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Molybdenum-Catalyzed Deoxygenative Cyclopropanation of 1,2-Dicarbonyl or Mono-carbonyl Compounds

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Abstract: The transition-metal catalyzed cyclopropanation of alkenes via the decomposition of diazo compounds is a powerful and straightforward strategy to produce cyclopropanes. However, the potentially explosive nature of the diazo substrates tempers the appeal of further application of this strategy. Herein we report the first Mo-catalyzed regiospecifically deoxygenative cyclopropanation reaction of the readily available and bench stable 1,2-dicarbonyl compounds, in which one of the two carbonyl groups acts as a carbene equivalent upon deoxygenation, thus engaging in the subsequent cyclopropanation process. With a commercially available molybdenum catalyst, an array of valuable cyclopropanes were obtained in up to 90% yield and exclusive regioselectivity. The synthetic utility of this method is further demonstrated by gram-scale syntheses, late-stage functionalization, and application to the cyclopropanation of a simple mono-carbonyl compound. Preliminary mechanistic studies suggest that phosphine (or silane) is both a mild reductant and a good oxygen acceptor that could efficiently regenerate the catalytically active Mo-catalyst through reduction of the Mo-oxo complexes.

As a unique and important structure motif, cyclopropane ring is widely occurred in many biologically active natural products and pharmaceuticals,[1,2] such as mitrephorone A,[2a-b] ingenol,[2c-d] duocarmycin A,[2e-f] saxagliptin,[2g] and beclabuvir[2h] (Figure 1). To this end, numerous efforts have been devoted to the syntheses of functionalized cyclopropanes.[3] Among the various synthetic strategies for the generation of these unique carbocycles, the cyclopropanation of alkenes with transition-metal carbene species is powerful and straightforward (Scheme 1A).[4,5] The metal carbene species, usually generated in situ through the decomposition of α-diazo carbonyl compounds promoted by transition-metal catalysts (Rh, Pd, Cu, Au, *etc*.), are deemed as key intermediates in these processes.[6] Unfortunately, the highly energetic diazo compounds are potentially explosive. In addition, hazardous reagents and multiple synthetic steps are often required for the preparation of the diazo substrates.[4,7] Therefore, developing operationally safe and readily available alternatives to the diazo carbonyl compounds as carbene precursors would benefit the synthetic applications, especially in the industrial scale synthesis.[8,9]

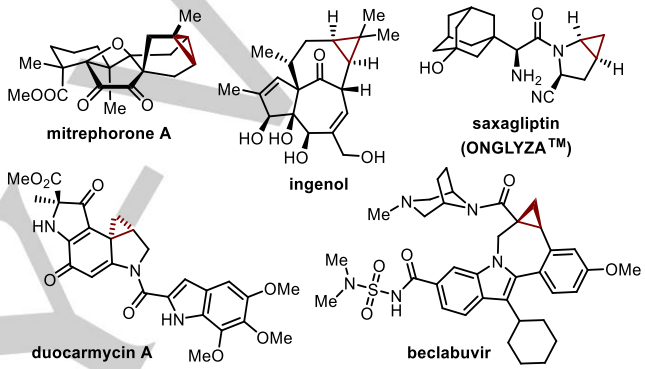

Figure 1. Representative cyclopropane ring-containing natural products and pharmaceuticals.

The 1,2-dicarbonyl compounds are readily available and often serve as valuable building blocks in organic synthesis.[10] Specifically, these bench stable compounds may be used to prepare the α-diazo carbonyl compounds.[7] Accordingly, we questioned whether the 1,2-dicarbonyl compounds could be directly utilized as carbene equivalents through transition-metal-catalyzed regioselective deoxygenation for the syntheses of cyclopropanes, thus avoiding the tedious preparation and use of the hazardous diazo compounds (Scheme 1B). Although conceptually simple in design, several fundamental requirements need to be met to achieve such a transition-metal-catalyzed regioselectively deoxygenative cyclopropanation reaction. Specifically, a powerful transition-metal catalyst that is capable of promoting a regioselective deoxygenation process of a 1,2-dicarbonyl compound and inhibiting side reactions such as dimerization and competitive C−H bond insertion when allylic substrates are applied has to be identified. In addition, a mild reductant and an oxygen acceptor that will not directly reduce the 1,2-dicarbonyl group, but could efficiently regenerate the catalytically active transition-metal catalyst through reduction of the metal-oxo complexes should be realized. Furthermore, the generation of carbene equivalents through transition-metal-catalyzed regioselectively direct deoxygenation of 1,2-dicarbonyl compounds is challenging. In practice, carbonyl compounds rarely served as direct precursors of carbenes except a few examples using either stoichiometric metal reagents and reductants[11] or low-valent transition-metal complexes.[12] In

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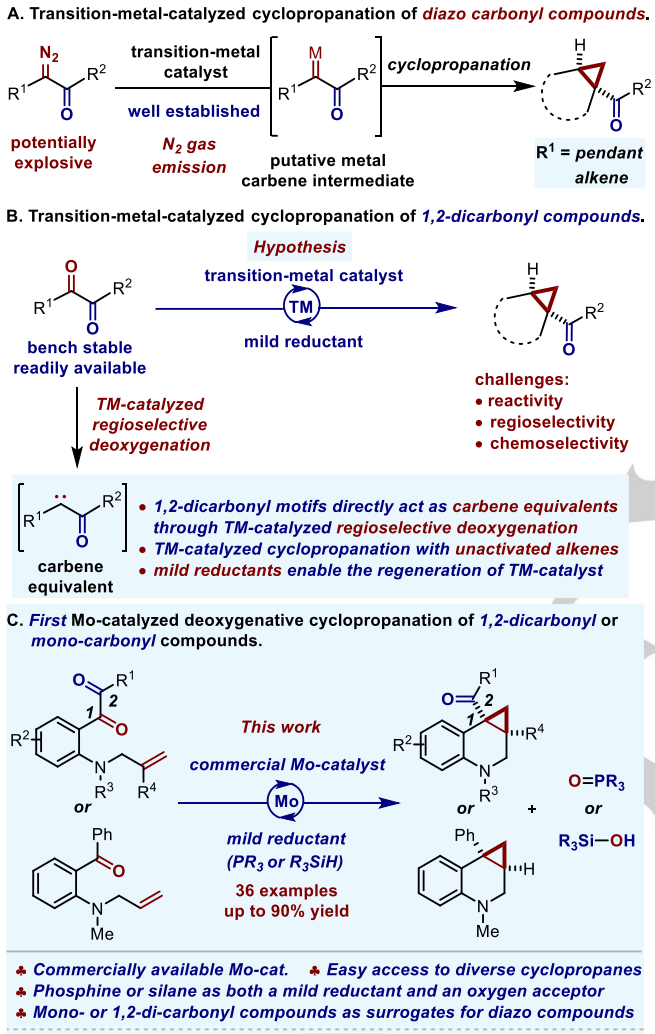
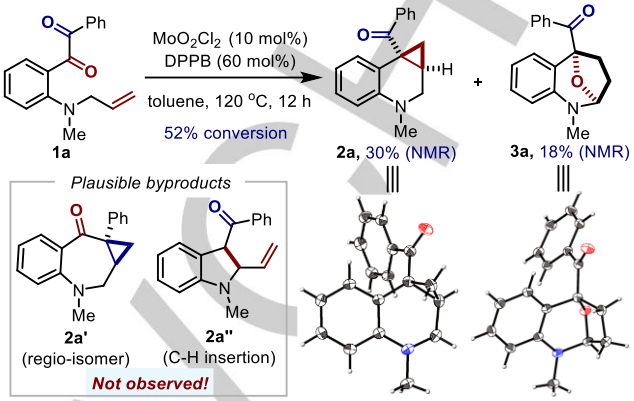
addition, to the best of our knowledge, there is no general method for the generation of carbene equivalents via transition-metal-catalyzed regioselective deoxygenation of 1,2-dicarbonyl compounds, thereby engaging in subsequent cyclopropanation with unactivated alkenes to produce cyclopropanes. Herein, we describe the first Mo-catalyzed deoxygenative cyclopropanation of 1,2-dicarbonyl or mono-carbonyl compounds (Scheme 1C). With the commercially available molybdenum catalyst and diphosphine or silane as a mild reductant as well as an oxygen acceptor, various substituted cyclopropanes were obtained in up to 90% yield and exclusive regioselectivity.



Scheme 1. 1,2-Dicarbonyl or mono-carbonyl compounds directly serve as surrogates for diazo compounds in the Mo-catalyzed deoxygenative cyclopropanation reactions.

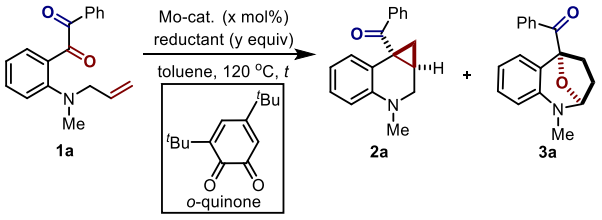
The general feasibility of our hypothesis for the Mo-catalyzed regiospecifically deoxygenative cyclopropanation was evaluated using 1,2-dicarbonyl compound **1a** as a model substrate, 10 mol% of commercially available MoO_2Cl_2 as a catalyst[13] and 60 mol% of 1,4-bis(diphenylphosphino)butane (DPPB) as both a reductant and an oxygen acceptor (Scheme 2). Intriguingly, under these reaction conditions, the deoxygenative cyclopropanation reaction of **1a** occurred in moderate conversion, providing the desired cyclopropane **2a** as a single regio-isomer (**2a**:**2a'** > 99:1) in 30% NMR yield and the 1,3-oxazine derivative **3a** which was formed via a keto-ene/cyclization tandem reaction[14] in 18% NMR yield. The structures of compounds **2a** and **3a** were unambiguously confirmed by X-ray crystallographic analyses.[15] Notably, the probably competitive C-H insertion product **2a''** was not detected at all under these Mo-catalytic conditions.



Scheme 2. Proof of concept.

Encouraged by these results, we carried out further optimization of the reaction conditions (Table 1). Various commercially available molybdenum catalysts were then investigated (entries 2−7). Interestingly, a Mo-catalytic system derived from $Mo(CO)_6$ and 3,5-di-*tert*-butyl-*o*-benzoquinone, which was elegantly developed by Asako, Takai and coworkers for the syntheses of indolines, indoles and pyridoisoindoles,[12j,k] was found to be able to catalyze the deoxygenative cyclopropanation of **1a** efficiently in the presence of 60 mol% of DPPB (entry 7). The *o*-quinone was proposed to oxidize the $Mo(CO)_6$ to the catalytically active molybdenum(II) species.[12f,j] Next, reductants such as phosphine, HBpin, silane and Me_6Si_2 were examined (entries 8−15). Pleasingly, Ph_2MeSiH was discovered to promote the reaction also in good yield (entry 14). To be noted, the cyclopropanation reaction also proceeded well when the reaction temperature was decreased or the catalyst loading was reduced (entries 16−17). In addition, among other transition-metal carbonyl complexes {$W(CO)_6$, $Cr(CO)_6$, $Fe_2(CO)_9$, $Ru_3(CO)_{12}$, and $Mn_2(CO)_{10}$} screened, none of them were capable of promoting the transformation, which demonstrated the unique efficiency of the Mo-catalytic system towards this reaction.[16] Finally, the conditions {10 mol% of $Mo(CO)_6$, 10 mol% of *o*-quinone, and 0.6 equiv of DPPB in toluene at 120 °C} were identified to be optimal in terms of yield, chemoselectivity and efficiency. Under these conditions, the cyclopropane **2a** was obtained in 83% yield (entry 7).

Table 1. Optimization of the reaction conditions.[a]



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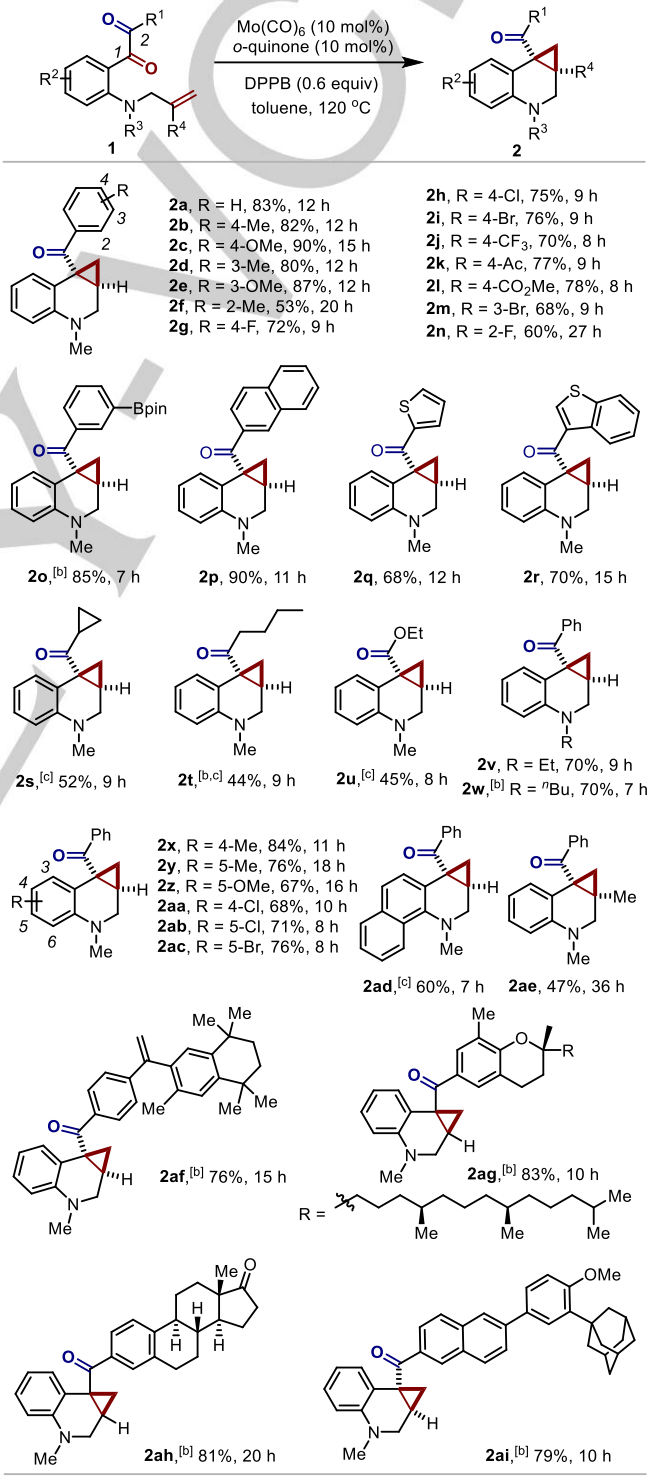
entry	Mo-cat.	x (mol%)	reductant	y (equiv)	*t* (h)	yield[b] (%)	
						2a	**3a**
1	MoO_2Cl_2	10	DPPB	0.6	12	30	18
2	$MoO_2(acac)_2$	10	DPPB	0.6	12	27	trace
3	$[Mo(OAc)_2]_2$	10	DPPB	0.6	12	n.d.[c]	15
4	$MoCl_5$	10	DPPB	0.6	12	n.d.[c]	23
5	MoO_3	10	DPPB	0.6	12	n.d.[c]	21
6	$Mo(CO)_6$	10	DPPB	0.6	12	n.d.[c]	22
7[d]	$Mo(CO)_6$	10	DPPB	0.6	12	90 (83)[e]	10
8[d]	$Mo(CO)_6$	10	DPPE	0.6	12	75	11
9[d]	$Mo(CO)_6$	10	DCPB	0.6	12	24	18
10[d]	$Mo(CO)_6$	10	PPh_3	1.2	12	66	16
11[d]	$Mo(CO)_6$	10	PCy_3	1.2	12	37	18
12[d]	$Mo(CO)_6$	10	HBpin	1.2	12	48	8
13[d]	$Mo(CO)_6$	10	$PhMe_2SiH$	1.2	16	81	7
14[d]	$Mo(CO)_6$	10	Ph_2MeSiH	1.2	16	83 (76)[e]	7
15[d]	$Mo(CO)_6$	10	Me_6Si_2	1.2	12	21	17
16[d,f]	$Mo(CO)_6$	10	DPPB	0.6	12	37	< 5
17[g]	$Mo(CO)_6$	5	DPPB	0.6	30	84	16

[a] Reaction conditions: Mo-cat. (x mol%), reductant (y equiv), and **1a** (0.2 mmol) in toluene (2.0 mL) at 120 ℃. [b] Yield was determined by ^{1}H NMR analysis using CH_2Br_2 as internal standard. [c] Not detected. [d] 10 mol% of 3,5-di-*tert*-butyl-*o*-benzoquinone (*o*-quinone) was added. [e] Isolated yield in the parenthesis. [f] The reaction was performed at 100 ℃. [g] The reaction was performed with 5 mol% of $Mo(CO)_6$ and 5 mol% of *o*-quinone. DPPE: 1,2-bis(diphenylphosphino)ethane; DCPB: 1,4-bis(dicyclohexylphosphino)butane.

With the optimized reaction conditions in hand, various substituted 1,2-dicarbonyl compounds **1** were tested to establish the generality of the process (Table 2). Reactions of 1,2-dicarbonyl substrates containing either electron-donating or electron-withdrawing groups on the aromatic ring (R^1) attached to the 2-carbonyl moiety all gave the corresponding products in moderate to good yields (**2b**−**2n**). Notably, different kinds of aryl halides (F, Cl, Br, **2g**−**2i** & **2m**−**2n**), acetyl moiety (**2k**) and ester group (**2l**) were well tolerated under these mild reductive conditions. Interestingly, substrate **2o**, bearing a Bpin group that could be easily utilized in the following functionalization, also reacted smoothly, affording the desired product **2o** in 85% yield. In addition, the reaction also proceeded smoothly with either heteroaromatic substituted substrates **1q** & **1r** or substrates **1p** & **1s**−**1t** in which 2-naphthyl or alkyl substituents were directly attached to the 2-carbonyl moiety (**2p**−**2t**). The reaction also occurred when the α-keto ester substrate **1u** was applied. In addition, reactions of substrates bearing different alkyl substituents on the nitrogen atom of aniline moiety (R^3) also underwent smoothly, affording the corresponding cyclopropane products in moderate yields (**2v**−**2w**). Moreover, substrates containing either electron-donating or electron-withdrawing groups on the aromatic ring of the aniline moiety (R^2) were probed. The reactions occurred smoothly, affording the corresponding cyclopropane products in moderate to good yields (**2x**−**2ac**). The reaction of 1-naphthylamine containing 1,2-dicarbonyl substrate **1ad** proceeded smoothly as well. Furthermore, the reaction of the 2,2-disubstituted alkene **1ae** also occurred, providing the desired cyclopropane **2ae** with two contiguous quaternary carbon centers. Unfortunately, when the 2-phenyl substituted (R^4 = Ph) or the 1-propyl substituted alkene substrates were used under these reaction conditions, complicated mixtures were obtained.[16]

Table 2. The substrate scope.[a]



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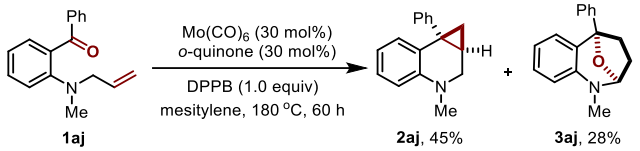
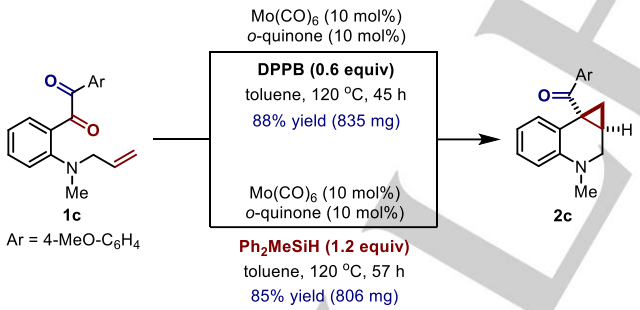
[a] Reaction conditions: 10 mol% of $Mo(CO)_6$, 10 mol% of *o*-quinone, 0.2 mmol of **1**, 0.12 mmol of DPPB in toluene (2.0 mL) at 120 °C. Isolated yields are reported. [b] The reaction was performed on 0.1 mmol scale. [c] 30 mol% of $Mo(CO)_6$ and *o*-quinone were used.

Pleasingly, the present method was able to be applied to the late-stage functionalization of the derivatives of natural products and drug molecules, providing an easy access to several cyclopropane-containing complex molecules (**2af**−**2ai**, Table 2) in good yields. Intriguingly, this molybdenum-based system was also capable of promoting the deoxygenative cyclopropanation of a simple mono-carbonyl compound (**1aj**, Scheme 3).



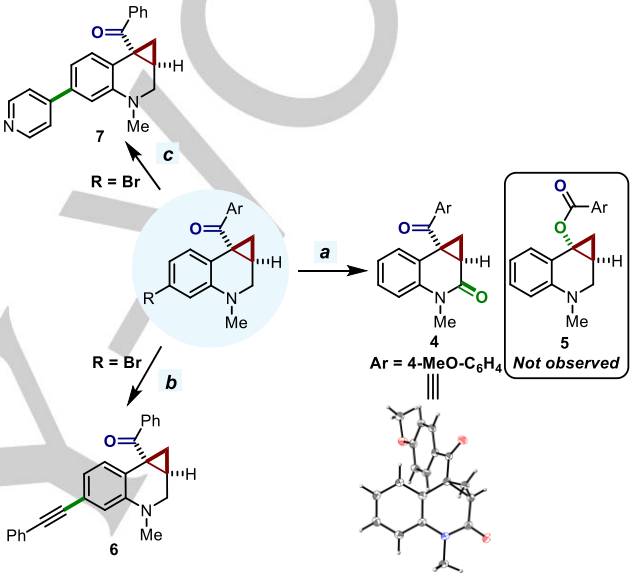
Scheme 3. Deoxygenative cyclopropanation of a simple mono-carbonyl compound.

To further demonstrate the synthetic utility of the present methodology, gram-scale syntheses and several transformations of the heterocycle fused cyclopropanes were carried out. Under the Mo-catalytic conditions, the gram-scale production of cyclopropane **2c** was obtained in excellent yields using either diphosphine or silane as the reductant (Scheme 4). In addition, these cyclopropane products are readily transformed to other valuable building blocks through *m*-CPBA oxidation, Sonogashira cross-coupling, and Suzuki cross-coupling (paths ***a-c***, Scheme 5). Interestingly, the amide **4** instead of the Baeyer-Villiger oxidation product **5** was obtained in 54% yield when the reaction was performed under the Baeyer-Villiger oxidation conditions.[17,18]

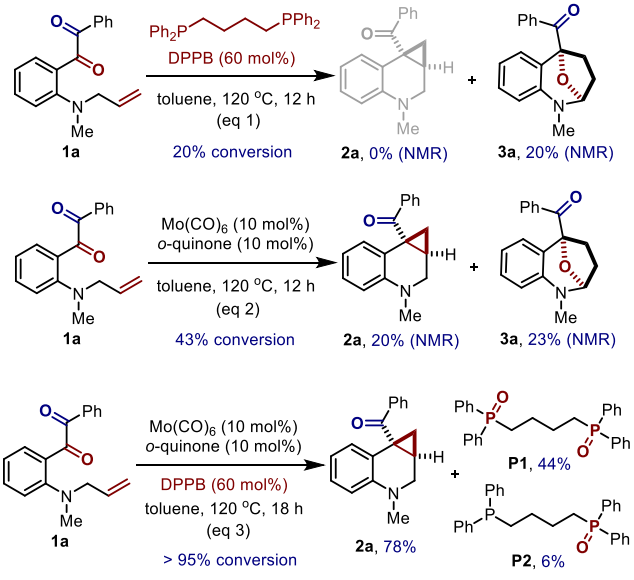


Scheme 4. Gram-scale syntheses of cyclopropane product **2c**.

To shed light on the reaction mechanism, preliminary mechanistic studies were carried out. Initially, the control experiment showed that cyclopropane **2a** was not observed when the cyclopropanation reaction was carried out in the absence of the Mo-catalyst (eq 1, Scheme 6). These results clearly exclude the plausible reaction pathway involving the Kukhtin–Ramirez adducts[19] which are often formed via the addition of a trivalent phosphorus to 1,2-dicarbonyl compounds. Intriguingly, 20% yield of the desired cyclopropane **2a** was obtained when the reaction was carried out without DPPB, which indicates the Mo-catalyst generated in situ from 10 mol% of $Mo(CO)_6$ and *o*-quinone is capable of promoting the cyclopropanation for two catalytic cycles and readily to accept two oxygen atoms from the 1,2-dicarbonyl substrate (eq 2, Scheme 6). In contrast, with 0.6 equiv of DPPB, the Mo-catalyzed cyclopropanation reaction of **1a** occurred in full conversion, affording the desired product **2a** in 78% yield along with 44% yield of diphosphine oxide **P1** and 6% yield of diphosphine monoxide **P2** (yields calculated based on substrate **1a**), which indicated the one of the two carbonyl oxygen atoms in substrate **1a** was almost completely transferred to the diphosphine (eq 3, Scheme 6). These results clearly demonstrate that DPPB is a good oxygen acceptor and plays an important role in the regeneration of the catalytically active molybdenum complex.



Scheme 5. Synthetic transformations. Reaction conditions: a) *m*-CPBA, TsOH, CH_2Cl_2, rt, 54% yield. b) $Pd(PPh_3)_4$ (10 mol%), CuI (20 mol%), phenylacetylene, Et_3N, rt−80 °C, 94% yield. c) $Pd(PPh_3)_4$ (10 mol%), pyridin-4-ylboronic acid, Na_2CO_3, toluene/MeOH/H_2O, 80 °C, 94% yield.



Scheme 6. Control experiments.

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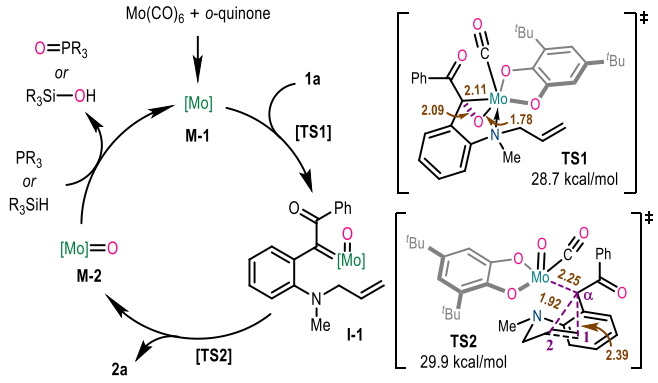
Based on the above experimental observations and computational studies,[20-21] a plausible reaction pathway was proposed, as shown in Scheme 7. Firstly, the formation of oxo-Mo-carbene complex **I-1** is promoted by the Mo-complex **M-1** via a regioselective C=O double bond cleavage transition state **TS1**.[12f, j-k] Then, the oxo-Mo-carbene complex **I-1** undergoes the concerted intramolecular cyclopropanation via **TS2** to afford the product **2a** and the oxo-Mo-complex **M-2**. Finally, the Mo-catalyst **M-1** is regenerated through reduction of the oxo-Mo-complex **M-2** with either phosphine[22] or silane as a reductant.



Scheme 7. A plausible reaction pathway. The transition states are optimized at DLPNO-CCSD(T)/def2-TZVPP//B3LYP-D3(BJ)/def2-SVP level of theory. The bond distances are in Å (See the SI for details).

In summary, we have achieved the first Mo-catalyzed deoxygenative cyclopropanation reaction of 1,2-dicarbonyl or mono-carbonyl compounds, thus providing an easy access to valuable substituted cyclopropanes in up to 90% yield. The reaction is distinguished by its broad substrate scope, commercially available Mo-catalytic system, use of either phosphine or silane as both a mild reductant and an oxygen acceptor, operationally safe and simple procedure, and application to the late-stage functionalization and gram-scale syntheses. Moreover, the 1,2-dicarbonyl compounds could be directly utilized as carbene equivalents through the Mo-catalyzed regiospecific deoxygenation for the first time. This strategy allows the preparation of cyclopropanes via catalytic cyclopropanation of the readily available and bench stable 1,2-dicarbonyl or mono-carbonyl compounds instead of the potentially explosive diazo compounds. Further studies on the reaction mechanism and the development of other diazo-free transformations are ongoing in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: deoxygenative cyclopropanation • molybdenum catalysis • carbene equivalent • 1,2-dicarbonyl compound • regiospecific deoxygenation

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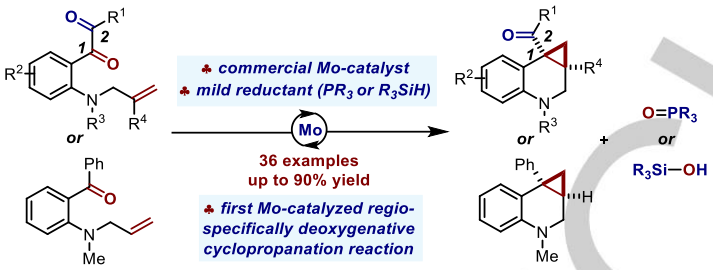

The first Mo-catalyzed regiospecifically deoxygenative cyclopropanation reaction of the readily available and bench stable 1,2-dicarbonyl compounds is described. An array of valuable cyclopropanes were obtained in up to 90% yield and exclusive regioselectivity. This strategy could further be applied to a cyclopropanation reaction of a simple mono-carbonyl compound.