

Rhodium(II)-catalyzed multicomponent assembly of α,α,α -trisubstituted esters via formal insertion of O-C(sp³)-C(sp²) into C-C bonds

Dan Ba¹, Si Wen¹, Qingyu Tian¹, Yanhui Chen¹, Weiwei Lv¹ & Guolin Cheng¹  [✉]

The direct cleavage of C(CO)–C single bonds, delivering otherwise inaccessible compounds, is a significant challenge. Although the transition metal-catalyzed insertion of functional groups into C(CO)–C bonds has been studied, strained ketone substrates or chelating assistance were commonly required. In this article, we describe a rhodium(II)-catalyzed three-component reaction of 1,3-diones, diazoesters, and *N,N*-dimethylformamide (DMF), leading to an unusual formal insertion of O-C(sp³)-C(sp²) into unstrained C(CO)–C bonds. This procedure provides a rapid entry to a gamut of otherwise inaccessible α,α,α -trisubstituted esters/amide from relatively simple substrates in a straightforward manner. 55 examples of highly decorated products demonstrate the broad functional group tolerance and substrate scope. The combination of control experiments and isotope-labeling reactions support that O, C(sp³), and C(sp²) units derive from 1,3-diones, diazoesters, and DMF, respectively.

¹College of Materials Science & Engineering, Huaqiao University, 361021 Xiamen, China. ✉email: glcheng@hqu.edu.cn

Ketones are widely present in natural products and synthetic molecules, and are one of the most fundamental feedstocks in organic synthesis. But while there are many reactions involving the α -functionalization and transformation of carbonyl group of ketones, the selective and catalytic cleavage of C(CO)–C single bonds is still a significant challenge^{1–26}. Especially, the direct insertion of functional groups into C(CO)–C single bonds, enabling the formation of otherwise inaccessible compounds, is considerably appealing²⁷. For example, the traditional Baeyer–Villiger reaction²⁸ and Büchner–Curtius–Schlotterbeck reaction^{29–32} could directly insert one-atom into C(CO)–C bonds to give esters and homologated ketones, respectively (Fig. 1a). Recently, transition metal-catalyzed chemoselective insertion of unsaturated units (alkene, allene, alkyne, ketone, and imine) into strained C(CO)–C bonds has been extensively studied by Dong^{33–38}, Murakami^{39,40}, Cramer^{41,42}, Martin⁴³, Chi⁴⁴, and Krische (Fig. 1b)⁴⁵. However, successful transformation for the catalytic insertion of functional groups into unstrained C(CO)–C bonds is extremely rare, wherein chelating assistance is required⁴⁶. In 2018, Bi and co-workers reported the first example that involve the formal insertion of carbenoids into acyclic C(CO)–C bonds using Ag catalyst (Fig. 1c)^{47,48}. Undoubtedly, the development of multiple functional groups, particularly deriving from different molecules, and insertion into unstrained C(CO)–C bonds is of great interest from both practical synthetic applications and mechanistic investigations.

In the course of developing transition metal-catalyzed deacylative cross-coupling of 1,3-diones with carbene precursors, we unexpectedly observed the α,α,α -trisubstituted ester products by using *N,N*-dimethylformamide (DMF) as solvent^{49–52}. Herein we report a multicomponent synthesis of α,α,α -trisubstituted esters from 1,3-diones, diazoesters, and DMF using a rhodium(II) catalyst, in which one-oxygen, one-carbon (sp^3), and one carbon (sp^2), deriving from 1,3-diones, diazoesters, and DMF, respectively, are inserted into C(CO)–C bonds (Fig. 1d). This process represents a method for catalytic skeletal remodeling and a complement to cut and sew strategies based on C–C bonds cleavage²⁷.

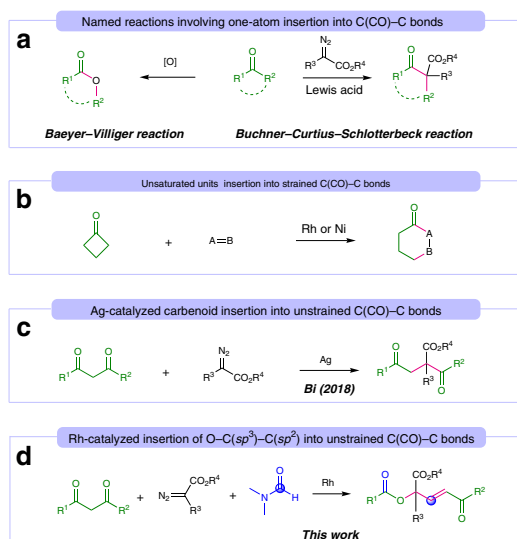


Fig. 1 Functional groups insertion into C(CO)–C bonds. **a** Named reactions involving one-atom insertion into C(CO)–C bonds. **b** Unsaturated units insertion into strained C(CO)–C bonds. **c** Ag-catalyzed carbenoid insertion into unstrained C(CO)–C bonds. **d** Rh-catalyzed insertion of O–C(sp^3)–C(sp^2) into unstrained C(CO)–C bonds.

Results

Reaction development. We commenced our study by examining the multicomponent reaction of 1,3-diphenylpropane-1,3-dione (**1a**), methyl α -phenyldiazoacetate (**2a**), and DMF in the presence of a catalytic amount of $[\text{RuCl}_2(p\text{-cymene})]_2$ at ambient temperature under air atmosphere for 12 h. The three-component reaction product (**3a**) was obtained in 51% yield (Table 1, entry 1). The structure of **3a** was unambiguously verified by single-crystal X-ray diffraction. We then explored the efficiency of the reaction using different transition metal catalysts. $\text{Rh}_2(\text{OAc})_4$ and AgOAc catalysts could give the desired product in 65% and 60% yields, respectively (entries 2 and 3), whereas no product was detected using $\text{Pd}(\text{OAc})_2$ and $\text{Cu}(\text{OAc})_2$ catalysts (entries 4 and 5). The choice of Rh salts was also critical to this reaction. Rh(III) and Rh(I) salts exhibited inferior reactivity compared to Rh(II) salt (entries 6 and 7). A similar yield of **3a** was obtained when $\text{Rh}_2(\text{esp})_2$ was used instead of $\text{Rh}_2(\text{OAc})_4$, and no reaction occurred without a catalyst (entries 8 and 9). Remarkably, we noticed that 4 Å MS had a significant effect on the reactivity and gave **3a** in 85% yield (entry 10). Further investigation of the loading of catalyst and additive, as well as the concentration of the reaction afforded no better results (entries 11–15). A comparative yield was observed when the reaction was carried out under nitrogen atmosphere (entry 16).

Interestingly, the carbenoid insertion (one-carbon insertion) product was not detected in any of the investigations of the reaction parameters^{47,48}.

Substrate scope. With the optimized reaction conditions in hand, we explored the substrate scope with respect to 1,3-diones. As shown in Fig. 2a, 1,3-diarylpropane-1,3-diones bearing diverse substituents (methyl, *tert*-butyl, methoxyl, halogen, and trifluoromethyl) on their aryl rings smoothly underwent reactions to generate the desired α,α,α -trisubstituted esters in 60–97% yields (**3b–p**). The reactivity of this reaction was slightly

Table 1 Optimization of the transition metal-catalyzed C(CO)–C bonds insertion reaction (reaction conditions: **1a (0.2 mmol), **2a** (0.1 mmol), catalyst, and additive (50 mg) in DMF (0.5 mL) at room temperature under air atmosphere for 12 h).**

Entry	Catalyst (x mol %)	Additive	Yield (%) ^a
1	$[\text{RuCl}_2(p\text{-cymene})]_2$ (5)	—	51
2	$\text{Rh}_2(\text{OAc})_4$ (2)	—	65
3	AgOAc (10)	—	60
4	$\text{Pd}(\text{OAc})_2$ (10)	—	0
5	$\text{Cu}(\text{OAc})_2$ (10)	—	0
6	$[\text{RhCp}^*\text{Cl}_2]_2$ (2)	—	24
7	$[\text{Rh}(\text{cod})\text{Cl}]_2$ (2)	—	Trace
8	$\text{Rh}_2(\text{esp})_2$ (2)	—	62
9	—	—	0
10	$\text{Rh}_2(\text{OAc})_4$ (2)	4 Å MS	85
11 ^b	$\text{Rh}_2(\text{OAc})_4$ (2)	4 Å MS	70
12 ^c	$\text{Rh}_2(\text{OAc})_4$ (2)	4 Å MS	81
13	$\text{Rh}_2(\text{OAc})_4$ (1)	4 Å MS	67
14	$\text{Rh}_2(\text{OAc})_4$ (5)	4 Å MS	84
15 ^d	$\text{Rh}_2(\text{OAc})_4$ (2)	4 Å MS	80
16 ^e	$\text{Rh}_2(\text{OAc})_4$ (2)	4 Å MS	84

^aIsolated yields based on **2a**.

^b4 Å MS (25 mg) was used.

^c4 Å MS (75 mg) was used.

^d1 mL of DMF was used.

^eReaction was carried out under nitrogen atmosphere. esp: $\alpha,\alpha,\alpha,\alpha'$ -Tetramethyl-1,3-benzenedipropionic acid.



Fig. 2 Scope of substrates. **a** Scope of 1,3-diones. **b** Scope of diazoesters. Reaction conditions: **1** (0.2 mmol), **2** (0.1 mmol), Rh₂(OAc)₄ (2 mol %), and 4 Å MS (50 mg), in DMF (0.5 mL) at room temperature under air atmosphere for 12 h. Isolated yields based on **2** are shown.

influenced by the electronic properties of the aryl rings. 1,3-dia-*ortho*-diarylpropane-1,3-diones with electron-donating groups (**3b** and **3c**) afforded lower yields of the corresponding products than those with electron-withdrawing groups (**3d–g**). Importantly, the steric

hindrance of the aryl rings was not observed to affect the reaction efficiency, and high yields were obtained when substrates with an *ortho*-substituent on phenyl rings were used (**3l–n**). Substrates containing naphthalene and thiophene rings can be successfully

converted to the desired products (**3o** and **3p**). Remarkably, aryl alkyl 1,3-diketones delivered the desired products in good to excellent yields with exclusive chemoselectivity, and the C(CO)–C bonds cleavage reactions were found to occur selectively at the alkanoyl–carbon bonds (**3q–z** and **3aa–ae**). It is worth mentioning that the reaction is amenable to a wide range of heteroaryl-substituted 1,3-diones (**3ab–ad**). Finally, a ferrocene unit could be incorporated into the product with high efficiency (**3ae**).

Subsequently, we examined the substrate scope of α -aryldiazoacetates (Fig. 2b). We first set out to investigate the effect of substituents on the phenyl rings of α -phenyldiazoacetates. A variety of substituted methyl α -phenyldiazoacetates reacted smoothly with **1a**, furnishing the desired products (**4a–l**) in moderated to good yields. The electronic nature of the substituents on the phenyl rings had an obvious effect on the yields, wherein electron-poor groups were less favorable for this reaction (**4e–h**). In addition, the steric hindrance of the substrates had a negligible effect on the reactivity (**4i–k**). Moreover, α -naphthyl and α -indolyl diazoacetates were proved to be suitable substrates, giving the corresponding product in 67% and 89% yields, respectively (**4m** and **4n**). We then evaluated the generality of substituents on the ester moieties of α -aryldiazoacetates. Gratifyingly, ethyl, isopropyl, benzyl, allyl, cinnamyl, 3-hexenyl, homopropargyl, and 2-bromoethyl groups were well tolerated, affording the desired products (**4o–v**) in 57–87% yields. Notably, α -phenyl-*N*-methyl-*N*-phenyl diazoacetamide underwent the reaction to provide α,α,α -trisubstituted amide (**4w**) in 55% yield.

Despite the broad substrate scope shown herein (Fig. 2), this transformation is not without limitations. For example, when acetylacetone, ethyl acetoacetate, and *N*-methyl-3-oxobutanamide were subjected to the reaction, no desired products were observed. In addition, the donor–acceptor diazoesters are always required, and α -alkyl and α -H diazoesters failed to give the corresponding products. This might be explained by rapid decomposition of the carbene precursors in the presence of a rhodium(II) catalyst.

Synthetic applications. This three-component reaction was amenable to a gram-scale synthesis. Ester (**3a**) could be produced without modifying the standard conditions in 78% yield on a 5 mmol scale (Fig. 3). The ester and enone groups of the products of this reaction offer handles for further elaboration. To illustrate this point, several transformations of **3a** were studied. First, the 1,4-dione products (**5a** and **5b**) could be obtained via hydrolyzation/decarboxylation/isomerization cascaded reaction from **3a** and **3ae**, respectively in excellent yields, which could serve as a precursor of Paal–Knorr pyrrole synthesis. Second, treatment of **3a** with K_2CO_3 /MeOH solution led to the transesterification/Michael addition product (**6**) in 90% yield. Moreover, the reduction of **3a** with $NaBH_4$ proceeded efficiently to produce alcohol (**7**).

Preliminary investigation of reaction mechanism. To gain an insight into this Rh-catalyzed C(CO)–C bonds insertion reaction, we performed mechanistic investigations. The reactions were not inhibited by adding 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 1,1-diphenylethylene (DPE), which indicated that a radical pathway is unlikely to operate in this reaction system (Fig. 4a). The result of the reaction of unsymmetrical 1,3-dione (**1af**) and **2a** demonstrated that the chemoselectivity was slightly influenced by the electron density of aryl-groups, and the C(CO)–C bond cleavage tended to occur at the electron-poor moiety (Fig. 4b). Then, the reaction of **1a** and **2a** in

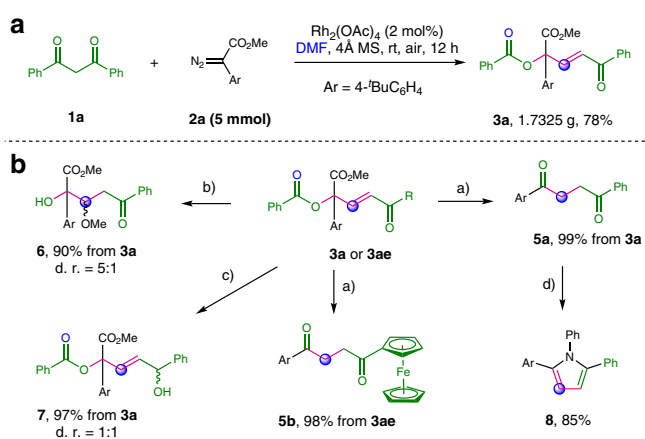


Fig. 3 Gram-scale reaction and functional group transformations. **a** Gram-scale reaction. **b** Functional group transformations. Reaction conditions: **3a** (0.1 mmol), LiOH (2 equiv) in THF/H₂O 4:1 (1 mL) at room temperature. **3a** (0.1 mmol), K_2CO_3 (2 equiv) in MeOH (1 mL) at room temperature. **3a** (0.1 mmol), $NaBH_4$ (1.5 equiv) in MeOH (1 mL) at room temperature. **5a** (0.1 mmol), $PhNH_2$ (1.2 equiv) and TsOH (0.1 equiv) in toluene (1 mL) at 100 °C.

N,N-diethylformamide was carried out, leading to **3a** in 77% yield, whereas no product was formed using *N,N*-dimethylacetamide as solvent. When *N*-methyl-*N*-phenylformamide was used as solvent, **3a** and *N*-methylaniline could be isolated in 21% and 15% yields, respectively (Fig. 4c). Importantly, the reaction with DMF-formyl-¹³C as solvent gave **3a**-¹³C in 86% yield with 99% incorporation (Fig. 4d). The result of the reaction with DMF-dimethyl-¹³C₂ indicated that the one carbon source could hardly originate from the *N*-methyl group of DMF (Fig. 4e). Furthermore, we carried out deuterium-labeling experiments using DMF-*D*₇ (Fig. 4f). The full incorporation of deuterium was observed at β position of the ester product (**3a-D-1**). These results suggest that the formyl group of DMF may serve as the one-carbon source⁵³. Next, when the reaction was conducted in the presence of 5 equiv of D₂O, the incorporation of deuterium at γ position of product (**3a-D-2**) was observed (Fig. 4g). Moreover, 5% of the oxygen atom of ester (**3q-¹⁸O-1**) was labeled using 2 equiv of H₂¹⁸O, and no ¹⁸O-labeled transesterification/Michael addition product (**6**) was detected (Fig. 4h). These reactions indicate that water may be generated during the reaction process, and the benzoyl oxygen atom of **3a** originates from the in situ generated water. Finally, when the ¹⁸O-labeled 1,3-dione (**1q-¹⁸O**) was subjected to the reaction, 22% and 12% of the oxygen atom of **3q-¹⁸O-2** and **6-¹⁸O** were labeled, respectively, which indicate that the oxygen atom at α position of **3q** derives from 1,3-dione (Fig. 4i).

On the basis of the control experiments and literature reports, we proposed a plausible reaction mechanism (Fig. 5). Initially, the reaction of α -aryldiazoacetate (**2**) with Rh(II) catalyst generates Rh(II) carbene complex (**A**), which is captured by enolate (**B**) to give oxonium ylide (**C**). Then, the nucleophilic addition of oxonium ylide (**C**) to DMF affords aldehyde intermediate (**D**), followed by intramolecular aldol reaction of **D**, affording the dihydrofuran intermediate (**E**). Finally, intermediate **E** could be converted into α,α,α -trisubstituted esters (**3** and **4**) via a *retro*-Baylis–Hillman-type reaction.

Discussion

In conclusion, we demonstrate an example of Rh(II)-catalyzed formal insertion of O–C(sp³)–C(sp²) into unstrained C(CO)–C

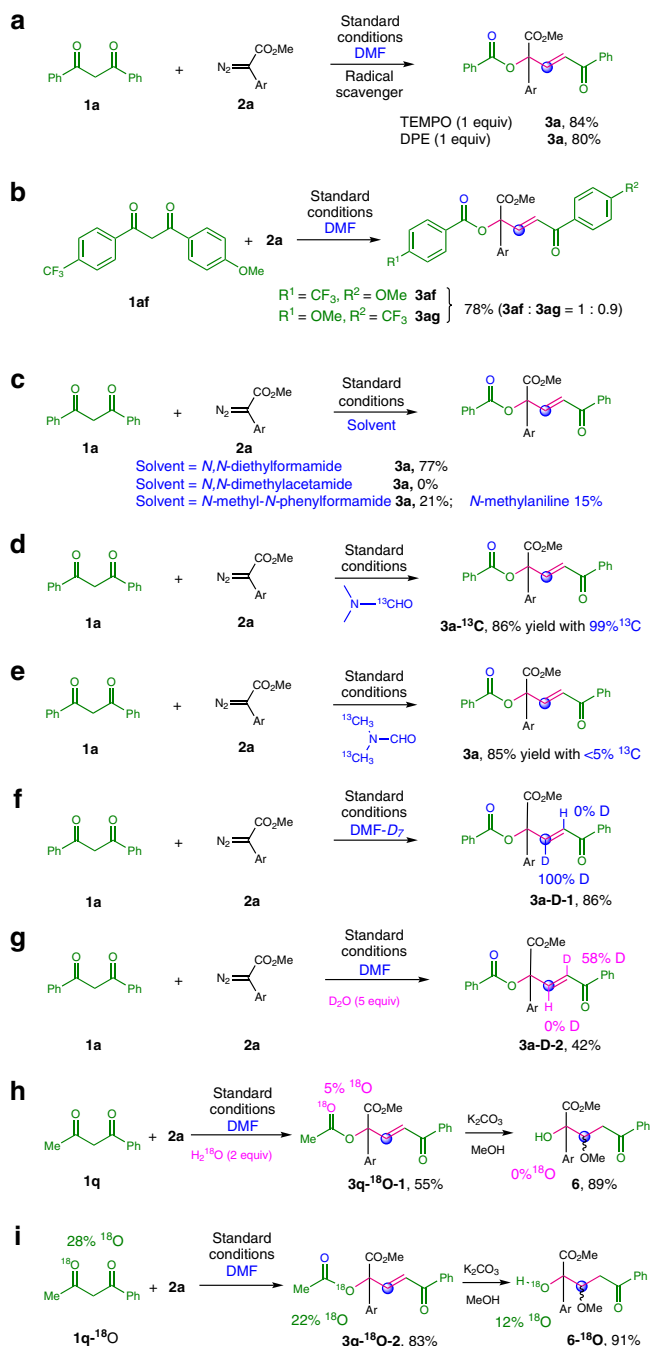


Fig. 4 Control experiments and isotope-labeling reactions. **a** Radical trapping experiments. **b** The reaction of unsymmetrical 1,3-dione. **c** The reactions using other amide solvents. **d** ^{13}C -labeled experiment using DMF-formyl- ^{13}C as solvent. **e** ^{13}C -labeled experiment using DMF-dimethyl- $^{13}\text{C}_2$ as solvent. **f** Deuterium-labeling experiments using DMF- D_7 as solvent. **g** Deuterium-labeling experiments in the presence of D_2O . **h** ^{18}O -labeled experiment in the presence of H_2^{18}O . **i** The reactions of ^{18}O -labeled 1,3-dione.

bonds. A preliminary mechanistic study reveals that O, $\text{C}(\text{sp}^3)$, and $\text{C}(\text{sp}^2)$ units originate from 1,3-diones, diazoesters, and DMF, respectively. This transformation proceeds under mild reaction conditions and opens up a versatile synthetic entry to highly decorated α,α,α -trisubstituted esters/amide from readily accessible starting materials. The development of asymmetric version of this procedure is currently under investigation in our laboratory.

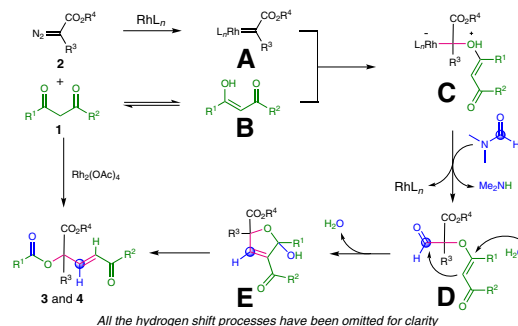


Fig. 5 Plausible reaction mechanism. A plausible mechanism involves the carbene insertion reaction of intermediates **A**, **B** to afford oxonium ylide **C**, subsequent nucleophilic addition, intramolecular aldol reaction, and retro-Baylis–Hillman-type reaction to form the desired products **3** and **4**.

Methods

General procedure for preparation of 3. A screw-capped reaction vial was charged with 1,3-diones (**1**) (0.2 mmol, 2 equiv), methyl 2-(4-(*tert*-butyl)phenyl)-2-diazoacetate (**2a**) (23.2 mg, 0.1 mmol, 1 equiv) 4 Å MS (50 mg), and DMF (0.5 mL), followed by the addition of $\text{Rh}_2(\text{OAc})_4$ (0.8 mg, 0.002 mmol, 2 mol%). The resulting mixture was stirred at room temperature for 12 h, until TLC showed the complete consumption of **2a**. After the reaction was completed, the reaction mixture was evaporated under reduced pressure to leave a crude mixture, which was purified by column chromatography on silica gel (eluting with ethyl acetate/petroleum = 1:10) to afford **3**.

Data availability

All relevant data are available in Supplementary Information and from the authors. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers CCDC: 1975575 (**3a**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Author contributions

D.B. developed the C(CO)–C bond cleavage reaction. S.W., Q.T., Y.C., and W.L. explored the substrate scope. G.C. conceived and supervised the project. G.C. wrote the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to G.C.

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