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Rhenium- and manganese-catalyzed carbon–carbon bond formation using 1,3-dicarbonyl compounds and alkynes*

Yoichiro Kuninobu‡, Atsushi Kawata, Salprima S. Yudha, Hisatsugu Takata, Mitsumi Nishi, and Kazuhiko Takai‡

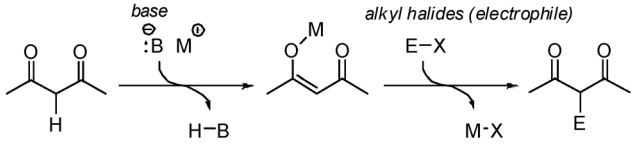
Division of Chemistry and Biochemistry, Graduate School of Natural Science and Technology, Okayama University, Tsushima, Kita-ku, Okayama 700-8530, Japan

Abstract: A rhenium complex, $[ReBr(CO)_3(thf)]_2$, catalyzed insertion of terminal alkynes into a C–H bond of active methylene sites of 1,3-dicarbonyl compounds. When a catalytic amount of isocyanide or molecular sieves was added to the reaction mixture, the reaction course changed markedly, and insertion of alkynes into a C–C single bond between α- and β-positions of cyclic and acyclic β-keto esters occurred. The formed acyclic δ-keto esters could be converted to 2-pyranones, which were applied to the synthesis of multisubstituted aromatic compounds via the Diels–Alder reaction and successive elimination of carbon dioxide. In the case of the rhenium-catalyzed reactions between terminal alkynes and β-keto esters without substituent at the α-position, tetrasubstituted benzenes were produced regioselectively by two-to-one reaction of the components. The yields of tetrasubstituted benzenes were improved by using a manganese catalyst.

Keywords: alkyne; carbon–carbon bond formation; 1,3-dicarbonyl; insertion; manganese; organic synthesis; rhenium; ring enlargement; substituted benzene.

INTRODUCTION

For many years, 1,3-diketones have been used for constructing carbon skeletons because the nucleophilic enolates can be easily handled. Enolates are usually prepared by deprotonation with bases and are alkylated with alkyl halides (eq. 1). However, this process results in stoichiometric amounts of metal halides as by-products. One method to overcome this problem is to start from formal C–H bond activation and successive insertion of unsaturated molecules (eq. 2).



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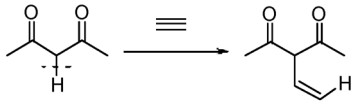

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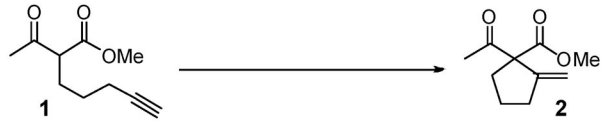
‡Corresponding authors

Recently, there have been a few reports on metal-catalyzed addition reactions of active methylene compounds with terminal alkynes under mild conditions, without needing to prepare an enolate. For example, gold and nickel/ytterbium catalysts were used for intramolecular cyclization of acetylenic 1,3-dicarbonyl compound **1** leading to **2** (eq. 3) [1]. However, as far as we know, there have been very few reports on an intermolecular version of this reaction, where the In-catalyzed transformation is carried out with the addition of catalytic amounts of bases (eq. 4) [2]. For a metal catalyst to promote the reaction, it needs to have an affinity to alkynes and generate nucleophilic species from 1,3-dicarbonyl compounds. In our work, we have focused our attention on a rhenium complex, which is a group 7 metal, as a result of the observations described below.



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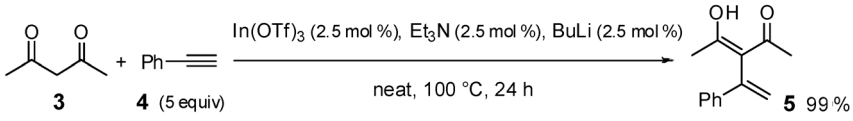

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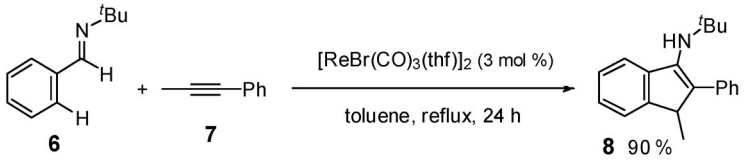
In 2005, while investigating C–C bond formation with rhenium catalysts, we noticed that low-valent rhenium complexes had an ability to activate C–H bonds [3]. For example, when a mixture of aryl imine **6** and 1-phenyl-1-propyne (**7**) in toluene was treated with a catalytic amount of $[ReBr(CO)_3(thf)]_2$, indene derivative **8** was obtained in 90 % yield (eq. 5) [4]. In this transformation, the rhenium complex activated a C–H bond of the *ortho*-position of **6** and the acetylenic bond of **7** could be inserted into the Re–C bond that was formed (Scheme 1). Thus, the rhenium complex **9** acts as a soft Lewis acid to bring the π-bond closer to the rhenium center.



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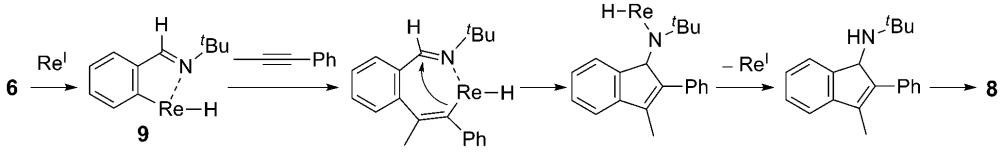
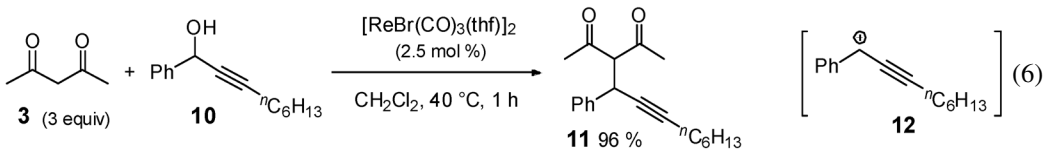


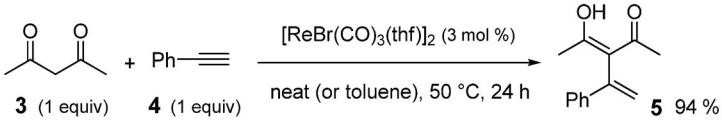
Scheme 1 Proposed mechanism for Re-catalyzed synthesis of indenes.

We also observed that the rhenium complex catalyzed a coupling reaction between 1,3-diketone **3** and propargyl alcohol **10** leading to **11** (eq. 6) [5]. Here, the rhenium complex, $[ReBr(CO)_3(thf)]_2$, acts as a Lewis acid and generates propargyl carbocation **12** from **10**. Following this, a nucleophilic attack to **12** occurs. The result suggests that the rhenium complex has an ability to generate nucleophilic species from **3**.



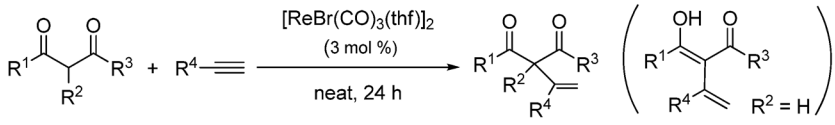
INSERTION OF ALKYNES INTO A C–H BOND OF 1,3-DICARBONYL COMPOUNDS

At first, we examined reactions between 1,3-diketones and terminal alkynes with the rhenium catalyst, $[ReBr(CO)_3(thf)]_2$. The reaction proceeded as expected. For example, treatment of a mixture of 1,3-diketone **3** and phenylacetylene (**4**) with $[ReBr(CO)_3(thf)]_2$ in toluene at 50 °C for 24 h gave the alkenylated adduct **5** in 94 % yield (eq. 7) [6]. In this reaction, a regioisomer generated by C–C bond formation at the terminal carbon atom of the alkyne was not observed. The reaction also proceeded under solvent-free conditions. Under higher temperature conditions (90 °C and reflux), the yield of product **5** decreased owing to the polymerization of the alkyne.



The products that result from the insertion of several terminal alkynes into the C–H bond of active methylene compounds are shown in Table 1. An ether group connected at the benzyl position of the terminal alkyne remained intact during the reaction (Table 1, entry 2). The reaction of 1-ethynylcyclohex-1-ene with **3** also proceeded in excellent yield (entry 3). A substituent at the α-position did not disturb the reaction. For example, a reaction between 2-acetylcyclohexanone and phenylacetylene proceeded in excellent yield (entry 4), and a reaction of 1-hexyne with 3-methylpentane-2,4-dione gave the corresponding alkenyl derivative in 95 % yield (entry 5). The reaction of ethyl 2-methyl-3-oxobutanoate (**13**), and phenylacetylene gave an alkenyl derivative in 67 % yield (entry 6). In this case, addition of dysprosium triflate, $Dy(OTf)_3$, as a co-catalyst improved the yield markedly. Ethyl 2-oxocyclohexanecarboxylate (**14**) could be used as an active methylene compound, and the corresponding product **15** was obtained in 95 % yield (entry 7).

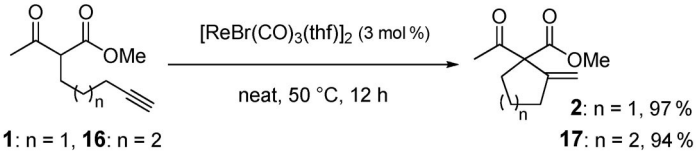
Table 1 Insertion of alkynes into a C–H bond of 1,3-dicarbonyl compounds.



entry	R^1	R^2	R^3	R^4	alkyne / equiv	temp / °C	yield / %
1	Me	H	Me (**3**)	Ph	1.0	50	94
2	Me	H	Me	$PhCH_2OCH_2$	2.0	40	86
3	Me	H	Me		1.1	50	94
4	-$(CH_2)_4$-		Me	Ph	1.5	40	92
5	Me	Me	Me	$^nC_6H_{13}$	1.2	50	95
6	Me	Me	OEt (**13**)	Ph	1.5	50	67 (95)[a]
7	-$(CH_2)_4$-		OEt (**14**)	Ph	1.5	40	95 (**15**)

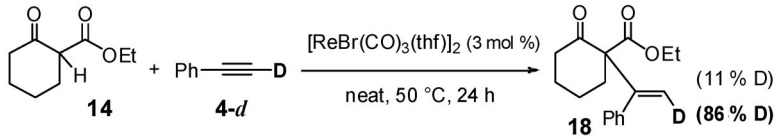
[a] additive: $Dy(OTf)_3$ (5 mol%)

The reaction could also be applied in an intramolecular fashion, which is the same transformation as the Conia-ene reaction (eq. 8).



(8)

Deuterium-labeling experiments were conducted to obtain more information about the mechanism of the reaction. The reaction of keto ester **14** and deuterated phenylacetylene **4**-*d* selectively afforded alkenyl derivative **18**, in which the deuterium locates *anti* to the β-keto ester moiety (eq. 9). On the other hand, when the deuterated keto ester **14**-*d* was reacted with phenylacetylene (**4**), the product **19** had the deuterium *syn* to the β-keto ester group (eq. 10).



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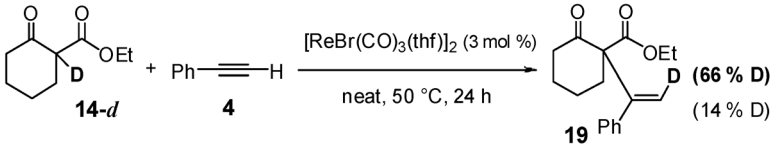
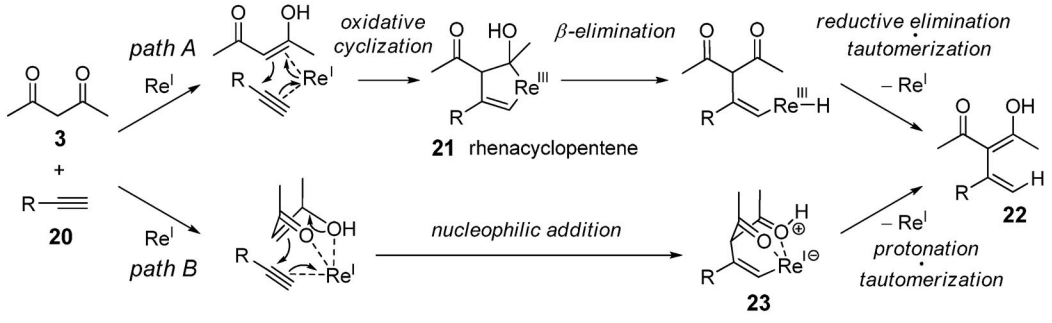


(10)

From the deuterium-labeling results, we can propose two possible reaction pathways (Scheme 2). In path A, oxidative cyclization of the enol of **3**, alkyne **20**, and rhenium complex gives rhenacyclopentene intermediate **21**. Then, β-hydride elimination followed by reductive elimination and tautomerization affords adduct **22**. In path B, the rhenium catalyst coordinates to terminal alkyne **20** and the enol of **3**. Then, nucleophilic addition of the enol to the Re-coordinated alkyne gives alkenyl-rhenium intermediate **23**. After protonation, the rhenium catalyst is regenerated and adduct **22** is formed.

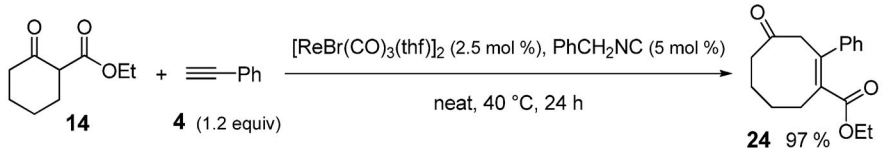


Scheme 2 Proposed mechanism for insertion of alkynes into a C–H bond of 1,3-diketones.

INSERTION OF ALKYNES INTO A NONSTRAINED C–C SINGLE BOND OF β-KETO ESTERS AND ITS APPLICATION TO THE SYNTHESIS OF 2-PYRANONES

As described in Table 1, entry 7, treatment of a mixture of cyclic β-keto ester **14** and phenylacetylene (**4**) with a rhenium catalyst, $[ReBr(CO)_3(thf)]_2$, gave the corresponding alkenylated product **15** in 95 % yield. In order to enhance the catalytic activity of the rhenium complex, 5 mol % of benzylisocyanide

was added to the reaction mixture. Instead of producing the same adduct, we obtained an eight-membered ring product, **24**, quantitatively (eq. 11) [7]. The structure of the eight-membered carbocycle was confirmed by X-ray crystallographic analysis of the corresponding thioacetal of **24**. The result suggests that the rhenium catalyst promotes the insertion of the terminal alkyne into a C–C single bond of the nonstrained cyclic compound **14** under mild conditions. Although the yield was low, this reaction proceeded even at room temperature.

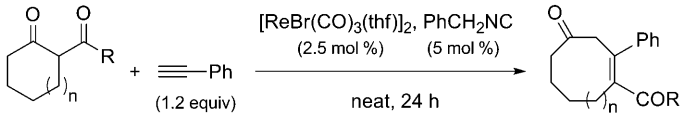


(11)

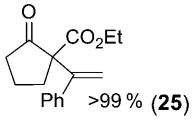
It is generally difficult to carry out the dissociation of C–C bonds under mild conditions due to their strong bond energy. Because of this, most transformations have been limited to either stoichiometric reactions, or catalytic reactions using highly strained substrates, such as three- or four-membered rings, in which the release of the strain energy is the driving force for the reactions [8]. In contrast to the strained molecules, there have been only a few reports on transformations starting from the dissociation of nonstrained C–C bonds [9].

As shown in Table 2, 8-, 9-, and 10-membered δ-keto esters could be produced from the corresponding cyclic β-keto esters in good to excellent yields (Table 2, entries 1–3), although the formation of the 10-membered ring required heating the mixture at 90 °C or the absence of benzyl isocyanide (entry 4). In the case of a 5-membered β-keto ester (entry 5), a ring-enlargement product was not obtained, and instead, insertion of phenylacetylene into the C–H bond occurred to give **25**. 1,3-Diketone was less reactive than the corresponding β-keto ester; therefore, the reaction was conducted at 100 °C (entry 6). Aliphatic alkyne **26** inserted into the C–C bond of **14** to give the desired compound **27** almost quantitatively; however, the reaction also required heating at 80 °C (eq. 12).

Table 2 Insertion of alkynes into a C–C bond of cyclic 1,3-dicarbonyl compounds.

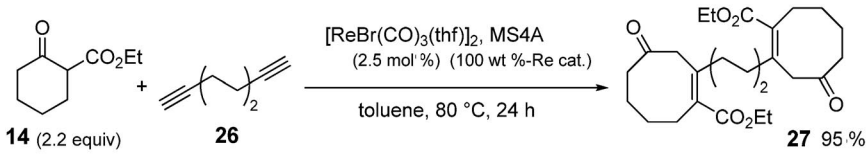


entry	R	n		temp / °C	yield / %
1	OEt	1	(**14**)	40	97
2	OEt	2		40	87
3	OEt	3		90	50
4	OEt	3		50	78[a]
5	OEt	0		40	0[b]
6	Me	1		100	61[c]



>99 % (**25**)

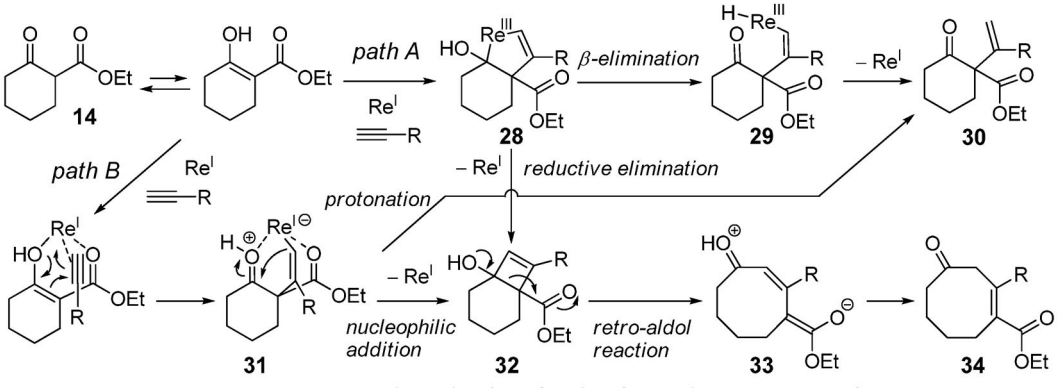
[a] Without addition of $PhCH_2NC$. [b] See the text. [c] Solvent: CH_2ClCH_2Cl.



(12)

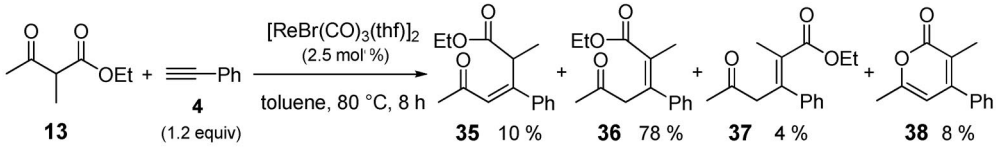
In order to examine the possibility of the ring-enlargement from alkenylated product **15**, **15** was exposed to similar reaction conditions. However, the ring-expansion reaction did not proceed, and the starting material **15** was recovered completely. The result suggests that the ring expansion does not occur via the alkenylated β-keto ester.

As described in Scheme 2, alkenylated product **30** could be produced by two possible pathways: a metalacyclopentene path and a carbometalation path. Ring-enlargement product **34** could be formed via the same intermediate **32** (Scheme 3). In the metalacyclopentene path, if reductive elimination from **28** occurs faster than β-elimination, cyclobutene intermediate **32** would be generated. The same intermediate **32** can be generated if nucleophilic addition from **31** proceeds faster than protonation in the carbometalation path. The C–C bond cleavage by the retro-aldol reaction of the β-hydroxy ester **32** can occur smoothly due to the ring strain of the cyclobutene, and eight-membered ring **33** is generated. Isomerization of the double bond gives the more stable keto ester **34**. The total sequence resembles the de Mayo reaction, i.e., photo-induced [2 + 2] addition of an olefin and enol of 1,3-diketone gives cyclobutane, whose C–C bond is cleaved by a retro-aldol reaction.



Scheme 3 Proposed mechanism for the ring-enlargement reaction.

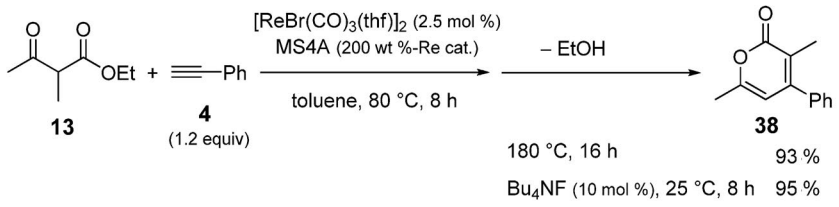
Next, we investigated this reaction with acyclic β-keto esters. Similar insertion of the alkyne into a C–C single bond of the β-keto ester proceeded. In addition, 2-pyranone **38**, generated via cyclization with the elimination of ethanol from **35**–**37**, was produced as a side product (eq. 13) [10]. Because 2-pyranones are useful building blocks in organic synthesis, we focused our attention on applying the olefinic isomers **35**–**37** in the formation of 2-pyranone derivative **38**.



(13)

The addition of molecular sieves proved to be important in promoting the reaction efficiently. For example, when the reaction mixture of eq. 13 was heated at high temperature without isolation, the desired 2-pyranone **38** was obtained in 93 % yield (eq. 14). The temperature could be lowered substan-

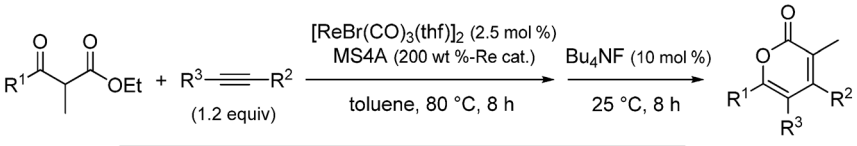
tially when tetrabutylammonium fluoride (TBAF) was added. TBAF can act as a base to accelerate the cyclization.



(14)

Arylacetylenes with an electron-donating or -withdrawing group at the *para*-position provided 2-pyranones in 93–95 % yields (Table 3, entries 2 and 3). The reaction of 1-ethynylcyclohex-1-ene with **13** also proceeded in excellent yield (entry 4). When alkylacetylene **39** was used, a 2-pyranone was obtained even though the yield was slightly lower (entry 5). Phenyl-substituted β-keto ester **40** could also be used for the reaction (entries 6 and 7). Insertion of internal alkynes into a C–C bond of β-keto esters was found to occur (entries 7 and 8). In the case of a dialkylacetylene, a higher temperature was necessary to promote the reaction (entry 7). 1-Phenyl-1-propyne afforded two regioisomeric 2-pyranones in 94 % yield in a regioselective manner (entry 8).

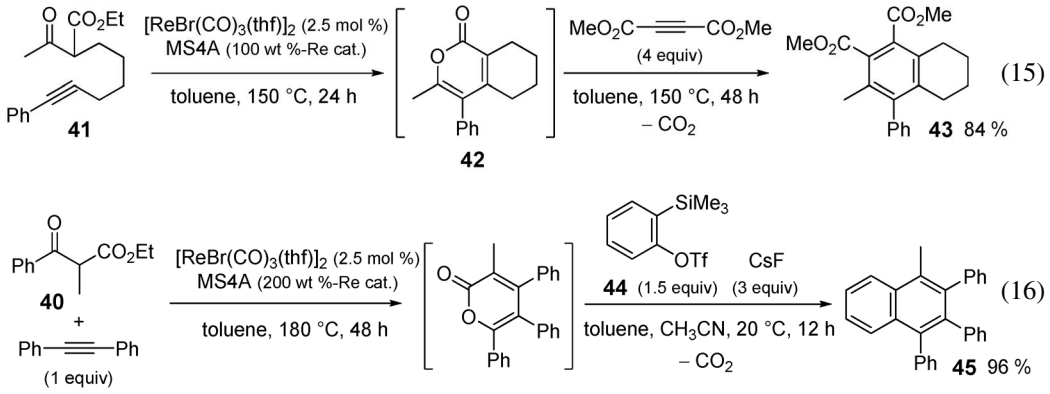
Table 3 Syntheis of 2-pyranones.



entry	R^1	R^2	R^3	yield / %
1	Me (**13**)	Ph	H	95
2	Me	*p*-$MeOC_6H_4$	H	93
3	Me	*p*-$CF_3C_6H_4$	H	93
4	Me		H	92
5	Me	$^nC_{10}H_{21}$	H (**39**)	83
6	Ph (**40**)	Ph	H	82
7	Ph	$^nC_5H_{11}$	$^nC_5H_{11}$	79[a]
8	Me	Ph	Me	88[b]

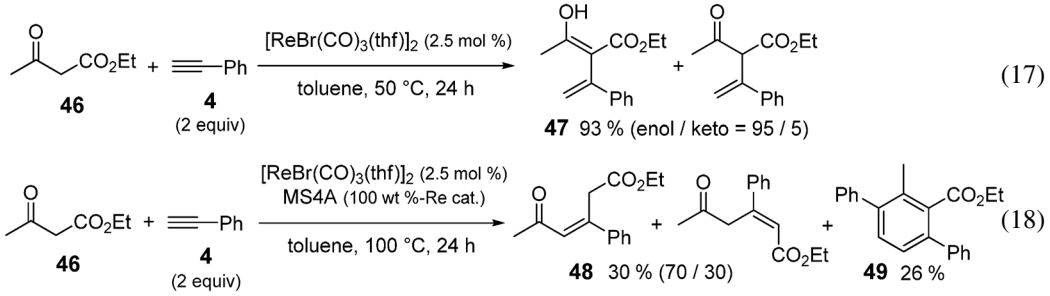
[a]150 °C, 24 h [b]A regioisomer (R^2 = Me, R^3 = Ph) was obtained in 6 % yield.

The 2-pyranone synthesis could be applied to an intramolecular reaction. By heating β-keto ester **41** in toluene at 150 °C with the rhenium catalyst and molecular sieves gave 2-pyranone **42** in 95 % yield. When the formed 2-pyranone **42** was treated in situ with acetylene dicarboxylate at 150 °C, tetrahydronaphthalene derivative **43** was obtained in one-pot (eq. 15) [11]. As a second alkyne component, benzyne generated in situ from 2-(trimethylsilyl)phenyl triflate (**44**) and cesium fluoride could be employed. This led to naphthalene derivative **45** in 96 % yield (eq. 16) [11].

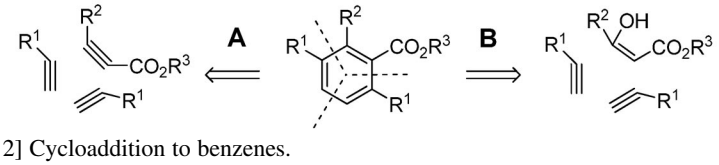


REGIOSELECTIVE SYNTHESIS OF TETRASUBSTITUTED BENZENES

When a mixture of phenylacetylene (**4**) and β-keto ester **46** without an α-substituent was treated with a catalytic amount of $[ReBr(CO)_3(thf)]_2$ in toluene at 50 °C for 24 h, the C–C triple bond of **4** inserted into the C–H bond of **46**, and enol and keto forms of the product **47** were obtained in 93 % combined yields (eq. 17) [6]. In contrast, when the reaction was conducted at 100 °C in the presence of molecular sieves, the triple bond of **4** inserted into the C–C bond of the β-keto ester **46** to give a mixture of olefinic isomers **48**. In addition, we accidentally found that tetrasubstituted aromatic compound **49** was formed as a by-product. Only a small difference in the reaction conditions brings about a remarkable change in the product distribution.

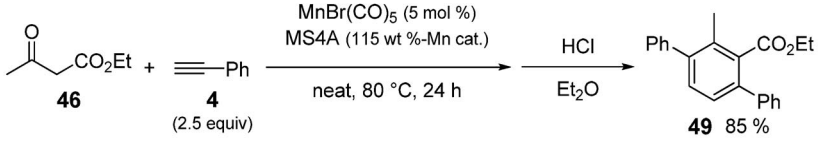


There are many ways to construct aromatic rings, and probably the most well known and efficient approach is the transition-metal-catalyzed [2 + 2 + 2] cycloaddition of three alkynes (Scheme 4). However, the construction of the desired substituted benzene rings from two or more alkynes is difficult due to the low pair- and regioselectivity. This method is a regioselective synthesis of *p*-terphenyls from two phenylacetylenes and one 1,3-dicarbonyl compound via dehydration. Because such *p*-terphenyl derivatives are important building blocks for the synthesis of organic materials, the result encouraged us to carry out further investigations to see if we could improve the yield of this aromatic compound.

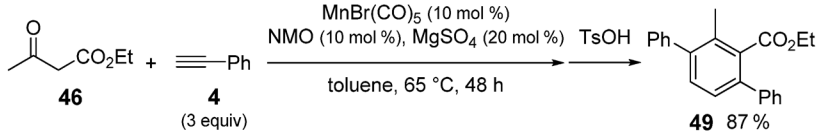


Scheme 4 [2 + 2 + 2] Cycloaddition to benzenes.

We finally found that a combination of $MnBr(CO)_5$ and molecular sieves had a higher catalytic activity and wide applicability compared to the rhenium system. For example, treatment of β-keto ester **46** and phenylacetylene (**4**) with a catalytic amount of the manganese system at 80 °C under solvent-free conditions, followed by acidification, gave benzoic ester **49** in 85 % yield (eq. 19) [12]. Later, we learned that Tsuji and Nakamura also discovered a similar Mn-catalyzed reaction (eq. 20) [13]. The reaction conditions were also quite similar to ours.



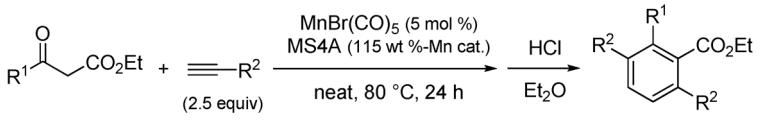
(19)

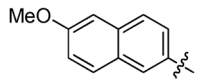


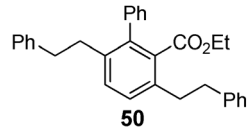
(20)

Table 4 shows the scope and limitations of our Mn-catalyzed [2 + 2 + 2] cycloaddition reactions. In the case of arylacetylenes, *p*-terphenyl derivatives were obtained selectively in all cases (Table 4, entries 1–6). The C–Br bond remained intact during the reaction (entry 4). When alkylacetylene was used as an alkyne component, two regioisomeric benzenes **50** and **51** were obtained in a ratio of about 3:1 (entry 7). Internal alkynes, however, did not react under the conditions.

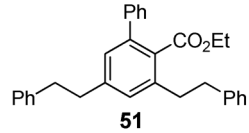
Table 4 Regioselective synthesis of tetrasubstituted benzenes.



entry	R^1	R^2	yield / %
1	Me	Ph	85
2	Ph	Ph	88
3	Ph	*p*-$MeOC_6H_4$	77
4	Ph	*p*-BrC_6H_4	86
5	Ph	*o*-$MeOC_6H_4$	74
6	Ph		71
7	Ph	$Ph(CH_2)_2$	88[a]



50

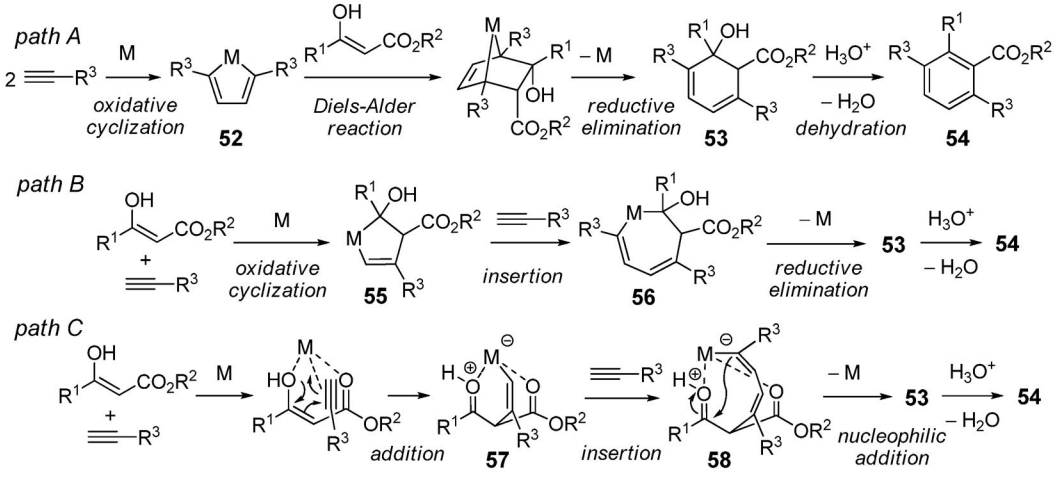


51

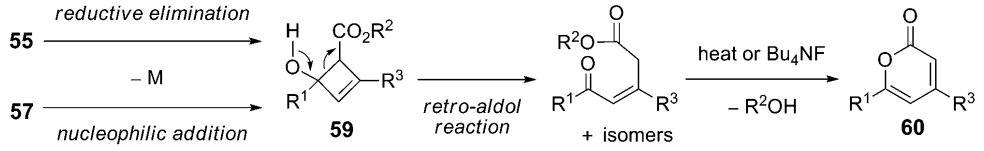
[a]A combined yield of two regioisomers **50** and **51**.
The ratio of the two isomers, **50** and **51**, is 73 / 27.

There are three possible pathways for the formation of the precursor **53**, a six-membered hydroxy ester, as shown in Scheme 5. In path A, metalacyclopentadiene **52** is formed from two terminal alkynes. A Diels–Alder reaction followed by reductive elimination gives an intermediate **53**. The regioselectivity of this cycloaddition can be explained by the favorable location of both aryl substituents at the 2- and 5-positions of **52**. However, no dimer of the alkynes was observed when α-substituted β-keto esters were used. Therefore, we do not think that path A occurs. The other two pathways B and C reflect the same mechanism as for the 2-pyranone synthesis at least up to the midpoint. Reductive elimination of

55 or nucleophilic cyclization of **57** gives four-membered β-hydroxy ester **59** leading to 2-pyranone **60** (Scheme 6). The difference is that further insertion of the terminal alkyne occurs into metal-sp^2 carbon bonds of intermediates **55** or **57**. Reductive elimination from **56** or nucleophilic addition from **58** gives **53**. One issue that remains is the reason why the insertion occurs in a regioselective manner. Concerning this issue, Nakamura has recently given an explanation using the density functional theory (DFT) calculation in path C [14]. However, it is still not clear why the second insertion of the alkyne into **55** (in path B) or **57** (in path C) does not occur in the case of α-substituted β-keto esters.



Scheme 5 Proposed mechanism for the synthesis of tetrasubstituted benzenes.



Scheme 6 Proposed mechanism for the synthesis of 2-pyranones.

CONCLUSIONS

During investigations to find new reactivities of rhenium complexes, we discovered several new reactions that were quite unexpected. Depending on the reaction conditions, terminal alkynes insert into a C–H bond of active methylene sites, or into a C–C single bond between α- and β-positions. In the case of acyclic β-keto esters, further treatment with TBAF gives 2-pyranones, which are useful synthetic intermediates for the synthesis of multisubstituted benzenes. In addition, *p*-terphenyl derivatives, which are important building blocks for the synthesis of organic materials, can be synthesized regioselectively from β-keto esters and terminal alkynes by using a manganese catalyst. We hope these reactions offer many new possibilities, especially in the synthesis of organic functional materials.

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