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Catalytic Allylic Alkylation via the Cross-Dehydrogenative-Coupling Reaction between Allylic sp^3 C−H and Methylenic sp^3 C−H Bonds

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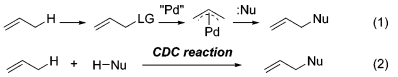
The palladium-catalyzed allylic alkylation (the Trost−Tsuji reaction, eq 1) is one of the most important reactions for constructing C−C bonds in modern organic synthesis.[1] The methodology allows the easy tuning of chemo-, regio-, and stereoselectivities in complex organic transformations.[2] As a general protocol, a carboxylate (or another leaving group) is required at the allylic position, which is activated by a palladium catalyst during the reaction with a pronucleophile.[3] In theory, the direct utilization of an allylic C−H bond rather than an allylic functional group would avoid the need to synthesize the allylic functional group, thus leading to increased synthetic efficiency.[4] In the pioneering work using allylic C−H bonds directly to form π-allyl palladium complexes, Trost and co-workers reported an allylic alkylation from an allylic sp^3 C−H in two steps in the late 1970s.[5] However, because the in situ reoxidation of the reduced Pd(0) into Pd(II) is difficult, this reaction was stoichiometric with respect to Pd(II), serving as both the catalyst and the oxidant.

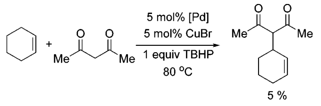
Recently, we and others have developed various cross-dehydrogenative-coupling (CDC) reactions for forming new C−C bonds by using two different C−H bonds.[6] The development of a catalytic allylic alkylation via a CDC reaction would be quite desirable. Herein, we report the first catalytic allylic alkylation directly using allylic sp^3 C−H and methylenic sp^3 C−H bonds (eq 2).



(1)

(2)

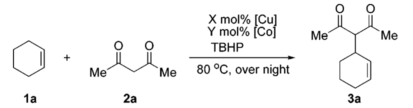
To begin our study, we chose cyclohexene and 2,4-pentadione as the standard substrates to search for potential catalysts and suitable reaction conditions. When a palladium catalyst was used, together with a catalytic amount of CuBr and a stoichiometric amount of *tert*-butyl hydroperoxide (TBHP),[7] the desired product was obtained in 5% yield as shown by the ^{1}H NMR of the crude reaction mixture (eq 3). Unfortunately, we were unable to improve the product yield beyond 5%, which indicated that the reaction with palladium was stoichiometric. After countless failures, we found that the yield of the desired product[8] was improved to 25% by using a combination of a copper catalyst (CuBr)[9] and a cobalt catalyst (CoCl$_2$)[10] (Table 1, entry 1). The product formation was further optimized by examining various reaction conditions, and the results are shown in Table 1. The ratio of CuBr and CoCl$_2$ was found to be important for the reaction (Table 1, entry 1−5). Increasing the amounts of alkene and TBHP improved the yields of the desired product (Table 1, entry 6). By decreasing the amounts of the catalysts, the yield was slightly reduced (Table 1, entry 7 vs 8). Under the same reaction conditions, CuCl provided results similar to those obtained with CuBr (Table 1, entry 7 vs 11); however, CoCl$_2$ gave the best yield of the desired product among the cobalt catalysts tested (Table 1, entries 12 and 13). Whereas the use of a cobalt catalyst alone gave the desired product in 10% yield, no product was obtained with only CuBr as the catalyst (Table 1, entries 14 and 15).



(3)

With the optimized reaction conditions established, various substrates were subjected to the allylic alkylation reactions, and representative results are shown in Table 2. Various 1,3-dicarbonyl compounds reacted smoothly with cyclohexene under the standard reaction conditions. When substituted 1,3-dicarbonyl substrates were used, the desired quaternary products were obtained with reasonable yields (Table 2, entries 6−8). Other cyclic alkenes (five-, seven-, and eight-membered rings) were also transformed into the desired products when reacted with the diketones. When 1-phenylcyclohexene was reacted with 2,4-pentadione (Table 2, entry 9), the major product was obtained via the reaction of the less sterically hindered allylic C−H bond.

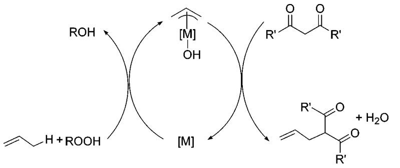
Table 1. Optimization of Reaction Conditions



entry	**1a** (mmol)	**2a** (mmol)	[Cu]^a (mol %)	[Co]^a (mol %)	TBHP (mmol)	yield (%)^c
1	2.5	1.0	5	5	1.0	25
2	2.5	1.0	5	2.5	2.0	12
3	1.0	2.0	5	5	1.0	6
4	2.5	1.0	5	10	1.0	36
5	2.5	1.0	10	10	1.5	29
6	5.0	1.0	1	10	2.0	62
7	5.0	1.0	2.5	10	2.0	71
8	5.0	1.0	1.25	5	2.0	60
9	5.0	1.0	2.5 (CuI)	10	2.0	57
10	5.0	1.0	2.5 (CuBr$_2$)	10	2.0	60
11	5.0	1.0	2.5 (CuCl)	10	2.0	70
12	5.0	1.0	2.5	10 (CoI$_2$)	2.0	10
13	5.0	1.0	2.5	10 (CoF$_2$)	2.0	trace
14	2.5	1.0	0	5	1.0	10
15	2.5	1.0	5	0	1.0	0

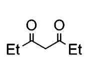
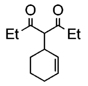
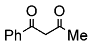
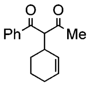
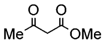
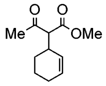
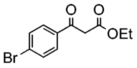
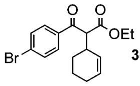
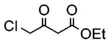
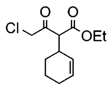
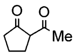
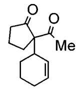
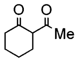
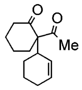
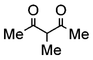
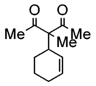
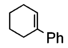
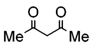
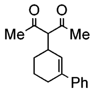
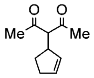
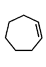
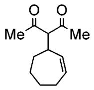
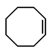
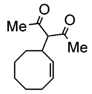
^{a} CuBr was used, unless otherwise noted. ^{b} CoCl$_2$ was used, unless otherwise noted. ^{c} NMR yields using an internal standard.

Scheme 1



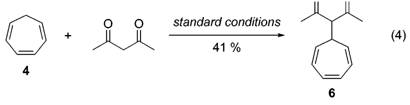
10.1021/ja056541b CCC: $33.50

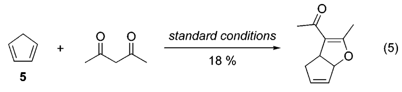
Table 2. Cross-Dehydrogenative-Coupling Reactions of Allylic C−H and β-Dicarbonyl C−H[a]

Entry	Alkene	Diketone	Product	Yield (%)[b]
1	 **1a**	 **2b**	 **3b**	61
2	**1a**	 **2c**	 **3c**	64 (1:1)
3	**1a**	 **2d**	 **3d**	41 (1:1)
4	**1a**	 **2e**	 **3e**	71 (1:1)
5	**1a**	 **2f**	 **3f**	55 (1:1)
6	**1a**	 **2g**	 **3g**	31 (1:1)
7	**1a**	 **2h**	 **3h**	46 (1.7:1)
8	**1a**	 **2i**	 **3i**	41
9	 **1b**	 **2a**	 **3j**	34
10	 **1c**	**2a**	 **3k**	53[c]
11	 **1d**	**2a**	 **3l**	30
12	 **1e**	**2a**	 **3m**	35

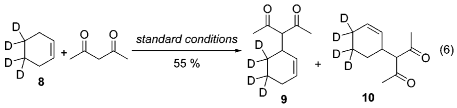
[a] Conditions: 0.025 mmol of CuBr, 0.1 mmol of $CoCl_2$, 5.0 mmol of alkene, 1.0 mmol of 1,3-dicarbonyl compound, and 2.0 mmol of TBHP. [b] Isolated yields were based on 1,3-dicarbonyl compounds; the ratio of two diastereomers is given in parentheses. [c] At 50 °C.

When cycloheptatriene **4** was reacted with 2,4-pentadione, tropylacetylacetone **6**[11] was obtained in 41% isolated yield (eq 4). Interestingly, if cyclopentadiene **5** was used, the major product obtained was dihydrofuran derivative **7**[12] (eq 5), which was most likely due to the further transformation of the alkylation product in situ.





On the basis of these observations, a tentative mechanism is proposed in Scheme 1. A π-allyl copper or allyl cobalt complex is formed via the allylic H-abstraction[13] followed by coordination. A subsequent standard allylic alkylation followed by oxidation provided the alkylation product and regenerated the catalyst. As an insight into the mechanism of the reaction, a deuterated experiment between **8** and 2,4-penadione provided a 1:1 mixture of **9** and **10** (eq 6), which implies the involvement of an allyl metal intermediate during the catalytic cycle. However, the exact function of the combination of a copper catalyst and a cobalt catalyst in the reaction is not clear at the present stage.



(**9** : **10** = 1 : 1)

In summary, we have developed a novel catalytic allylic alkylation via a CDC reaction between allylic sp^3 C−H and methylenic sp^3 C−H bonds catalyzed by copper bromide and cobalt chloride. This novel methodology provides a way to directly use allylic sp^3 C−H bonds for the purpose of C−C bond formation. The scope, mechanism, and synthetic application of this reaction are under investigation.

Acknowledgment. We are grateful to the Canada Research Chair (Tier I) foundation (to C.J.L.), the CFI, NSERC, Merck Frosst, and McGill University for support of our research.

Supporting Information Available: Representative experimental procedure and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) ***CAUTION!*** Mixing a metal salt and peroxide can cause an explosion. See: Jones, A. K.; Wilson, T. E.; Nikam, S. S. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1995; Vol. 2, p 880.
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JA056541B