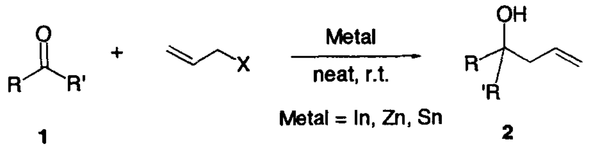
SYNTHETIC COMMUNICATIONS, 28(16), 2999-3009 (1998)

METAL-MEDIATED BARBIER-TYPE CARBONYL ALLYLATION UNDER SOLVENT-FREE CONDITIONS

Xiang-Hui Yi, John X. Haberman, and Chao-Jun Li*
Department of Chemistry, Tulane University, New Orleans, LA 70118, USA

Abstract: Zinc, tin, and indium mediated Barbier-type cross coupling between carbonyl compounds and allyl halides have been investigated without additional solvent. The indium mediated reactions proceed effectively under solvent free conditions. To a more limited extent, the reactions were found to be mediated by zinc and tin. Various carbonyl compounds are transformed into the corresponding allylation product in this way. No apparent competing pinacol-coupling or homo-coupling of the allyl halide was observed.

Recently, there has been a considerable interest in the study of no-solvent conditions for organic reactions and synthesis because of environmental concerns and more drastic restrictions on 'solvent pollution'.[1] The metal-mediated reaction between a carbonyl compound and an organic halide (the Barbier-Grignard type reaction) is a fundamental reaction in organic chemistry and one of the most useful methods for carbon-carbon bond formation.[2] Various metals, such as zinc,[3] magnesium,[4] and lithium,[5] have been developed to effect such a reaction. However, under solvent free conditions, all reactants are in close contact and formation of various by-products would be expected in the Barbier-Grignard processes due to the complex nature of such a reaction process. Herein we report our study of metal-mediated reactions under solvent-free conditions. In particular, we found that the indium[6] mediated coupling between carbonyl compounds and allyl bromides under solventless conditions is very facile, giving the cross-coupled product selectively (Eq. 1). Tin and zinc were both found to mediate this reaction. However, longer reaction times were generally required, and the yields obtained were not as high as those in the indium mediated reactions. Also exothermic polymerization seemed to be facilitated in a number of the reactions. This occurred despite lowering the temperature of the reaction in water and ice water baths. Though the yields in the tin reactions were not optimized, the reactivity of the tin seems to paralell that of zinc.



(1)

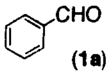
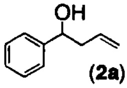
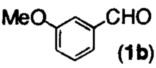
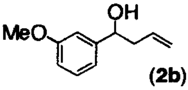
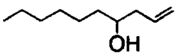
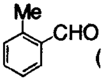
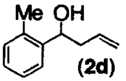
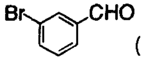
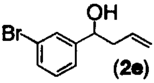
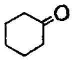
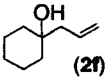
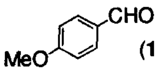
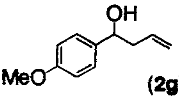
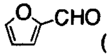
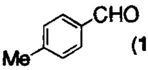
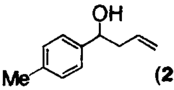
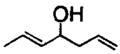
To start this research, a mixture of benzaldehyde, allyl bromide, and indium powder was stirred at room temperature and under an atmosphere of air. Within a few minutes, an exothermic reaction took place and the mixture turned yellowish. When the stirring was continued for about an hour, instant polymerization occurred. The reaction mixture turned, in a few seconds, into a solid that was insoluble in both diethyl ether and 1N aqueous HCl. It is not clear, at this moment, what causes the instant polymerization. By controlling the reaction temperature at or below room temperature with a water bath, in which the reaction mixture was constantly maintained as a liquid, no polymerization was observed even after a longer stirring period. The reaction was then stopped by quenching with 1N aqueous HCl followed by extraction with diethyl ether. After work-up, the ^{1}H NMR of the crude material revealed that the coupling product was cleanly formed together with a very small amount of the unconverted aldehyde. It was a surprise to notice that no appreciable amount of by-product, e.g., pinacol coupling product,[7] was observed by ^{1}H NMR of the crude reaction mixture. Subsequently, flash column chromatography on silica gel provided an 88% isolated yield of the desired product. Allyl chloride can also be used in place of allyl bromide. However, the rate of the reaction is much slower. After stirring a mixture of allyl chloride, benzaldehyde and indium for 80 min, about 17% conversion was observed. The allylation with allyl bromide was then carried out on a variety of carbonyl compounds (Table 1). In all cases during our investigation, the corresponding products were obtained smoothly with very little by-product being detected, except for furaldehyde, which polymerized rapidly. Aliphatic aldehydes gave yields comparable to those of aromatic aldehydes (Entries 6 and 13). Cyclohexanone reacted similarly (Entry 9). The reaction of an α,β-unsaturated aldehyde gave the 1,2-addition product exclusively (Entry 13). For the aromatic aldehydes, the presence of various substituents, e.g., a methyl, a methoxy, or a bromo, on the aromatic ring did not have a significant effect on the rate or yield of the reaction.

Mechanistic Discussions:

The allylation of carbonyl compounds with an organometallic reagent is generally regarded as proceeding through the following mechanism (Scheme 1).[2] Although a six-membered ring transition state has been accepted as a standard in the carbon-carbon bond formation stage,[8] the way the allylmetal species is formed is still the subject of controversy. It is generally assumed that the reaction begins with a single-electron-transfer (SET) mechanism involving a radical or a radical anion.[9]

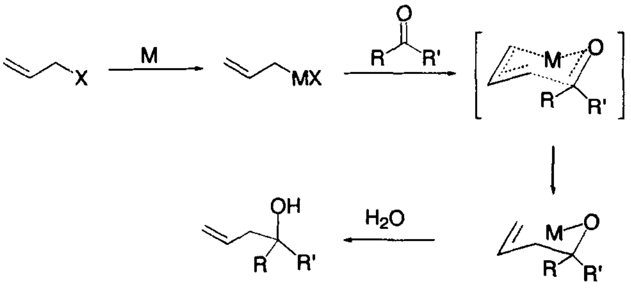
If indeed that is the case, then under solvent-free conditions, at least three potential reactions are competing with one another: the homo-coupling of carbonyl compounds, the homo-coupling of allyl bromide, and the cross coupling between the carbonyl compounds and allyl bromide. However, in each case during our study with indium, the cross coupling product was formed almost exclusively and the contributions of the other competing reactions, seemingly equally feasible, are minimal.

Table 1. Metal-Mediated Allylation of Carbonyl Compounds under Neat Conditions

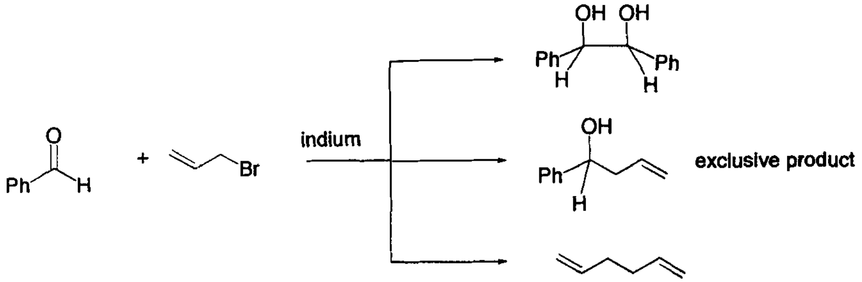
Entry	Carbonyl Compound (1)	Metal	Product (2)	Yield(%)
1	 **(1a)**	In	 **(2a)**	88
2		Zn		67^{a}
3		Sn		60^{b}
4	 **(1b)**	In	 **(2b)**	79
5		Zn		36^{a}
6	 **(1c)**	In	 **(2c)**	62
7	 **(1d)**	In	 **(2d)**	72
8	 **(1e)**	In	 **(2e)**	78
9	 **(1f)**	In	 **(2f)**	72
10	 **(1g)**	In	 **(2g)**	83
11	 **(1h)**	In	polymerized	
12	 **(1i)**	In	 **(2i)**	60
13	 **(1j)**	In	 **(2j)**	66

All the reactions were carried out at room temperature for 1h with the ratio of reactants as: carbonyl/halide/indium=1/2/1.5. Yields were isolated ones after column chromatography on silica gel and have not been optimized. a: 12h. b: 12h and yield was estimated from ^{1}HNMR.

Scheme 1.



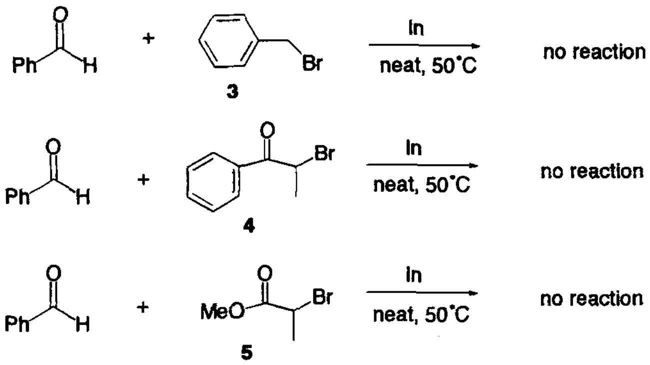
Scheme 2.



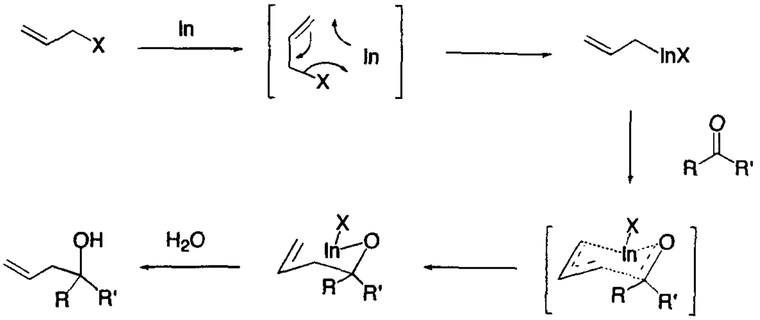
This observation was further confirmed by interrupting a reaction between benzaldehyde and allyl bromide mediated by indium and directly measuring ^{1}H NMR of the reaction mixture (Scheme 2). Again, no substantial by-product was observed.

In addition, cross-coupling was examined between an aldehyde and benzylic bromide (**3**), as well as between an aldehyde and α-halo carbonyl compounds (**4** and **5**). Because both types of halides would have lower reductive potentials, a similar or even higher reactivity would expected with these coupling reactions. However, no

Scheme 3.



Scheme 4. Proposed Mechanism for Indium Mediated Allylation under Solvent-Free Conditions



reaction was observed in either case under a variety of conditions including a higher reaction temperature (Scheme 3).

These interesting observations led us to consider alternative path-ways for the formation of allylmetal species from the allyl halide and metal. We thus tentatively propose a [4+2] thermo process for the formation of allylindium species. Then, following another pseudo [4+2] process, the corresponding allylation product is formed. In this proposed mechanism, it would be expected that no reaction would be observed when the allyl bromide is absent. This is indeed the case. Such a modified mechanism can also explain the lack of reactivity with benzyl bromide and α-halo carbonyl compounds. Because, in the former case, no [4+2] process is possible, whereas in the latter cases, a higher activation energy is required for indium to attack the carbonyl oxygen.

In conclusion, indium mediated carbonyl allylation was found to be very effective under solvent-free conditions. The use of zinc or tin for such a reaction was less effective. The potential competing reactions were not observed under the indium mediated reaction conditions. A [4+2] process is proposed for the formation of allylindium species from allyl halide and indium metal.

Experimental Section

Commercially available compounds were used without further purification. Flash chromatography employed E. Merck silica gel (Kiesegel 60, 230-400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ from G.E. Omega 400 (400 MHz) instrument, with TMS as an internal standard. Infra-Red spectra were performed on FT-IR (Mattson Cygnus 100).

General Procedure for the Allylation Reaction:

A neat mixture of benzadehyde (217 mg, 2.05 mmol), allyl bromide (500 mg, 4.13 mmol) and indium powder (348 mg, 3.03 mmol) was stoppered and stirred vigorously for 1 hr at room temperature. The reaction was then quenched by adding 1 N HCl aqueous solution and was followed by extracting with diethyl ether 3 mL (x3). The ethereal solution was then washed with saturated sodium bicarbonate aqueous solution and brine. After being dried over magnesium sulfate, the solution was filtered and concentrated under vacuum to give the crude product, which was subsequently purified by flash chromatography on silica gel to give the desired 1-phenyl-3-buten-1-ol (266 mg, 88%).

Characerization of the Products:

All compounds involved in this study are previously known and the spectroscopy data have been compared with authetic samples. The CA-registration numbers of all compounds are listed at the end of the text.

1-Phenyl-3-buten-1-ol (**2a**): IR(film): 3370, 3070, 1640 cm^{-1}. ^{1}H NMR(400 MHz, $CDCl_3$, ppm): δ 2.2-2.3(br, 1H), 2.45-2.57(m, 2H), 4.72(dd, J = 7.2, 5.6 Hz, 1H), 5.12-5.20(m, 2H), 5.75-5.87(m, 1H), 7.25-7.40(m, 5H). ^{13}C NMR(100 MHz, $CDCl_3$, ppm): δ 43.8, 73.4, 118.3, 125.9, 127.6, 128.4, 134.6, 143.9.

1-(3-Methoxyphenyl)-3-buten-1-ol (**2b**): IR(film): 3370, 3070, 1640 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.20-2.35(br, 1H), 2.42-2.56(m, 2H), 3.78(s, 3H), 4.68(dd, J = 7.6, 5.6 Hz, 1H), 5.10-5.20(m, 2H), 5.74-5.86(m, 1H), 6.78-6.85(m, 1H), 6.89-6.95(m, 2H), 7.22-7.30(t, J = 8.0 Hz, 1H). ^{13}C NMR(100 MHz, $CDCl_3$, ppm): δ 14.1, 22.6, 25.6, 29.3, 31.8, 36.8, 41.9, 70.6, 118.0, 134.9

1-Decen-4-ol (**2c**): IR(film): 3370, 3070, 1640 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 0.86(t, J = 6.8 Hz, 3H), 1.20-1.50(m, 10H), 1.65-1.77(br, 1H), 2.08-2.16(m, 1H), 2.25-2.32(m, 1H), 3.59-3.64(m, 1H), 5.08-5.15(m, 2H), 5.76-5.87(m, 1H). ^{13}C NMR(100 MHz, $CDCl_3$, ppm): δ 14.1, 22.6, 25.6, 29.3, 31.8, 36.8, 41.9, 70.6, 118.0, 134.9.

1-(2-Methylphenyl)-buten-1-ol (**2d**): IR(film): 3370, 3070, 1640 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.10-2.20(br, 1H), 2.35(s, 3H), 2.39-2.55(m, 2H), 4.96(dd, J = 8.0, 3.6 Hz, 1H), 5.13-5.24(m, 2H), 5.81-5.93(m, 1H), 7.12-7.28 (m, 3H), 7.49 (d, J = 7.2Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 19.1, 42.6, 69.7, 118.2, 125.3, 126.3, 127.2, 130.3, 134.4, 134.8, 142.0.

1-(3-Bromophenyl)-3-buten-1-ol (**2e**): IR(film): 3360, 3070, 1640 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.35-2.53(m, 3H), 4.65(dd, J = 8.0, 5.2 Hz, 1H), 5.10-5.20(m, 2H), 5.70-5.81(m, 1H), 7.16-7.26(m, 2H), 7.39(dt, J = 7.6, 2.0 Hz, 1H), 7.49(t, J =1.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 43.7, 72.6, 118.8, 122.5, 124.5, 128.9, 130.0, 130.5, 133.9, 146.2.

1-(2-Propenyl)-cyclohexanol (**2f**): IR(film): 3400, 3070, 1640 cm^{-1}. ^{1}H NMR(400 MHz, $CDCl_3$, ppm): δ 1.20-1.70 (m, 11H), 2.20(d, J = 7.2Hz, 2H), 5.06-5.20(m, 2H), 5.82-5.95(m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 22.2, 25.7, 37.3, 46.7, 70.9, 118.7, 133.7.

1-(4-Methoxyphenyl)-3-buten-1-ol (**2g**): IR(film): 3370, 3070, 1640 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 2.24-2.30(br, 1H), 2.48(t, J = 6.8 Hz, 2H), 3.79(s, 3H), 4.65(t, J = 6.4 Hz, 2H), 5.08-5.18(m, 2H), 5.72-5.90(m, 1H), 6.87(dt, J = 8.4, 2.0 Hz, 2H), 7.26(dt, J = 8.4, 2.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 43.7, 55.2, 73.0, 113.7, 117.9, 127.2, 134.8, 136.2, 158.9.

1-(4-Methylphenyl)-buten-1-ol (**2i**): IR(film): 3360, 3070, 1640 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 1.90-2.10(br, 1H), 2.35 (s, 3H), 2.48-2.52 (m, 2H), 4.70 (dd, J = 6.0, 7.2 Hz, 1H), 5.11-5.19(m, 2H), 5.75-5.86(m, 1H), 7.16(d,J = 8.0 Hz, 2H), 7.25(d,J = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 21.1, 43.8, 73.2, 118.3, 125.8, 129.1, 134.6, 137.2, 140.9.

1, 5-Heptadien-4-ol (**2j**): IR(film): 3360, 3070, 1640 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 1.67(d, 3H, J = 6.4 Hz), 1.82-1.92(br, 1H), 2.19-2.33(m, 2H), 4.08(dd, 1H, J = 6.4, 12.8 Hz), 5.05-5.15(m, 2H), 5.44-5.53(m, 1H), 5.61-5.71(m, 1H), 5.72-5.84(m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 17.7, 41.9, 71.8, 117.9, 126.9, 133.3, 134.5.

Registration Numbers: 1-Phenyl-3-buten-1-ol (**2a**), [936-58-3]; 1-(3-Methoxyphenyl)-3-buten-1-ol (**2b**), [24165-65-9]; 1-Decen-4-ol (**2c**), [36971-14-9]; 1-(2-Methylphenyl)-3-buten-1-ol (**2d**), [24165-62-6]; 1-(3-Bromophenyl)-3-buten-1-ol (**2e**), [114095-73-7]; 1-(2-Propenyl)-cyclohexanol (**2f**), [1123-34-8]; 1-(4-Methoxyphenyl)-3-buten-1-ol (**2g**), [24165-60-4]; 1-(4-Methylphenyl)-3-buten-1-ol (**2i**), [24165-63-7]; 1,5-Heptadien-4-ol (**2j**), [81027-99-8].

ACKNOWLEDGMENT. We gratefully acknowledge support by the US NSF-EPA Joint Program for a Sustainable Environment. We thank Profs. L. Byers and H. Ensley for discussions.

References:

1. For a recent review on solvent-free reactions, see: Dittmer, D. C. *Chem. Ind.* **1997**, 779.
2. Blomberg, C. *The Barbier Reaction and Related One-Step Processes*; Springer-Verlag, 1993.
3. Frankland, E. *Ann.* **1849**, *71*, 171; Reformatsky, A. *Ber.* **1887**, *20*, 1210.
4. Barbier, P. *Compt. Rend.* **1899**, *128*, 110; Grignard, V. *Compt. Rend.* **1900**, *130*, 1322.
5. Wittig, G. *Newer Methods of Preparative Organic Chemistry* **1948**, 571.
6. For some examples of indium mediated reactions, see: Chao, L. C.; Rieke, R. D. *J. Org. Chem.* **1975**, *40*, 2253; Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831; Araki, S.; Katsumura, N.; Ito, H.; Butsugan, Y. *Tetrahedron Lett.* **1989**, *30*, 1581. Li, C. J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 7017; Chan, T. H.; Li, C. J. *J. Chem. Soc., Chem. Commun.* **1992**, 747; Kim, E.; Gordon, D. M.; Schmid, W.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 5500; Paquette, L.; Mitzel, T. M. *J. Am. Chem. Soc.*, **1996**, *118*, 1931; Li, C. J.; Chen, D. L.; Lu, Y. Q.; Haberman, J. X.; Mague, J. T. *J. Am. Chem. Soc.* **1996**, *118*, 4216; Li, X. R.; Loh, T. P. *Tetrahedron: Asymmetry*, **1996**, *7*, 1535.
7. For a recent review, see: Wirth, T. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 61.
8. Far a recent review about allylation reaction of carbonyl compounds with

allylmetal reagents, see: Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.

9. Molle, G.; Bauer, P. *J. Am. Chem. Soc.* **1982**, *104*, 3481.

(Received in the USA 05 March 1998)