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Mn(III)-mediated radical C–C bond formation: regioselective α′-allylation of α,β-unsaturated ketones

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Abstract—$Mn(OAc)_3$-mediated regioselective α′-allylation of α,β-unsaturated enones is described. α′-Allyl α,β-unsaturated enones are obtained through a radical process in good yields. © 2002 Elsevier Science Ltd. All rights reserved.

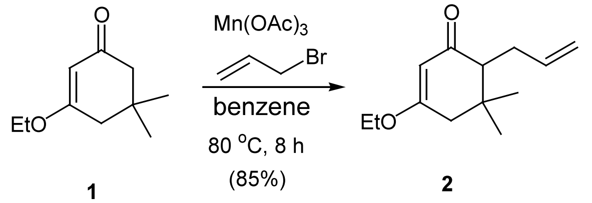
1. Introduction

Experimental studies on the synthesis of targets with wide complexity has resulted in the development of reactions which emphasize chemo-, regio-, and stereoselectivity. In defining strategies and reactions to construct complex molecules, regioselectivity is required.[1] Metal-mediated allylation generally has a central position in the synthesis of various complex natural products. A wide variety of allylation reactions are well known in the literature as useful methods for carbon–carbon bond formation, i.e. metal-mediated allyl addition to carbonyl compounds[2,3] and direct allylation on the α-position of ketones.[4,5] In the last decade, Mn(III)-based oxidative free-radical reactions have been developed into a versatile protocol for the formation of highly functionalised products from simple precursors.[6] In 1976, Williams and Hunter reported that $Mn(OAc)_3 \cdot 2H_2O$ oxidation of enones in HOAc at reflux affords α′-acetoxy enones in low yields.[7] In connection with our synthetic studies with manganese(III) acetate,[8] we found that trapping the α′-keto radicals obtained from β-alkoxy α,β-unsaturated ketones by benzene used as a solvent is much faster than acetoxylation, affording good yields of tandem oxidation products.[8d] These interesting results prompted us towards the development of a new method in the field of the regioselective direct allylation of α,β-unsaturated ketones. We describe herein the results obtained from the $Mn(OAc)_3$-mediated allylation of various α,β-unsaturated enones and optimization of the reaction conditions.

2. Results and discussion

As a starting point, we studied the use of manganese(III) acetate as a potential useful mediator for metal-promoted regioselective α′-allylation of 3-ethoxy-5,5-dimethylcyclohex-2-enone **1** chosen as a model compound. Reaction of **1** in benzene with 2 equiv. of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv. of allyl bromide for 8 h at reflux afforded 85% of 6-allyl-3-ethoxy-5,5-dimethylcyclohex-2-enone **2** (Scheme 1).

As a natural extension of this study, we pursued a complementary investigation aimed at subjecting various α,β-unsaturated cyclic ketones to this reaction. When 3-methylcyclopent-2-enone **3c** was stirred with 2 equiv. of $Mn(OAc)_3 \cdot 2H_2O$ and 1 equiv. of allyl bromide in benzene for 8 h at reflux, 81% of 5-allyl-3-methylcyclopent-2-enone **4c** was isolated. When 3 equiv. of $Mn(OAc)_3 \cdot 2H_2O$ was used, the isolated yield of the allylation product drastically decreased to 53% and 25% of the α′-acetoxylation product was isolated. Changing the amount of $Mn(OAc)_3 \cdot 2H_2O$ to 1 equiv. decreased the yield of the allylation product (64%) and no α′-acetoxylation product was observed. Subsequently, a variety of cyclopentenones and cyclohexenones were tested with this allylation method (Scheme 2). Selected examples are listed in Table 1.



Scheme 1.

Keywords: enones; manganese and compounds; allylation.

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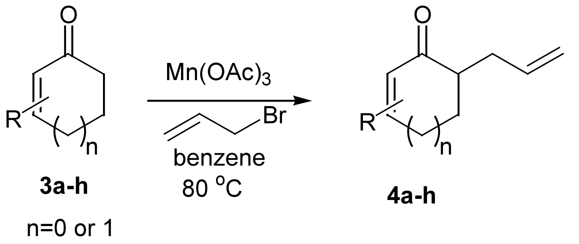


Scheme 2.

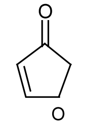
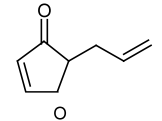
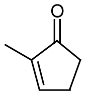
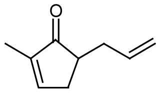
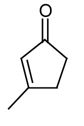
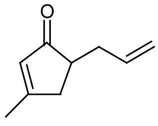
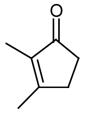
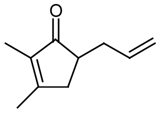
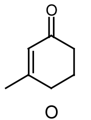
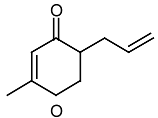
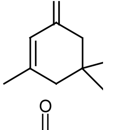
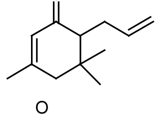
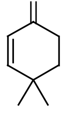
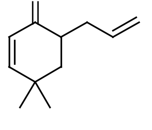
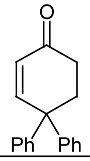
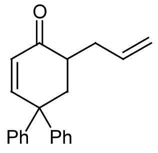
The following mechanistic scheme is consistent with these results (Scheme 3). The reaction presumably proceeds via the formation of the Mn(III) enolate **5**, which by one-electron oxidation gives the α′-keto radical **6**.[9] Reaction of this radical with allyl bromide then yields the α′-allyl α,β-unsaturated cyclic ketone **4**. Vinogradov and co-workers reported that α′-keto radicals generated from higher ketones result in the formation of secondary radicals which dimerize or tertiary radicals which are prone to further oxidation.[10] In accordance with this conclusion, in this study, dimerization of product **4** was observed for entries 1, 2 and 3.

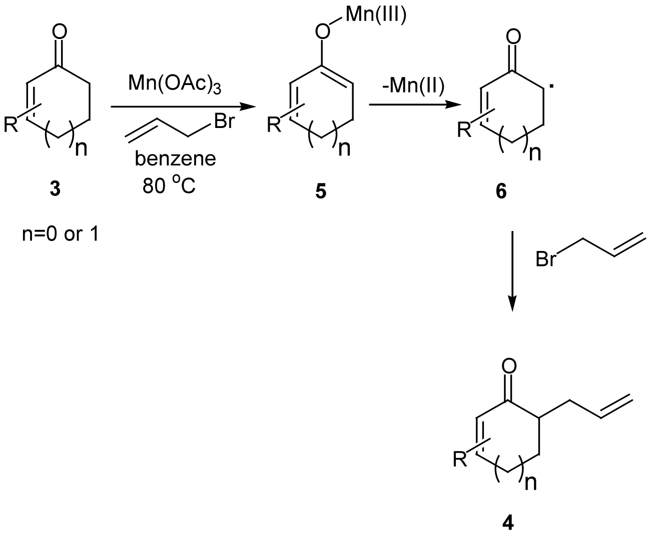
In the next step of this study, 3-methylcyclopent-2-enone **3c** (entry 3) was chosen as a model compound and the $Mn(OAc)_3 \cdot 2H_2O$-mediated allylation reaction was performed in the presence of nitrobenzene which was used to examine the effect of a radical scavenger on the reaction propagation. As expected from the proposed reaction mechanism, no formation of product was observed.

In conclusion, manganese(III) acetate is highly effective for mediating α′-allylation of α,β-unsaturated cyclic ketones. This one-step reaction offers complete regioselectivity toward α′-allylation of cyclic enones and opens up a new class of $Mn(OAc)_3$ reactions.

Table 1. α′-Allylation of α,β-unsaturated enones mediated with $Mn(OAc)_3$ in benzene

α′-Allylation of α,β-unsaturated enones mediated with $Mn(OAc)_3$ in benzene

entry	Reactant	Product	4[11]	Yield (%)	Time (h)
1			**4a**	79	8
2			**4b**	80	8
3			**4c**	81	8
4			**4d**	83	10
5			**4e**	78	12
6			**4f**	68	12
7			**4g**	67	10
8			**4h**	72	12



Scheme 3.

3. Experimental

3.1. General procedure for the $Mn(OAc)_3$-mediated allylation of α,β-unsaturated ketones 3

A mixture of $Mn(OAc)_3 \cdot 2H_2O$ (3.25 g, 14.0 mmol) in benzene (or another similar solvent) (150 ml) was refluxed for 45 min using a Dean–Stark trap. The mixture was cooled to room temperature and the α,β-unsaturated ketone (7.0 mmol) and allyl bromide (0.85 g, 7.0 mmol) were added. The mixture was allowed to reflux until the dark brown colour disappeared and was also monitored by TLC. The reaction mixture was diluted with an equal amount of ethyl acetate and the organic phase was washed with 1N HCl followed by saturated $NaHCO_3$ and brine. The organic phase was dried over $MgSO_4$ and evaporated in vacuo. The crude product was separated by flash column chromatography using ethyl acetate/hexane as eluent to afford the product.

3.1.1. 6-Allyl-3-ethoxy-5,5-dimethylcyclohex-2-enone 2. (1.24 g, 85%). IR: 3019, 2960, 1740, 1640, 1598, 1456, 1372 cm^{-1}. ^1H NMR: δ 0.93 (s, 3H), 1.02 (s, 3H), 1.29 (t, $J=7.1$ Hz, 3H), 1.99–2.03 (m, 1H), 2.15 (d, $J=17.6$ Hz, 1H), 2.24–2.31 (m, 2H), 2.55 (d, $J=17.6$ Hz, 1H), 3.82 (q, $J=7.1$ Hz, 2H), 4.90 (d, $J=10.3$ Hz, 1H), 4.94 (d, $J=17.2$ Hz, 1H), 5.21 (s, 1H), 5.76–5.87 (m, 1H). ^{13}C NMR: δ 14.4, 14.5, 31.2, 35.5, 42.4, 57.3, 61.8, 64.4, 101.1, 115.5, 138.1, 174.6, 201.6. HRMS *m*/*e* (observed): 208.1463, (calculated): 208.1464.

3.1.2. 5-Allyl-3-methylcyclopent-2-enone 4c. (0.77 g, 81%). IR: 3066, 2973, 1690, 1648 cm^{-1}. ^1H NMR: δ 2.12 (s, 3H), 2.13–2.14 (m, 1H), 2.29 (d, $J=18.1$ Hz), 2.49–2.63 (m, 2H), 2.69 (dd, $J=6.3$ and 18.1 Hz, 1H), 5.03 (d, $J=10.5$ Hz, 1H), 5.07 (d, $J=17.3$ Hz), 5.70–5.79 (m, 1H), 5.92 (s, 1H). ^{13}C NMR: δ 19.7, 35.9, 39.2, 46.1, 117.0, 130.2, 135.7, 178.0, 211.4. HRMS *m*/*e* (observed): 136.0893, (calculated): 136.0888.

3.1.3. 1,1′-Diallyl-4,4′-dimethylbicyclopentyl-3,3′-diene-2,2′-dione dimerized product of 4c. IR: 3059, 2910, 2874, 1703, 1635 cm^{-1}. ^1H NMR: δ 2.10 (s, 6H), 2.60 (dd, $J=6.2$ and 14.1 Hz, 2H), 2.76 (dd, $J=7.4$ and 14.1 Hz, 2H), 3.03 (s, 4H), 5.15 (d, $J=10.1$ Hz, 2H), 5.16 (d, $J=16.6$ Hz, 2H), 5.64–5.77 (m, 2H), 5.97 (s, 2H). ^{13}C NMR: δ 19.8, 43.8, 49.4, 60.7, 120.3, 127.3, 132.7, 174.8, 203.4. HRMS *m*/*e* (observed): 270.1614, (calculated): 270.1620.

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11. All the products were characterized by ^{1}H, ^{13}C NMR, IR and HRMS.