids for the allylation reaction of benzaldehyde (1 equiv) with allyltributyltin (1.2 equiv) in a typical aqueous media, H_2O–EtOH = 1:9 (6 mL/1 mmol of benzaldehyde) (Table 1). Among Lewis acids tested, indium perchlorate and cadmium perchlorate were found to catalyze allylation very effectively (entries 7 and 9). Furthermore, it is noteworthy that, when quenched in 6 h, cadmium perchlorate gave the corresponding allylation product in the highest yield (entry 7). It has been reported that a stoichiometric amount of metallic Cd promoted Barbier-type allylation reactions in aqueous media.[6] On the other hand, cadmium-catalyzed reactions (catalytic use of cadmium components) are rare in synthetic reactions even in organic solvents,[7] and, as far as we know, the present system is the first example of cadmium-catalyzed allylation of carbonyl compounds.

Table 1 Screening of Lewis Acids in Allylation in Aqueous Media



Entry	Lewis acid	Yield (%)
1	$Sc(OTf)_3$	49
2	$Y(OTf)_3$	20
3	$La(OTf)_3$	5
4	$Cu(OTf)_2$	21
5	AgOTf	5
6	$Zn(OTf)_2$	59
7	$Cd(ClO_4)_2$	90 (85[a])
8	$Ga(OTf)_3$	34
9	$In(ClO_4)_3$	89 (73[a])
10	$Sc(OTf)_2$	34
11	$Pb(ClO_4)_2$	65

[a] Reaction time is 6 h.

Next, we investigated the effect of ligands in the cadmium-catalyzed allylation (Table 2), because ligand acceleration is an interesting topic in metal-catalyzed organic reactions.[8] However, our initial attempts to realize ligand acceleration failed. For example, addition of amines such as **1a**, **1b**, and **1c** led to lower yields (entries 2-4) than in the case of no ligand (entry 1). Addition of methylated diamine **2a** and tetramine **2c** also led to lower yields (entries 5 and 7). These ligands did not accelerate the reaction but decelerated it. On the other hand, dramatic ligand acceleration was observed in the case of *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (**2b**, entry 6), and the product was obtained in excellent yield in 30 min. Figure shows the reaction profiles for the cadmium perchlorate-catalyzed allylation in the presence and absence of **2b**, indicating that

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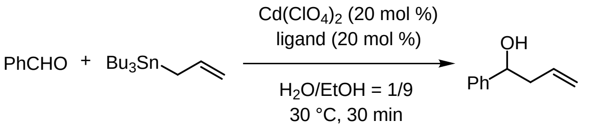
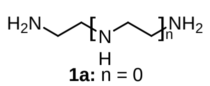
the ligand acceleration occurred. Using **2b**, we also succeeded in decreasing the amount of the catalyst. Five mol% of cadmium perchlorate and **2b** gave the product in 88% yield after 16 h. In the case of pyridine-type bidentate ligands, 2,2′-dipyridyl (**3**) and 1,10-phenanthroline (**4**), the product was obtained in lower yields (entries 8 and 9). However, 2,9-dimethylphenanthroline (**5**) gave excellent yield (entry 10). In this ligand acceleration, the methyl groups of the ligands play a very important role, and it should be noted that subtle structural differences in the ligands greatly affected the catalytic activity of cadmium. When this reaction was performed in dichloromethane, the reaction proceeded much more slowly, and ligand acceleration by **2b** or **5** was not observed (without ligand: 13% yield for 30 min; with **2b**: 10% yield; with **5**: trace). This result indicates that the ligand acceleration is a characteristic feature of the allylation reactions in aqueous media. Although 2,6-lutidine (**6**) has been reported to accelerate zinc triflate-catalyzed allylation of ketones,[9] it did not work well in the cadmium-catalyzed allylation in aqueous media (entry 11).

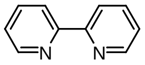
Table 2 The Effect of Ligands in Cadmium-Catalyzed Allylation



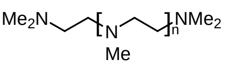
Entry	Ligand	Yield (%)
1	–	50
2	**1a**	40
3	**1b**	35
4	**1c**	14
5	**2a**	35
6	**2b**	91
7	**2c**	2
8	**3**	28
9	**4**	39
10	**5**	92
11	**6**	53



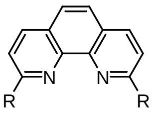
1a: n = 0
1b: n = 1
1c: n = 2



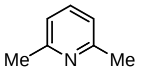
3



2a: n = 0
2b: n = 1
2c: n = 2



4: R = H
5: R = Me



6

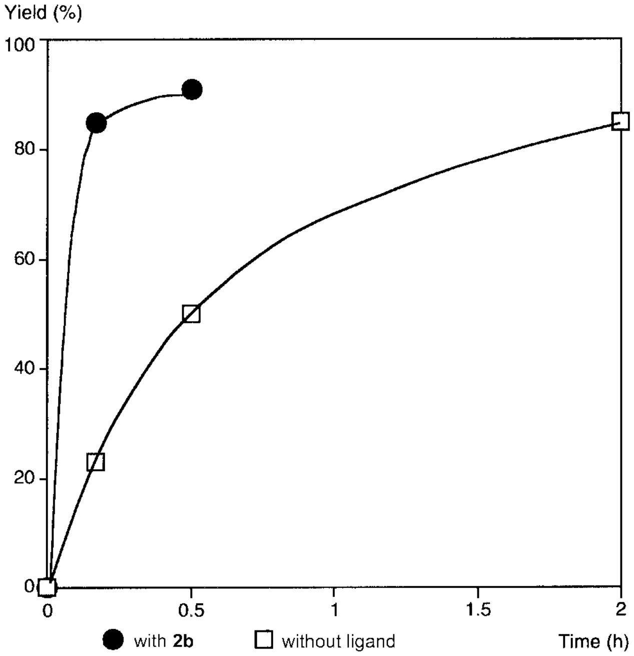


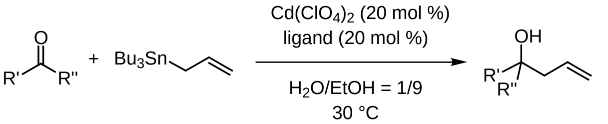
Figure Reaction profiles for the cadmium perchlorate-catalyzed reaction of benzaldehyde with allyltributyltin in H_2O–EtOH (1:9) at 30 °C.

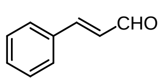
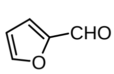
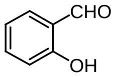
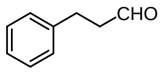
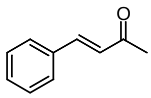
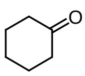
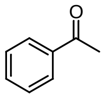
These catalytic systems were applied to allylation of various aldehydes and ketones (Table 3). Aldehydes gave their allylated adducts in excellent yields. In the case of ketones,[5a,9,10] the allylated adducts were obtained in high yields by increasing the equivalent of allyltributyltin. This is the first example of catalytic allylation reactions of ketones using allyltributyltin in aqueous media.

Considering toxicity of cadmium compounds, it is desirable to recover and reuse the cadmium catalyst. In the present catalytic system using cadmium perchlorate and **2b**, the recovery of the cadmium salt was realized by extraction with water (3 times) after diluting of a reaction mixture with ether. ICP-MS determination of cadmium amount in the organic phase showed that more than 99.999% cadmium was extracted with water. Furthermore, ligand **2b** was also extracted with water. Thus, it is possible, in principle, to reuse the catalyst and the ligand after concentrating the aqueous phase.

The mechanism of the cadmium-catalyzed allylation including the ligand acceleration has not yet been clarified. It is known that allylation reactions proceed via a Lewis acid pathway (activation of carbonyl compounds by metal coordination) or via a transmetalation pathway (formation of allylmetals from allyltins and metal salts).[11] The result that Lewis bases such as **2b** and **5** accelerate allylation reactions suggests that the allylation proceeds via the transmetalation pathway, because Lewis bases are likely to reduce the Lewis acidity of the cadmium cation.[12] The result that scandium triflate, which is regarded as a much stronger Lewis acid than cadmium salts, was inferior to cadmium perchlorate would also imply the transmetalation pathway.

Table 3 Cadmium-Catalyzed Allylation of Aldehydes and Ketones



Entry	Substrate	Time (h)	Ligand	Yield (%)
1		0.5	**5**	97
2		0.5	**2b**	86
3		10	**2b**	98
4		0.5	**2b**	91
5[a]		42	**5**	93
6[a]		48	**2b**	94
7[b]		48	**2b**	90

[a] Allyltributyltin (2 equiv) was used.

[b] Allyltributyltin (3 equiv) was used.

In conclusion, we have discovered that cadmium perchlorate catalyzes allylation reactions using allyltributyltin in aqueous media very efficiently. These cadmium-catalyzed allylation reactions are accelerated by ligands such as **2b** or **5**. This accelerated catalytic system gave allylation products of various aldehydes and ketones in high yields. As far as we know, this is the first example of allylation of ketones using allyltributyltin in aqueous media. Although the mechanism of the reaction and the ligand acceleration is not clear, it must be emphasized that slight changes of ligand structure drastically alter the catalytic activity of the metal. Further investigation on diastereo- and enantioselective allylation reactions in aqueous media using this novel catalyst system and elucidation of the mechanism of the ligand acceleration are currently in progress in our laboratory.

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