C–C Cleavage

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Manganese-Catalyzed Cleavage of a Carbon–Carbon Single Bond between Carbonyl Carbon and α-Carbon Atoms of Ketones**

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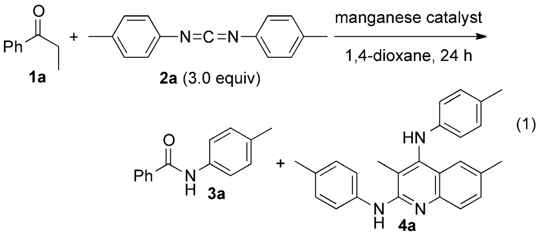
Olefin metathesis, which proceeds through a carbon–carbon (C–C) double bond cleavage, is a well-known and useful method in synthetic organic chemistry.[1] In contrast, cleavage of a C–C single bond is still one of the most difficult and challenging reactions in organic synthesis. Recently, there have been several reports on transition-metal-catalyzed transformations.[2] For example, reactions of strained molecules, such as three- and four-membered rings, have been reported.[3] In these reactions, release of the ring strain is the driving force for C–C single bond cleavage. As for reactions not involving ring strain, transformations using a directing group,[4] cleavage of a carbon–nitrile bond,[5] and transformations by retro-reactions, including retro-allylations,[6] retro-arylations,[7] retro-alkynylation,[8] retro-aldol reactions,[9,10] and deallylation[11] are also well known. To promote C–C single bond cleavage, we employed a manganese catalyst and carbodiimides. We report herein the cleavage of a unstrained C–C single bond between the carbonyl carbon and α-carbon atoms of ketones, and its application to the synthesis of amides.

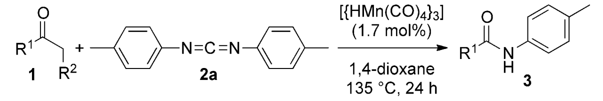
Treatment of propiophenone (**1a**) with 1.0 equivalent of 1,3-di-*p*-tolylcarbodiimide (**2a**) in the presence of a catalytic amount of a manganese complex, $[Mn_2(CO)_{10}]$, in 1,4-dioxane at 150 °C for 24 hours gave amide **3a** in 50 % yield.[12–14] This reaction also proceeds using either the iron complex $[Fe_2(CO)_9]$ or the cobalt complex $[Co_2(CO)_8]$ as a catalyst.[15] By increasing the amount of **2a** to 3.0 equivalents, the yield of amide **3a** was improved to 97 % [Eq. (1)]. In this reaction, quinoline **4a** was also formed in 73 % yield. The catalytic amount and reaction temperature could be reduced when the trinuclear manganese complex $[\{HMn(CO)_4\}_3]$ was used as the catalyst [Eq. (1)]. The C–C single bond of **1a** was cleaved regioselectively in this reaction. In the cleavage of unreactive bonds, novel transition-metal catalysts are usually employed; however, such transformations proceed efficiently with first-row transition metal catalysts (manganese, iron, or cobalt catalysts).

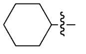
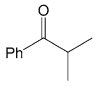


Manganese catalyst	*T*	3a	4a
$[Mn_2(CO)_{10}]$ (5.0 mol%)	150 °C	97%	73%
$[\{HMn(CO)_4\}_3]$ (1.7 mol%)	135 °C	96%	72%

First, we investigated the scope of the ketones (Table 1). Ketones with an electron-donating or electron-withdrawing group on the aromatic skeleton provided the corresponding amides **3b**, **3c**, and **3d** in yields in the range of 96–98 % (entries 1–3). Chlorine and bromine atoms on the aromatic ring were not lost under the reaction conditions, and amides **3e** and **3f** were obtained in 96 % and 62 % yields, respectively (entries 4 and 5). In the case of using acetophenone (**1g**) or the dialkyl ketone **1h**, amides **3a** and **3g** were provided in 60 % and 63 % yields, respectively (entries 6 and 7). Cyclohexyl ethyl ketone (**1i**) also produced amide **3h** in 50 % yield (entry 8). The amide **3h** was formed selectively without formation of the regioisomer, probably because of the steric hindrance of the cyclohexyl group of **1i**. A C–C single bond was cleaved using a ketone bearing a longer alkyl chain, **1j**

Table 1: Reactions between several ketones **1** and carbodiimide **2a**.[a]



Entry	R¹	R²			Yield [%][b]
1[c]	4-(MeO)C_6H_4	Me	**1b**	**3b**	98 (>99)
2	4-MeC_6H_4	Me	**1c**	**3c**	96 (>99)
3[c]	4-(CF_3)C_6H_4	Me	**1d**	**3d**	96 (>99)
4	4-ClC_6H_4	Me	**1e**	**3e**	96 (>99)
5	4-BrC_6H_4	Me	**1f**	**3f**	62 (65)
6[c]	Ph	H	**1g**	**3a**	60 (63)
7	*n*-C_5H_{11}	*n*-C_4H_9	**1h**	**3g**	63 (69)
8		Me	**1i**	**3h**	50 (–)
9	Ph	*n*-C_5H_{11}	**1j**	**3a**	72 (74)
10	Ph	Ph	**1k**	**3a**	95 (96)
11	 Ph O		**1l**	**3a**	62 (65)

[a] **2a** (3.0 equiv). [b] Yield of isolated product. The yield determined by ¹H NMR spectroscopy is reported within parentheses. [c] $[Mn_2(CO)_{10}]$ (5.0 mol%) was used as the catalyst, and the reaction temperature was 150 °C.

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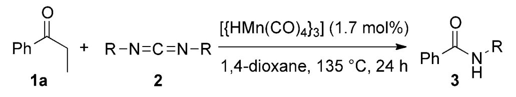
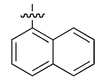
(entry 9). Benzyl phenyl ketone (**1k**) showed high reactivity and amide **3a** was produced in 95% yield (entry 10). The corresponding amide **3a** was formed in 62% yield when a ketone bearing a secondary alkyl group, **1l**, was employed as a substrate (entry 11). In this reaction, a hydrogen atoms at the α position of ketones **1** is necessary to promote the reaction; the reaction did not proceed using adamantyl ethyl ketone. In addition, the corresponding amide was not formed by the reaction between benzophenone and carbodiimide **2a**.

Next, the scope and limitations of the carbodiimides were investigated (Table 2). Diaryl carbodiimides with or without an electron-donating or electron-withdrawing group at the *para* position (**2b**–**2d**) gave the corresponding amides (**3i**–**3k**) in yields within the range of 41–98% (entries 1–3). The corresponding amides **3l** and **3m** were obtained with diaryl carbodiimides having either chlorine or bromine atom (**2e**, **2f**) without losing the chlorine or bromine atom (entries 4 and 5). The corresponding amide **3n** was afforded in 80% yield when di-1-naphthyl carbodiimide (**2g**) was used as a substrate (entry 6). The secondary aliphatic carbodiimide **2h** generated amide **3o** in 52% yield (entry 7). However, di-*tert*-butyl carbodiimide did not provide the corresponding amide.

Table 2: Reactions between ketone **1a** and several carbodiimides **2**.[a]

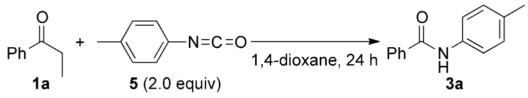


Entry	R			Yield [%][b]
1[c]	4-(MeO)C_6H_4	**2b**	**3i**	97 (>99)
2	Ph	**2c**	**3j**	98 (>99)
3[c]	4-(CF_3)C_6H_4	**2d**	**3k**	41 (45)
4[c]	4-ClC_6H_4	**2e**	**3l**	84 (87)
5[c]	4-BrC_6H_4	**2f**	**3m**	96 (>99)
6		**2g**	**3n**	80 (82)
7[c]	*i*Pr	**2h**	**3o**	52 (54)

[a] **2** (3.0 equiv). [b] Yield of isolated product. Yield determined by ^{1}H NMR spectroscopy is reported within parentheses. [c] $[Mn_2(CO)_{10}]$ (5.0 mol%) was used as the catalyst.

From the resulting structures of the products and by-products, a possible reaction mechanism is as follows (Scheme 1): 1) nucleophilic addition of the enol form of ketone **1** to carbodiimide **2**, which is activated by a manganese catalyst; 2) formation of azetidin-2-imine by intramolecular nucleophilic cyclization; 3) ring-opening reaction through the cleavage of a C–C single bond to give amide **3** and the ketenimine;[16] 4) aza-Diels–Alder reaction between the formed ketenimine and **2** to give a bicyclic intermediate; 5) tautomerization of the bicyclic intermediate, thus forming the quinoline derivative **4** as a side product.

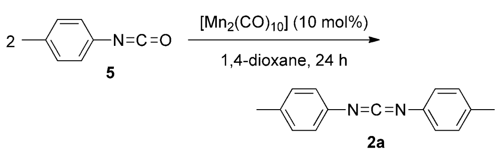
A C–C single bond cleavage also occurred when using an isocyanate instead of a carbodiimide. By the reaction of ketone **1a** with *p*-tolyl isocyanate (**5**) in the presence of the manganese catalyst $[\{HMn(CO)_4\}_3]$, amide **3a** was obtained in 15% yield [Eq. (2)]. By changing the catalyst to $[Mn_2(CO)_{10}]$, the yield of **3a** was increased to 73% [Eq. (2)].[17]



(2)

Reaction conditions		Yield [%]
$[\{HMn(CO)_4\}_3]$ (1.7 mol%)	135 °C	15
$[Mn_2(CO)_{10}]$ (10 mol%)	150 °C	73

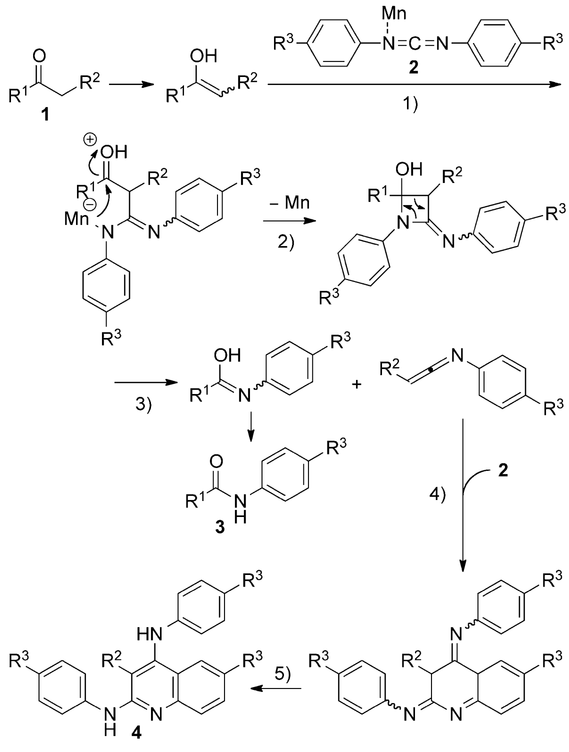
To elucidate the reaction mechanism in [Eq. (2)], isocyanate **5** was heated in the presence of $[\{HMn(CO)_4\}_3]$ [Eq. (3)]. As a result, carbodiimide **2a** was formed in 48% yield.[18] In the case of using $[Mn_2(CO)_{10}]$, **2a** was obtained in 62% yield [Eq. (3)]. These results indicate that carbodiimide **2a** was formed from two equivalents of the isocyanate **5**, and successive reaction between the formed carbodiimide **2a** and ketone **1a** produced amide **3a**.



(3)

Reaction conditions		Yield [%]
$[\{HMn(CO)_4\}_3]$ (1.7 mol%)	135 °C	48
$[Mn_2(CO)_{10}]$ (10 mol%)	150 °C	62

In summary, we have succeeded in the manganese-catalyzed synthesis of amides from ketones and carbodiimides. This reaction proceeds through the cleavage of a unstrained C–C single bond of ketones. The C–C single bond of a ketone was also cleaved using isocyanates instead of



Scheme 1. Proposed mechanism for the formation of amides **3**.

carbodiimides. We hope that this reaction will provide useful insight for synthetic organic chemistry.

Experimental Section

A mixture of propiophenone (**1a**, 67.1 mg, 0.500 mmol), 1,3-di-*p*-tolylcarbodiimide (**2a**, 333 mg, 1.50 mmol), [{HMn(CO)$_4$}$_3$] (4.2 mg, 8.3 μmol), and 1,4-dioxane (1.0 mL) was stirred at 135 °C for 24 h in a sealed tube. The solvent was then removed in vacuo, and the product was isolated by column chromatography on silica gel (*n*-hexane/ethyl acetate = 10:1) to give *N*-(4-methylphenyl)benzamide (**3a**, 102 mg, 97 % yield).

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Keywords: C–C cleavage · ketone · manganese · reaction mechanisms · synthetic methods

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[12] Investigation of different solvents. Yield is that of **3a**: THF: 0 %; 1,4-dioxane: 50 %; DMSO: 28 %; DMF: 54 %; DMA: 39 %.

[13] Investigation of different reaction temperatures (1,4-dioxane, 24 h). Yield is that of **3a**: 115 °C: 16 % (recovery of **1a**: 76 %); 135 °C: 44 % (**1a**: 29 %); 150 °C: 70 % (**1a**: 29 %); 180 °C: 55 % (**1a**: 21 %).

[14] Investigation of different reaction times (1,4-dioxane, 150 °C). Yield is that of **3a**: 1 h: 40 % (recovery of **1a**: 53 %); 3 h: 55 % (**1a**: 43 %); 8 h: 69 % (**1a**: 27 %); 24 h: 70 % (**1a**: 29 %).

[15] Investigation of different transition-metal complexes. Yield is that of **3a**: [MnBr(CO)$_5$]: 36 %; [Cr(CO)$_6$]: 4 %; [Mo(CO)$_6$]: 5 %; [W(CO)$_6$]: 1 %; [Fe(CO)$_5$]: 34 %; [Fe$_2$(CO)$_9$]: 43 %; [Fe$_3$(CO)$_{12}$]: 41 %; [Fe(CO)$_5$]: 34 %; [Co$_2$(CO)$_8$]: 51 %. No reaction: [Re$_2$(CO)$_{10}$], [ReBr(CO)$_5$], [{ReBr(CO)$_3$(thf)}$_2$], [Ru$_3$(CO)$_{12}$], [Rh$_4$(CO)$_{12}$], [Ir$_4$(CO)$_{12}$].

[16] There is another possible cleavage of four-membered cyclic intermediate, which gives the initial enol (or ketone **1**) and carbodiimide **2**.

[17] Investigation of different catalysts. Yield is that of **3a**: [Fe$_2$(CO)$_9$]: 57 %; [Fe$_3$(CO)$_{12}$]: 60 %; [Co$_2$(CO)$_8$]: 36 %.

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