Rhodium(II)-catalyzed multicomponent assembly of \(\alpha,\alpha,\alpha\)-trisubstituted esters via formal insertion of O–C(sp\(^3\))–C(sp\(^2\)) into C–C bonds

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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(sp\(^3\))–C(sp\(^2\)) into unstrained C(CO)–C bonds. This procedure provides a rapid entry to a gamut of otherwise inaccessible \(\alpha,\alpha,\alpha\)-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(sp\(^3\)), and C(sp\(^2\)) units derive from 1,3-diones, diazoesters, and DMF, respectively.
Ketones are widely present in natural products and synthetic molecules, and are one of the most fundamental feedstocks in organic synthesis. 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. Especially, the direct insertion of functional groups into C(CO)−C single bonds, enabling the formation of otherwise inaccessible compounds, is considerably appealing. For example, the traditional Baeyer−Villiger reaction and Büchner−Curtius−Schlotterbeck reaction 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, Murakami, Cramer, Martin, Chi, and Krische (Fig. 1b). However, successful transformation for the catalytic insertion of functional groups into unstrained C(CO)−C bonds is extremely rare, wherein chelating assistance is required. 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). 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 decylative cross-coupling of 1,3-diones with carbene precursors, we unexpectedly observed the α,α,α-trisubstituted ester products using N,N-dimethylformamide (DMF) as solvent. 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 (sp3), and one carbon (sp2) 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 cleavage.

**Results**

**Reaction development.** We commenced our study by examining the multicomponent reaction of 1,3-diphenylpropane-1,3-dione (1a), methyl α-phenyl diazoacetate (2a), and DMF in the presence of a catalytic amount of [RuCl2(p-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. Rh2(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 Pd(OAc)2 and Cu(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 Rh2(esp)2 was used instead of Rh2(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.

**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, methoxy, 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

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**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 (%) |
|-------|-------------------|----------|-----------|
| 1     | [RuCl2(p-cymene)]2 (5) | —        | 51        |
| 2     | Rh2(OAc)4 (2)       | —        | 65        |
| 3     | AgOAc (10)          | —        | 60        |
| 4     | Pd(OAc)2 (10)       | —        | 60        |
| 5     | Cu(OAc)2 (10)       | —        | 60        |
| 6     | [Rh(cod)Cl]2 (2)    | —        | 24        |
| 7     | [Rh(cod)Cl]2 (2)    | Ag (10)  | Trace     |
| 8     | Rh2(esp)2 (2)       | —        | 62        |
| 9     | —                  | 4 Å MS   | 70        |
| 10    | Rh2(OAc)4 (2)       | 4 Å MS   | 85        |
| 11    | Rh2(OAc)4 (2)       | 4 Å MS   | 61        |
| 12    | Rh2(OAc)4 (2)       | 4 Å MS   | 67        |
| 13    | Rh2(OAc)4 (2)       | 4 Å MS   | 84        |
| 14    | Rh2(OAc)4 (2)       | 4 Å MS   | 80        |
| 15    | Rh2(OAc)4 (2)       | 4 Å MS   | 84        |

*Isolated yields based on 2a.
4 Å MS (25 mg) was used.
4 Å MS (75 mg) was used.
1 mL of DMF was used.
Reaction was carried out under nitrogen atmosphere. esp: 1,1,1,3,3,3-hexamethyldisiloxane.
influenced by the electronic properties of the aryl rings. 1,3-diarylp propane-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 (3i–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 ferroene unit could be incorporated into the product with high efficiency (3ae).

Subsequently, we examined the substrate scope of α-aryl diazoacetates (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 moderate 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 (4i−h). Moreover, α-alkyl 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-aryl diazoacetates. 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,a,a-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 K2CO3/MeOH solution led to the transesterification/Michael addition product (6) in 90% yield. Moreover, the reduction of 3a with NaBH4 proceeded efficiently to produce alcohol (7).

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-13C2 as solvent gave 3a-13C in 86% yield with 99% incorporation (Fig. 4d). The result of the reaction with DMF-dimethyl-12C2 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-D7 (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 source. 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 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 a 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 dihydrafuran intermediate (E). Finally, intermediate E could be converted into α,a,a-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(sp3) into unstrained C(CO)−C bonds.
bonds. A preliminary mechanistic study reveals that O, C(sp³), and C(sp²) 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 a,a,a-trisubstituted esters/amide from readily accessible starting materials. The development of asymmetric version of this procedure is currently under investigation in our laboratory.

**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 Rh2(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 = 1:1) 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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