Silver-Catalyzed, Manganese-Mediated Allylation and Benzylation Reactions of Aldehydes and Ketones

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Silver bromide catalyzes Barbier-type allylation of aldehydes and ketones using unactivated manganese powder. Aliphatic and aromatic aldehydes and ketones react, and aryl chlorides, nitriles, electron-donating and electron-withdrawing groups are tolerated. Benzylation using benzyl bromide also

Introduction

Mild, functional group tolerant methods for the reaction of an allylic anion equivalent with an aldehyde are required, particularly for use in the late stages of natural product syntheses.^[1] Reactions that proceed through organomanganese(II) complexes^[2] are attractive because these compounds typically display broad functional-group tolerance and manganese-containing byproducts are generally considered to be non-toxic.^[3] Barbier-type reactions^[4] that generate allylmanganese complexes in situ from allylic halides are particularly practical because Mn⁰ powder is inexpensive,^[5] and allylic halides are common synthetic intermediates. In this Communication, we report that allyl bromide and benzyl bromide react with aldehydes and ketones in a silvercatalyzed, manganese-mediated reaction [Equation (1)]. The reaction exhibits good functional group tolerance. Mechanistic experiments are consistent with formation of a nucleophilic organometallic reagent in situ.



Preparation of organomanganese complexes can be accomplished using several methods, often by transmetallation of a Grignard reagent and MnX₂.^[6,7] Synthesis directly from the allylic bromide is most commonly accomplished proceeds smoothly under these reaction conditions. Preliminary mechanistic studies are consistent with the formation a nucleophilic allylmetal intermediate.

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using activated sources of Mn⁰ such as Rieke Mn.^[8–10] As an alternative to using activated Mn⁰, Cahiez and Chavant demonstrated that standard Mn⁰ powder is sufficiently reactive to mediate allylation of aldehydes and ketones with allylic halides in the presence of a catalytic quantity of ZnCl₂ at 50 °C.^[11,12] The catalyst is proposed to facilitate formation of a nucleophilic allylmanganese complex.^[6] Formation of heterobimetallic complexes, similar to those proposed as intermediates in Mn- and Cu-catalyzed reactions of Grignard reagents, is also a mechanistic possibility.^[13]

Results and Discussion

As part of our studies in the development of new methods for allylation and alkylation reactions, we sought to develop a reaction that avoids the cost of indium and the functional group incompatibilities associated with preformed Grignard reagents, highly reactive Rieke Mn, and chlorosilanes. We hypothesized that silver salts could catalyze the Mn-mediated allylation reaction.^[14-16] In the presence of catalytic quantities of AgBr and stoichiometric quantities of standard Mn⁰ powder, allylation of *p*-anisaldehyde with allyl bromide proceeds smoothly at room temperature (Table 1). Most silver salts are effective catalysts, although ligation by an N-heterocyclic carbene is detrimental to catalyst activity (Entry 9).^[17,18] We chose inexpensive AgBr as the catalyst for all subsequent studies. Lowering the number of equivalents of allyl bromide decreases the yield (Entry 10). We postulate that the low yield results from consumption of allyl bromide by adventitious Wurtz coupling,^[19] and found that slow addition of allyl bromide improves the yield of homoallylic alcohol 2a (Entries 11-13). Under the optimized reaction conditions, 96% yield of homoallylic alcohol can be obtained with 1.1 equiv. of allyl bromide and 2 equiv. of Mn⁰.



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Table 1. Optimization of silver-catalyzed, manganese-mediated reaction of allyl bromide with *p*-methoxybenzaldehyde.

H	3CO	0 H + 2 1a	Br X equiv.)	catalyst (10 mo Mn ⁰ (X equiv THF, 22 °C, 2	0I-%) /.) → Ar 0 h 2a
	Entry	Catalyst	Equivale Mn ⁰	ents Equivaler allyl brom	nts Yield (%) ^[a] ide
	1	none	3	3	<5
	2	AgF	3	3	97
	3	AgCl	3	3	95
	4	AgBr	3	3	97
	5	Agl	3	3	96
	6	$AgBF_4$	3	3	84
	7	$AgPF_6$	3	3	96
	8	AgOTf	3	3	90
	9	(IMes) ₂ AgE	3F ₄ 3	3	<5
	10	AgBr	3	1.5	78
	11	AgBr	3	1.5 ^{[t}	98
	12	AgBr	2	1.5 ^{[b}	97
	13	AgBr	2	1.1 ^{[b}	96

[a] Isolated yield of homoallylic alcohol **2** after chromatography. [b] Slow addition of allyl bromide, as a 1.2 M solution in THF, over 20 h.

The allylation reaction has good scope with respect to the aldehyde, and aromatic aldehydes react to afford the highest yield of products (Table 2). Nitriles and halides are tolerated, although 20 mol-% AgBr and 1.5 equiv. of allyl bromide are required for good yields (Entries 4 and 5).^[20] Regioselective 1,2-addition to cinnamaldehyde affords homoallylic alcohol **2g** (Entry 6). Aliphatic aldehydes react smoothly, particularly when α -branching slows competitive pinacol coupling.^[12,21] For example, cyclohexane carboxaldehyde reacts to afford 78% yield of homoallylic alcohol **2h** under the standard reaction conditions (Entry 7).

Both aromatic and aliphatic ketones undergo silver-catalyzed, manganese-mediated allylation reactions to afford tertiary alcohols (Scheme 1). Reactions of aromatic ketones are higher-yielding than those of aliphatic ketones. For example, acetophenone reacts smoothly under our reaction conditions to afford 74% yield of the requisite tertiary alcohol.

We hypothesized that alkyl halides that provide stable radical intermediates would be activated under our reaction conditions.^[16a,16b,22] This hypothesis was validated: benzyl bromide may be used as an alkylating agent with both alde-hydes and ketones (Scheme 2). Benzaldehyde and aceto-phenone react to afford alcohols **3** and **4** in 73 and 58% yield, respectively. These results contrast those observed in other metal-catalyzed, manganese-mediated reactions, which have not been reported with benzylic halides.^[9d,11,12]

We undertook experiments to distinguish between mechanisms wherein the active nucleophile is an allylic radical or an allylmetal species. Two substrates that probe for a radical addition are shown in Scheme 3. Addition of allyl Table 2. Aldehyde scope.^[a]

	ں ا	, + <i>P</i> r	AgBr (X ı Mn ⁰ (2 e	mol-%) C equiv.)	H
	۲ 1b-	i slow addition	THF, r.t.	., 20 h R	2b-i
Entry	Aldeh	iyde RCHO	AgBr (mol-%)	Equivalent allyl bromid	ts Yield (%) ^[c] e ^[b]
1	1b	СНО	10	1.1	96
2	1c	H ₃ CO H ₃ CO	10 10	1.1	97
3	1d	F ₃ C	O 10	1.1	72
4	1e	CI	20	1.5	85
5	1f	NC	20	1.5	79
6	1g	СНО	D 10	1.1	77
7	1h	СНО	10	1.1	78
8	1i	СНО	D 20	2.0	50

[a] See Supporting Information for full experimental details. [b] Allyl bromide was added as a 1.2 M solution in THF over 20 h using a syringe pump. [c] Isolated yield of homoallylic alcohol after chromatography, reported as an average of two runs.



Scheme 1. Allylation of ketones.



Scheme 2. Benzylation reactions.

radical to *o*-vinylbenzaldehyde would generate an oxygencentered radical, which would be expected to undergo a facile 5-*exo*-trig cyclization. Upon treatment with the standard reaction conditions, however, *o*-vinylbenzaldehyde affords the simple allylated product **5**. In a similar experiment, we



observed that allylation of **6** afforded **7** with no cyclization.^[23] An alternative mechanism would be single electron transfer to form a ketyl radical, which could recombine with an allyl radical.^[24] Upon formation of a ketyl radical, **8** should undergo a facile 5-*exo*-trig cyclization reaction.^[25] Allylation of **8**, however, proceeds smoothly to afford an 83% yield of homoallylic alcohol **9**. Therefore, at this preliminary stage, we propose that an organometallic intermediate, such as allylmanganese bromide, attacks the electrophile.^[26]



Scheme 3. Mechanistic experiments.

Conclusions

We report a new silver-catalyzed, manganese-mediated allylation reaction that provides good yields of homoallylic alcohols derived from aromatic and aliphatic aldehydes and ketones. Benzylation using benzyl bromide afforded good yields of the corresponding benzylic alcohols. This Barbiertype reaction is functional group tolerant and inexpensive, presenting an alternative to the use of highly reactive preparations of Mn⁰, preformed Grignard reagents, or indium. Investigation of the mechanism of the transformation and further development of related allylation and alkylation reactions are ongoing in our laboratories.

Experimental Section

General Experimental Procedure for Allylation of *p*-Anisaldehyde: A round-bottom flask was charged with ground Mn powder (325 mesh, 99%, 220 mg, 4.00 mmol, 2.00 equiv., see Supporting Information for full experimental details) and AgBr (38 mg, 0.20 mmol, 10 mol-%) in the glovebox. The flask was removed from the glovebox, and THF (3.0 mL) and *p*-anisaldehyde (240 μ L, 1.97 mmol, 1 equiv.) were added. The mixture was stirred at room temperature, and a solution of allyl bromide (190 μ L, 2.2 mmol, 1.1 equiv., dissolved in 2.0 mL of THF) was added over 20 h using a syringe pump. Care was taken to ensure the exclusion of light from the reaction flask and the solution of allyl bromide. After the addition was complete, Et₂O (15 mL) was added to the reaction flask and the brown mixture was quenched by adding 1 M HCl

(4 mL) over 10 min. Once the bubbling had subsided, the clear biphasic mixture was poured into a separatory funnel, using additional Et₂O (60 mL). The aqueous phase was separated and the organic phase was washed with 1 \times HCl (1 \times 25 mL) and brine (1 \times 25 mL). The organic phase was dried with MgSO₄, filtered, and concentrated in vacuo to provide a yellow oil. Purification by silica gel flash column chromatography, eluting with 10% EtOAc/ hexane, afforded homoallylic alcohol **2a** (348 mg, 97% yield) as a yellow oil.

Supporting Information (see also the footnote on the first page of this article): Experimental procedures and analytical data for reaction products.

Acknowledgments

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