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Manganese-Catalyzed Carboacylations of Alkenes with Alkyl Iodides

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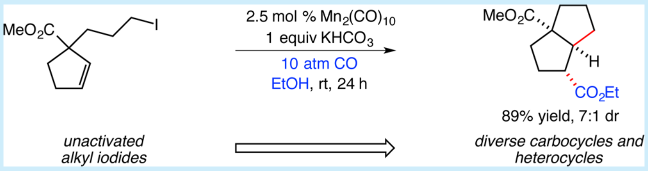
Supporting Information

ABSTRACT: A manganese-catalyzed carboacylation of alkenes with alkyl iodides and carbon monoxide is described. This carbonylative difunctionalization uses both primary and secondary alkyl iodides in reactions with a diverse array of cyclic and acyclic substrates. Examples of successful applications to the synthesis of five-, six-, and seven-membered rings are provided. The inexpensive, first-row catalytic system and mild reaction conditions are expected to facilitate applications in complex synthesis.



Catalytic reactions of unactivated alkyl halides have led to a diverse set of valuable C−C bond-forming reactions in chemical synthesis.[1] This class of transformations includes alkyl-Mizoroki-Heck-type reactions, constituting fundamental cross-couplings of unactivated alkyl halides with alkenes.[2] In prior studies, we developed a carbonylative variant of this reaction that yields cyclic enones from alkyl iodides and pendant alkenes (Figure 1).[3] We became interested in pursuing an alternative process involving alkene difunctionalization (carboacylation).[4] Prior to our studies there was limited precedent for this class of alkene difunctionalization; a photochemical palladium-catalyzed carboacylation has been reported, but requires excess alkyl iodide (1.5 equiv) and was limited to ketone synthesis using alkylboranes.[5]

We hypothesized that simple manganese catalysts [e.g., $Mn_2(CO)_{10}$] could facilitate the desired alkene carboacylation. These complexes have shown promise in both the activation and carbonylation of unactivated alkyl halides, particularly using intense irradiation or electrolysis.[6] Previous studies involving manganese-catalyzed radical cyclizations required activated α-halocarbonyls as substrates, however.[7] The use of an inexpensive, first-row metal instead of precious palladium catalysts commonly used in carbonylative processes of organohalides[8] would be an attractive feature of the carboacylation. Herein, we report the successful development of such a manganese-catalyzed alkene carboacylation widely applicable to carbocycle and heterocycle synthesis.

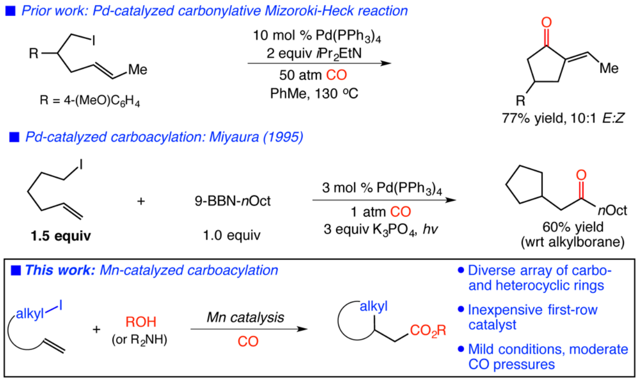
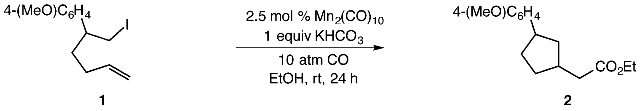


Figure 1. Metal-catalyzed, carbonylative alkene additions of alkyl iodides.

We began by studying the catalytic carboacylation of primary iodide **1** (Table 1). Inexpensive, commercially available manganese(0) carbonyl successfully catalyzed the carboacylation of **1**, delivering the substituted cyclopentyl ester **2** in good yield (84%, entry 1) in EtOH as solvent. Bromopentacarbonylmanganese(I) and cobalt(0) carbonyl were both ineffective as catalysts (entries 2−3), as was $Pd(PPh_3)_4$, which we have previously used in a number of catalytic C−C bond-forming reactions involving alkyl iodides (entry 4).[2e,3a,9] Amine bases

Table 1. Influence of Reaction Conditions on the Mn-Catalyzed Carboacylation[a]



1 **2**

entry	variation from standard conditions above	yield (%)[b]
1	none	84
2	5 mol % $Mn(CO)_5Br$ instead of $Mn_2(CO)_{10}$	14
3	2.5 mol % $Co_2(CO)_8$ instead of $Mn_2(CO)_{10}$	0
4	5 mol % $Pd(PPh_3)_4$ instead of $Mn_2(CO)_{10}$	0
5	1 equiv of $i$$Pr_2EtN$ instead of 1 equiv of $KHCO_3$	76
6	1 atm of CO instead of 10 atm of CO	0
7	5 atm of CO instead of 10 atm of CO	76
8	no ambient light	0
9	no $Mn_2(CO)_{10}$	0

[a]Reactions were performed with $[\text{substrate}]_0$ = 0.13 M. [b]Yields determined by ^1H NMR spectroscopy of crude reaction mixture using an internal standard.

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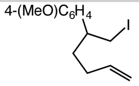
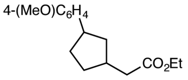
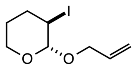
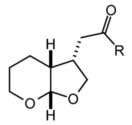
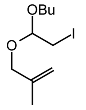
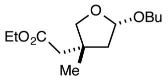
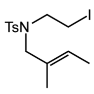
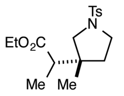
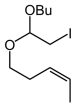
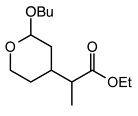
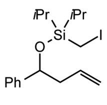
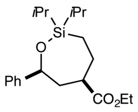
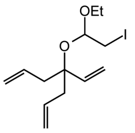
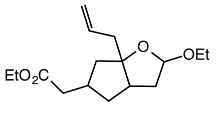
could be used in the reaction, although yields were slightly diminished (entry 5). Reactions performed at various levels of CO pressure indicated that while reactions using a balloon of CO (1 atm) were unsuccessful, high pressures were not required (entries 6–7). We chose 10 atm of CO as our standard condition owing to the convenience of using a pressurized glass tube. Interestingly, running the reaction in complete darkness shut down the catalytic process (entry 8), suggesting that ambient light plays a role in the catalytic reaction.[10] Control experiments in the absence of manganese provided no product (entry 9).

With a viable catalytic system in hand, we investigated the scope of the carboacylation across a diverse range of substrates (Table 2). Reactions involving both primary and secondary iodides were successful (entries 1–2). Notably, the carboacylation is not limited to alcohol nucleophiles; diethylamine and *N*-methylaniline both afforded amide products in good yields (entries 3–4). Reactions using a variety of alkenes demonstrated the notable scope of the carboacylation (entries 5–8). Reactions involving 1,1-disubstituted and 1,1,2-trisubstituted alkenes formed tetrahydrofuran and pyrrolidine derivatives containing quaternary stereocenters in good yield (entries 5–6). Importantly, the reaction is not limited to five-membered ring synthesis; acetal substrate **11** undergoes a 6-exo cyclization to deliver tetrahydropyran **12** (entry 7). Moreover, the carboacylation of silyloxy iodide **13** proceeded in 7-endo fashion to produce cyclic silyl ether **14** in good yield (78%, entry 8). The regioselectivity of this ring closure is consistent with lower energy endo transition states in radical cyclizations of halomethylsilyl substrates with terminal alkenes.[11] We have also demonstrated the potential for cascade carboacylation with triene substrate **15** (entry 9). The reaction of **15** proceeds via two sequential 5-exo cyclizations to deliver bicyclic product **16** in moderate yield (63%).

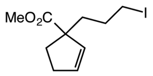
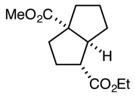
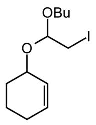
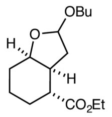
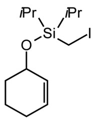
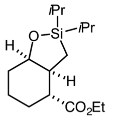
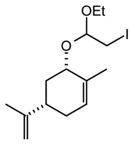
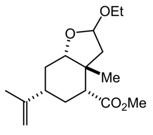
Table 2. Manganese-Catalyzed Carboacylations of Acyclic Alkenes[a]

entry	substrate	product	yield (%)[b]
1	 **1**	 **2**	83 2:1 dr
	 **3**		
2		**4**: R = OEt	77 10:1 dr
3		**5**: R = NEt$_2$	67^{c} 8:1 dr
4		**6**: R = NMePh	73^{c} 10:1 dr
5	 **7**	 **8**	77^{d} 8:1 dr
6	 **9**	 **10**	79^{d} 1:1 dr
7	 **11**	 **12**	$64^{d,e}$
8	 **13**	 **14**	78^{d} 3:1 dr
9	 **15**	 **16**	$77^{d,e}$

[a]See Table 1 for conditions. [b]Isolated yields. [c]2 equiv amine and KHCO$_3$ used. [d]5 mol % Mn$_2$(CO)$_{10}$ used. [e]Mixtures of diastereomers produced (see Supporting Information for more details).

Our studies continued with the carboacylations of five- and six-membered cycloalkenyl substrates (Table 3). These reactions allowed the construction of bicyclic compounds in efficient fashion, often with good levels of diastereoselectivity. The carboacylation of carvone-derived substrate **23** proceeded with lower diastereoselectivity, with a preference for carbonylation on the opposite face from the methyl group.

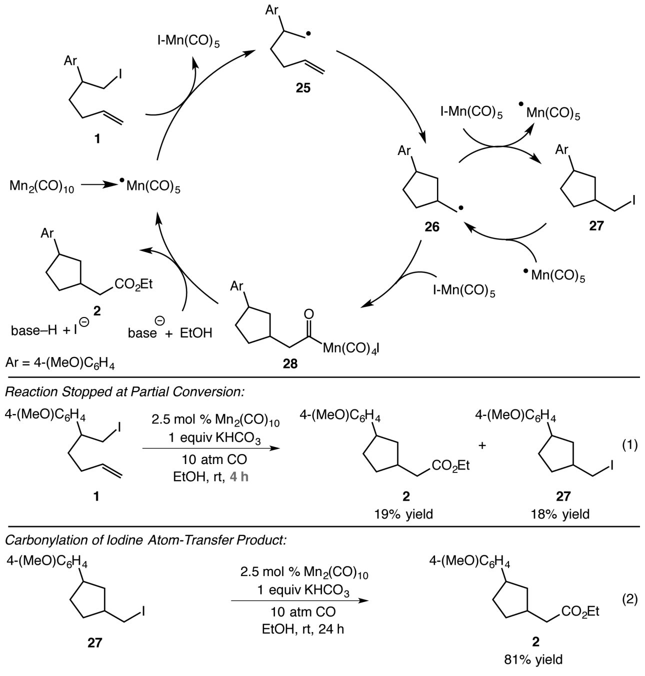
Table 3. Manganese-Catalyzed Carboacylations of Cycloalkenyl Substrates[a]

entry	substrate	product	yield (%)[b]
1	 **17**	 **18**	89 7:1 dr
2	 **19**	 **20**	90^{c} 7:1 dr
3	 **21**	 **22**	72 9:1 dr
4	 **23**	 **24**	$67^{c,d}$ 3:1 dr

[a]See Table 1 for conditions. [b]Isolated yields. [c]Diastereomeric ratio based on cyclization (see Supporting Information for more details). [d]10 mol % of Mn$_2$(CO)$_{10}$ used in MeOH as solvent.

A plausible catalytic cycle for the carboacylation is depicted in Scheme 1. Homolysis of the Mn–Mn bond of manganese carbonyl generates the $^{\bullet}$Mn(CO)$_5$ radical and initiates the catalytic pathway.[10] Iodine atom abstraction from the substrate (**1**) generates a carbon-centered radical (**25**), which undergoes an alkene addition to produce radical **26**. At this stage, radical **26** can either undergo carbonylation to provide acyl manganese **28**[6] or complete an iodine atom-transfer cyclization to deliver alkyl iodide **27**.[7] We have observed iodine atom-transfer intermediates in a number of our cyclizations; a representative example is shown in eq 1. Stopping the carboacylation of

Scheme 1. Plausible Catalytic Cycle



substrate **1** at partial conversion produces a mixture of both carboacylation product **2** and iodine atom-transfer cyclization product **27** in 19% and 18% yields, respectively (^{1}H NMR analysis). In a separate experiment, iodide **27** underwent efficient carbonylation under the carboacylation conditions to deliver ester **2** in 81% yield (eq 2). These experiments are consistent with iodine atom-transfer cyclization playing a role in these catalytic transformations, the degree of which is likely dictated by the particular substrate and the energetics of the iodine atom transfer step involved. Ultimately, once acylmanganese **28** is formed, nucleophilic substitution delivers the carboacylation product **2** and regenerates the active catalyst.

In conclusion, we have developed a manganese-catalyzed carboacylation of alkenes using unactivated alkyl iodides and moderate pressures of CO. This reaction exhibits broad scope in carbocycle and heterocycle synthesis, with the potential for good levels of diastereocontrol in the carboacylation process. The common molecular functionality and mild reaction conditions of this alkene difunctionalization are expected to facilitate future applications in complex molecule synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02154.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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