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Tetrahedron Letters 46 (2005) 6247–6251

Tetrahedron Letters

Barbier coupling in water: $SnCl_2$-mediated and $Co(acac)_2$-catalyzed allylation of carbonyls

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Received 11 May 2005; revised 5 July 2005; accepted 14 July 2005

Abstract—$Co(acac)_2{\cdot}2H_2O$ efficiently catalyzes $SnCl_2$-mediated Barbier coupling in water between carbonyls, including aromatic, aliphatic and α,β-unsaturated aldehydes, ketones, sugars and allyl bromide to afford the corresponding homoallylic alcohols in high yields. The catalyst was reused for several cycles with consistent activity.

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The Barbier reaction[1] is a century old C–C bond forming reaction involving a coupling reaction between a carbonyl function and an organic halide mediated by a metal to afford the corresponding alcohol. Its synthetic utility was overtaken mainly by Grignard and related organometallic reactions, largely because the classical Barbier reactions suffered from the problems of interference from a host of side reactions especially reductions and couplings (cf. pinacol coupling of carbonyls and Wurtz coupling of halides)[2] in organic solvents. Significantly, if it is carried out in an aqueous medium, the desired product is obtained, almost quantitatively, if not exclusively. This realization gained momentum through the elegant contributions of Luche,[3] Nakami,[4] Benezra,[5] Li and Chan,[2,6] Whitesides,[7] Roy[8] and Liu and Guo.[9] An important incentive in this development is that the solvent water satisfies the demands of 'Green Chemistry.'[10] The developments in Barbier reactions in water are: (i) a large number of reagents and reaction protocols have been developed for the synthesis of homoallylic alcohols,[3–9] (ii) many metals viz. aluminium,[11] indium,[6a,12] antimony,[6g] bismuth,[13] lead,[14] manganese,[6e] magnesium,[6f] zinc,[15] tin,[2,16] cadmium,[17] gallium[18] and copper[9a] have been reported to be effective. Being heterogeneous in nature, metal-mediated reactions often pose operational problems (e.g., stirring), in addition, the conversion of starting materials to the products can be incomplete presumably because of passivity of the catalyst caused by oxo or hydroxo metal coating in the course of the reaction. The use of hydrobromic acid[4a,b] or ultrasonication together with saturated aqueous NH_4Cl/THF[3] to activate the metal, improves the yields. Our experience in catalytic organic transformations[19] in conjunction with information in recent publications[2–9,11–18] on metal mediated C–C bond forming reactions, suggested to us that a combination of a water-soluble reductive salt (e.g., $SnCl_2$) as a mediator and an appropriately water soluble, redox active, reusable metal complex as the catalyst would perhaps serve as a general activator for the metal. The bimetallic nature of the reagent and the significant effect of water to facilitate the reaction by in situ generation of reactive hydrated/hydroxyl organotin species are important. A suitable catalyst would be cost effective, reusable over several cycles of reactions and have appreciable shelf life, some solubility in water without decomposition or hydrolysis and easily accessible variable oxidation states. An appropriate catalyst is essential since in water, $SnCl_2$ alone cannot mediate the desired reaction.

Four recent reports using Pd(II),[20] Cu(II)[8a,9a] or Ti(III)[9b] as efficient catalysts are of direct relevance to the present work. However, Pd and Ti based catalysts are expensive, the former also needing biphasic conditions, while $TiCl_3$ has inherent stability problems and requires careful handling. The Cu(II) catalyzed reactions were conducted under nitrogen since the active catalyst Cu(I) is prone to easy oxidation. $TiCl_3$ is not efficient for ketones[9b] and Cu(II) is poor in allylation of aldehydes, RCHO, with R being cinnamyl, *n*-hexyl or

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Keywords: Cobalt(II) acetylacetonate; Allylation; Water; Carbonyl; Ketones; Sugars.

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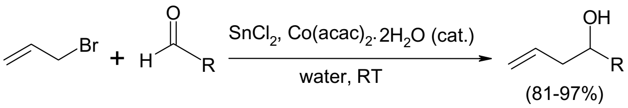
0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.07.060

2-furyl.[9a] Moreover, it is not clear if carbohydrate allylation would be possible with these catalysts.

We now disclose our results on the Barbier allylation of a variety of substrates using $SnCl_2$/$Co(acac)_2{\cdot}2H_2O$ as the reagent system.[21] Incidentally, we have reported a very easy access[22] to metal acetylacetonates including $Co(acac)_2{\cdot}2H_2O$. The chosen catalyst has easily accessible variable oxidation states, the required solubility in water with no apparent hydrolysis and is capable of acting as a Lewis acid (Scheme 1).



Scheme 1.

Table 1. $SnCl_2$-mediated and $Co(acac)_2$-catalyzed carbonyl allylation

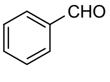
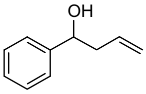
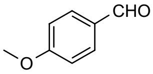
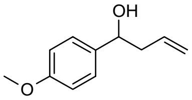
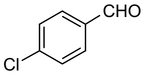
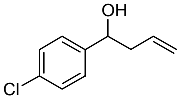
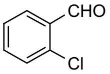
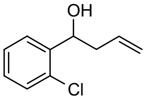
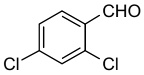
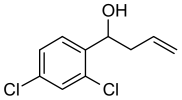
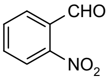
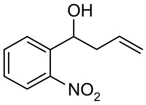
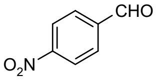
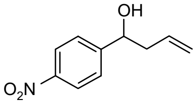
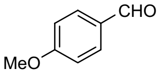
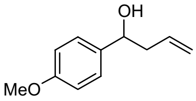
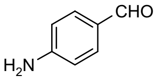
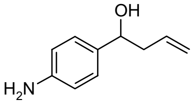
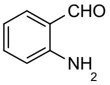
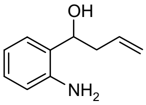
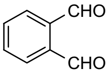
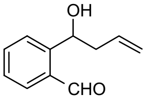
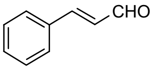
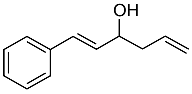
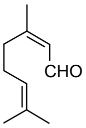
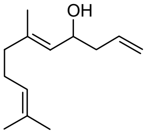
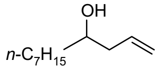
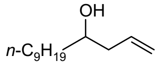
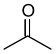
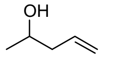
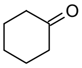
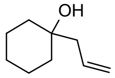
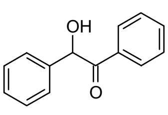
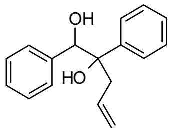
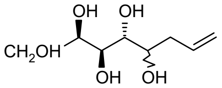
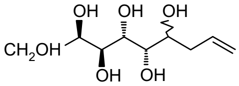
Entry	Substrate	Product	Time (h)	Yield%[a]
1			6	97
2			6	93
3			6	91
4			6	94
5			6	93
6			6	96
7			6	94
8			6	92
9			6	95
10			6	91
11			6	90
12			8	92
13			8	85

Table 1 (*continued*)

Entry	Substrate	Product	Time (h)	Yield%[a]
14	*n*-$C_7H_{15}CHO$		8	90
15	*n*-$C_9H_{19}CHO$		8	88
16			18	85
17			18	81
18			18	89
19	D-Arabinose		18	81
20	L-Mannose		18	83

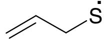
[a] Isolated yield.

No organic co-solvent or assistance of ultrasonic irradiation is required thereby providing a clear advantage over the reactions catalyzed by zero valent metals. The experimental results are summarized in Table 1. The identity of the products was confirmed by comparing the ^1H NMR (300 and 400 MHz) and FTIR spectral data with reported results.[7c,9,23]

Following our typical reaction procedure,[21] aldehydes and ketones (entries 1–15 and 16–18), aliphatic and aromatic carbonyls (entries 12–20 and 1–11) and nitro substituted substrates (entries 6 and 7) were allylated efficiently. For the substrates containing an active hydrogen, the reagent works well without any need for protection (entries 14–17). Similarly, for α,β-unsaturated aldehydes (entries 12 and 13) only 1,2-addition products were obtained. No pinacol coupling was observed in such reactions. All these results point to a large scope for the $SnCl_2/Co(acac)_2{\cdot}2H_2O$ system.

It is significant that the present protocol successfully effects allylation of unprotected sugars in water. Thus, the $SnCl_2/Co(acac)_2{\cdot}2H_2O$ combination brought about smooth reactions between D-arabinose or L-mannose and allyl bromide affording the corresponding homoallylic alcohols in 81% and 83% yields.

In order to further broaden the scope, a few reactions were conducted with allyl chloride. Thus, aromatic carbonyl substrates (Table 1, entries 1–3) were reacted with allyl chloride under conditions similar to those used for allyl bromide. The corresponding homoallylic products were obtained in comparable yields.

In view of a facile Co(II)–Co(III) redox cycling, it is possible that an allyl halide radical is first formed by the transfer of an electron from cobalt(II), which in turn interacts with $SnCl_2$ to give an  radical. This would then react with cobalt(III) to produce cobalt(II) and a neutral allylated derivative, which would finally add to the carbonyl group yielding the homoallylic alcohol. This reaction might also be facilitated by simultaneous Lewis acid (cf. Co(II)) catalyzed activation of the carbonyl group. We refrain from making any further comment on the mechanism at the moment in the absence of further results. A notable feature of the $Co(acac)_2{\cdot}2H_2O$ catalyst is its reusability. The results presented in

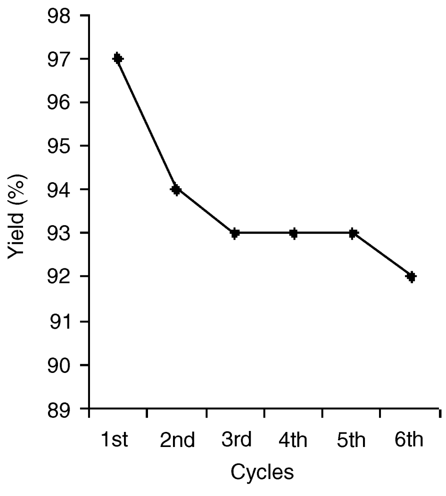


Figure 1. Recycling of the catalyst for the allylation of benzaldehyde.

Table 2. $SnCl_2$-mediated allylation of benzaldehyde using various metal acetylacetonate catalysts

Entry	Catalyst	Time (h)	Yield (%)
1	$Co(acac)_2\cdot 2H_2O$	6	97
2	$VO(acac)_2$	30	15
3	$Fe(acac)_3$	30	10
4	$Cr(acac)_3$	18	95

Figure 1 show that six cycles of the reaction could be conducted with high throughput and one time loading of the catalyst.

It may be relevant to mention that allylations of benzaldehyde using different metal acetylacetonate catalysts, for example, $VO(acac)_2$, $Fe(acac)_3$, $Cr(acac)_3$ and $Co(acac)_2\cdot 2H_2O$ (Table 2) did not proceed with equal alacrity. For $VO(acac)_2$ and $Fe(acac)_3$, the yields were very low (10–15%) even after 30 h of reaction. $Cr(acac)_3$ and $Co(acac)_2\cdot 2H_2O$ were far more effective in catalyzing the allylations although the former took relatively longer. Thus, $Co(acac)_2\cdot 2H_2O$ was the catalyst of choice.

In conclusion, $Co(acac)_2\cdot 2H_2O$ appears to be an effective, reusable catalyst for $SnCl_2$ mediated carbonyl allylation of a wide range of aldehydes, ketones and carbohydrates. The main advantages of the catalyst include ease of preparation, stability and high activity and solubility in water.

Acknowledgements

S.K.D. is an IITG research fellow. S.H. thanks the Council of Scientific and Industrial Research (CSIR), India, for providing a research fellowship.

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21. Typical procedure for allylation of carbonyls: To 15 mL of water, were added $Co(acac)_2\cdot 2H_2O$ (0.1 mmol, 0.029 g), $SnCl_2\cdot 2H_2O$ (1.2 mmol, 0.271 g), allyl bromide (1.2 mmol, 0.144 g) and benzaldehyde (1 mmol, 0.106 g), and the reaction mixture was stirred at room temperature for the

time given in Table 1. The reaction was monitored by TLC and on completion of the reaction, the product was extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with water several times until the aqueous layer became colourless, then dried (Na_2SO_4), concentrated and purified by column (silica) chromatography (hexane/ethyl acetate, 90/10, v/v) to afford the pure compound. Yield: 0.144 g, 97%. IR (cm^{-1}) 3400, 3070, 1641, 1600, 1496, 1446, 1049. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 7.40–7.25 (m, 5H), 5.90–5.75 (m, 1H), 5.20–5.14 (m, 2H), 4.75 (t, $J = 6.6$ Hz, 1H), 2.50–2.46 (m, 2H), 2.20–1.85 (br, 1H).

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