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Nickel-Catalyzed Direct Conjugate Addition of Simple Alkenes to Enones

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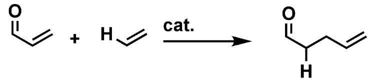
The introduction of an alkenyl group at the β-position of an enone by the addition of a C−H bond of a simple alkene has not been achieved because C−H bonds of simple alkenes are less reactive toward transition metals than those of enones (eq 1). In fact, the insertion of alkenes into the C−H bond of enones to give more substituted α,β-unsaturated carbonyl compounds occurs in the presence of ruthenium catalysts, since the oxidative addition of the C−H bond of an enone to ruthenium occurs prior to that of the simple alkenes (eq 2).[1−3] A nickel-catalyzed hydroalkenylation is also a potential method used to achieve a direct conjugate addition of alkenes to enones, although no example of the hydroalkenylation of enones with simple alkenes to form a carbon−carbon bond at the β-position has been reported.[4] To date, employing alkenyl metal compounds has been indispensable for the introduction of an alkenyl group at the β-position of an enone by conjugate addition (eq 3).[5,6] Although a variety of alkenyl groups are available for this reaction, the preparation of alkenyl metal compounds is required. Recently, Jamison reported a nickel-catalyzed reaction of enones with alkenes in the presence of Et_3SiOTf and Et_3N to give enol silyl ethers, which is a more straightforward method for introducing an alkenyl group at the β-position of enones.[7] However, to date, direct conjugate addition of alkenes to enones remains an elusive goal.



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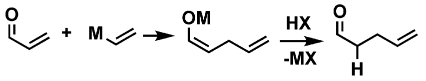
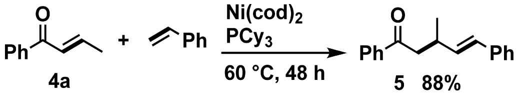


(3)

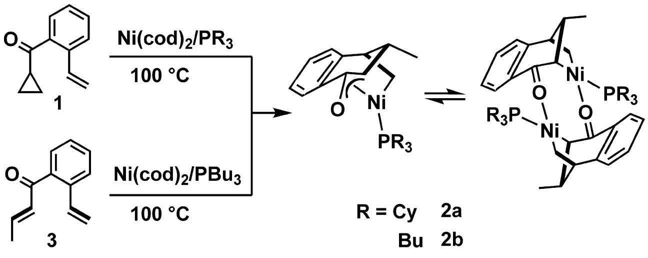
In the course of the study of the nickel-catalyzed [3 + 2] cycloaddition of cyclopropyl ketones,[8] the reaction of 2-vinylphenyl cyclopropyl ketone (**1**) with a nickel(0) complex was carried out to trap a cyclopropyl group with an intramolecular carbon−carbon double bond. Unexpectedly, an insoluble black crystal was obtained in 58% isolated yield, and X-ray crystallography showed that it has a dimeric nickelacycle structure (**2a** in Scheme 1). Similarly, the reaction of **1** with $Ni(cod)_2$ and PBu_3 also gave the corresponding soluble complex **2b** in 57% isolated yield. The Ni−C(carbonyl) distance of 2.4143(18) Å in **2b** is intermediate between that found in η^1-*C*-enolate nickel complexes (2.990 and 2.938 Å)[9] and that observed in η^3-oxaallylnickel complexes [2.024(3) and 2.034(4) Å].[8b] The ^{13}C NMR signal attributable to the carbonyl carbon of **2b** appears at δ 176, which is shifted to higher field by 30 ppm relative to that observed in the η^1-*C*-enolate nickel complex $Cp^*Ni(PPh_3)CH_2COPh$ (δ 206)[9a] and is close to those for η^3-oxaallylnickel complexes (δ 160).[8b] These facts suggest that the contribution of the η^3-oxaallyl structure to **2b** might be larger than that of the η^1-*C*-enolate structure in solution. At an early stage of the reaction of **1** with $Ni(cod)_2$ and PBu_3, the formation of en-enone **3**, an isomer of **1**, was observed. Formally, these nickel complexes can be generated by the intramolecular oxidative cyclization of **3** with nickel(0) complexes. Thus, we confirmed the occurrence of oxidative cyclization by the reaction of **3** with $Ni(cod)_2$ and PBu_3 at 100 °C to give **2b** quantitatively (Scheme 1), in which carbon−carbon bond formation occurred at the β-position of the carbonyl group.[10] The formation of an η^3-oxaallylnickel moiety might stabilize the generated complex and control the regiochemistry, leading to formation of a carbon−carbon bond at the β-position. The reaction was expanded to an intermolecular reaction, and we chose (*E*)-1-phenylbut-2-en-1-one (**4a**) as the enone and styrene as the alkene for the first combination. A stoichiometric reaction of **4a** and styrene with $Ni(cod)_2$ and PCy_3 was carried out. The formation of a μ-η^2-enonenickel dimer complex was observed at room temperature.[8a] Heating at 60 °C for 48 h led to the formation of the expected direct conjugate addition product **5** in 88% yield (eq 4):



(4)

In the intramolecular reaction, carbon−carbon bond formation between the β-carbon and the internal carbon of the styryl moiety occurred. In the intermolecular reaction, formation of a carbon−carbon bond between the terminal carbon of styrene and the β-carbon of **4a** occurred. These results inspired us to construct a nickel-catalyzed direct conjugate addition reaction of simple alkenes to enones, as shown in eq 1.

Scheme 1. Oxidative Cyclization of Alkene and Enone with Ni(0)



In the presence of a catalytic amount of $Ni(cod)_2$ and PCy_3, however, only a trace amount of **5** was obtained, and the precipitation of nickel black was observed. To suppress the formation of nickel black, the reaction was carried out in the presence of 4 equiv of PCy_3 at 100 °C for 4 h. Although **4a** was consumed, the expected direct conjugate addition product was obtained in only 39% yield because of the formation of oligomers of **4a**. In fact, in the absence of styrene, **4a** was consumed under the same reaction conditions to give a mixture of oligomers. Thus, in the presence of 2 equiv of styrene, **4a** was added slowly at 100 °C to avoid the occurrence of oligomerization, and **5** was obtained in 91% yield (Table 1, entry 1). Similarly, the reactions of **4a** with 4-trifluoromethylstyrene, 4-methoxystyrene, and 4-*tert*-

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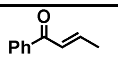
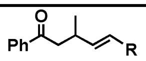
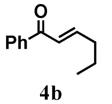
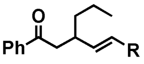
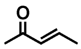
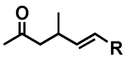
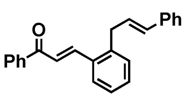
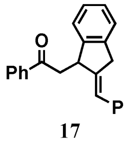
butylstyrene occurred to give the corresponding direct conjugate addition products **6**, **7**, and **8** (entries 2−4). Moreover, both octene and decene could also be employed as nucleophiles for **4a** to give the expected products **9** and **10** as mixtures of *E* and *Z* isomers in high yields (entries 5 and 6). The regioselectivity contrasted with that observed in Jamison's work.[7] A prolonged reaction time and a higher concentration were required. This might be due to a weaker coordination of 1-octene and 1-decene to the nickel(0) center, since the simultaneous coordination of an enone and an alkene to nickel(0) is required to undergo oxidative cyclization.[11] Similarly, (*E*)-1-phenylhex-2-en-1-one (**4b**) reacted with styrenes under the same reaction conditions to give the expected products (**11**, **12**, **13**) in high yields (entries 7−9). The reaction of (*E*)-3-penten-2-one (**4c**) with the same alkenes also occurred, affording the corresponding conjugate addition products (**14**, **15**, **16**) in moderate to high yields (entries 10−12). The reaction of **4c** with 1-octene gave an inseparable mixture of a trace mount of products and oligomers of **4c**.[12] Under the same reaction conditions, (*E*)-2-butenal underwent polymerization to give an insoluble white powder. Although **2a** and **2b** could be isolated as nickelacycle complexes, intramolecular direct conjugate addition of an alkene to an enone in **4d** proceeded catalytically to give the expected cyclic compound **17** (entry 13). The phenyl group and benzyl carbon of the styryl moiety in **4d** are on opposite sides of the double bond. On the other hand, those in **17** are on the same side. These observations suggest that rotation of the double bond and abstraction of the hydrogen on the same side as the phenyl group might occur during the reaction.

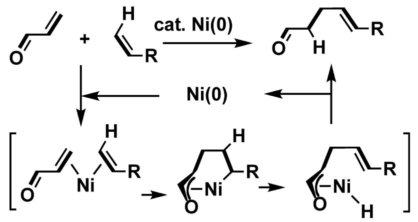
Table 1. Nickel-Catalyzed Direct Conjugate Addition[a]

Entry	Enone	Alkene	Product	Yield(%)
				
1	**4a**	R = Ph	**5**	91 (71)
2		R = *4*-$\mathrm{CF_3C_6H_4}$	**6**	80 (82)
3[b]		R = *4*-$\mathrm{MeOC_6H_4}$	**7**	71 (67)
4		R = *4*-$^t\mathrm{BuC_6H_4}$	**8**	99 (78)
5[c]		R = Hex	**9**	71 (64)[d]
6[c]		R = Oct	**10**	82 (65)[e]
				
7	**4b**	R = Ph	**11**	78 (67)
8		R = *4*-$\mathrm{CF_3C_6H_4}$	**12**	72 (58)
9		R = *4*-$\mathrm{MeOC_6H_4}$	**13**	65 (63)
				
10[b]	**4c**	R = Ph	**14**	54 (50)
11[b]		R = *4*-$\mathrm{CF_3C_6H_4}$	**15**	39 (32)
12[b]		R = *4*-$\mathrm{MeOC_6H_4}$	**16**	60 (44)
				
13[f]	**4d**		**17**	91[g] (58)

[a] General conditions: 2:1 alkene/enone, Ni(cod)$_2$ (10 mol %), PCy$_3$ (40 mol %), 100 °C, slow addition over 5 h followed by additional heating for 2 h. GC yields are given, with isolated yields in parentheses. [b] Additional heating for 4 h. [c] 10:1 alkene/enone. [d] 64:46 *E*/*Z*. [e] 58:42 *E*/*Z*. [f] Ni(cod)$_2$ (5 mol %), PCy$_3$ (20 mol %), 2.5 h. [g] NMR Yield.

A plausible reaction path is depicted in Scheme 2. Oxidative cyclization of an enone and an alkene to generate an η^3-oxaallylnickelacycle occurs, followed by β-hydrogen elimination and reductive elimination to give direct conjugate addition products. The coordination ability of enones toward the nickel(0) center is much stronger than that of the simple alkenes. Therefore, a slow addition of enones might be required in order to carry out the reaction at a low enone concentration, thereby simultaneously coordinating enones and alkenes and avoiding the occurrence of oligomerization of the enones.

Scheme 2. Plausible Reaction Path



In conclusion, we have demonstrated the first example of a direct conjugate addition of simple alkenes to enones catalyzed by a nickel(0) complex. This reaction is a very straightforward method for the introduction of an alkenyl group at the β-position of enones, since the conventional conjugate addition method requires the preparation of alkenyl metals and its metal must be discarded after the reaction. The regiochemistry of the carbon−carbon bond at the β-position might be controlled by the formation of an η^3-oxaallylnickel species that might stabilize the generated intermediate.

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Supporting Information Available: Detailed experimental procedures, analytical and spectral data for all new compounds, and crystallographic data (CIF) for **2a** and **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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