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Metathesis Reaction of Diazo Compounds and *para*-Quinone Methides for C–C Double Bond Formation: Synthesis of Tetrasubstituted Alkenes and Quinolinones

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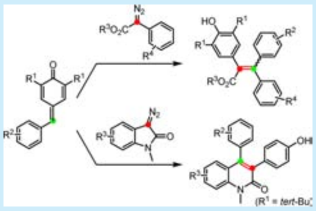
Ⓢ *Supporting Information*

ABSTRACT: The *para*-quinone methides (*p*-QMs) are activated by Lewis acid and then attacked by diazo compounds. The following rearrangement leads to nitrogen gas extrusion and C–C double bond formation to constitute a metathesis reaction process. Therefore, the diazoester is transformed into tetrasubstituted alkenes, whereas the diazo-oxindole delivers the quinolinone products. Furthermore, the ^{13}C-labeling experiments were also conducted to elucidate a possible mechanism.



The reaction with new modes of a C–C double bond formation is highly important and a challenging task in organic synthesis.[1] The classical methods rely on Wittig reaction and Tebbe olefination from phosphorus ylides and Tebbe's reagents.[2] The McMurry reaction represents another method toward double bond formation, with carbonyl compounds as starting materials and Zn/$TiCl_4$ as reductants.[3] On the other hand, the transition metal alkylidene-catalyzed metathesis reaction constitutes a facile and efficient strategy for approaching alkenes, demonstrating powerful utility in both academia and industry.[4] Recently, Lambert invented a remarkable organocatalytic carbonyl olefin metathesis reaction to obtain the C–C double bond.[5] Therefore, development of a metal alkylidene catalyst-free metathesis reaction for the construction of the C–C double bond is interesting and important.

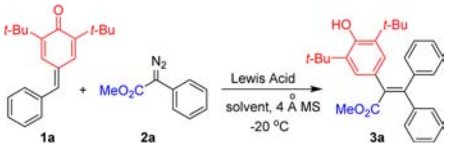
The *para*-quinone methides (*p*-QMs), which are structurally characterized by the assembly of carbonyl and olefinic moieties, exhibit unique chemical reactivity as a precursor of phenols.[6] Recently, *p*-QMs have been widely utilized as a Michael acceptor in various conjugate addition reactions, especially the asymmetric form.[7]

Diazo compounds are important and versatile building blocks in organic synthesis. The well-known transition-metal-catalyzed transformations of diazo compounds to carbenoids and their diversified reactivities have been well-developed.[8] Besides, diazo compounds also serve as mild nucleophilic reagents to carbonyls under acidic reaction conditions.[9−12] Therefore, exploration of diazo compounds with new reactivity, especially with new modes of C–C bond formation, remains attractive and interesting.

In continuation of our efforts in diazo compound transformation and heterocycle synthesis,[13] herein, we report a metathesis reaction of diazo compounds and *p*-QMs toward C–C double bond formation for accessing tetrasubstituted alkenes and quinolinones.

We commenced our study by investigating *p*-QMs **1a** and diazoester **2a** with $TiCl_4$ as the Lewis acid in dichloroethane (DCE). The reaction was initially carried out at −20 °C, and no new products were observed (Table 1, entry 1). When 4 Å powder molecular sieves were added as the additive, surprisingly, gas extrusion was observed while a new product **3a** was formed and isolated with a moderate yield (entry 2). Standard characterization including NMR and MS analysis was not able to identify the structure. To our delight, a crystal of the compound was obtained, and the X-ray analysis confirmed the

Table 1. Optimization of the Reaction Conditions[a]



entry	Lewis acid	amount of **2a**	solvent	yield (%)[b]
1[c]	$TiCl_4$	1.2 equiv	DCE	trace
2	$TiCl_4$	1.2 equiv	DCE	63
3	BF_3–Et_2O	1.2 equiv	DCE	trace
4	$SnCl_4$	1.2 equiv	DCE	trace
5	$Cu(OTf)_2$	1.2 equiv	DCE	trace
6	$TiCl_4$	2 equiv	DCE	77
7	$TiCl_4$	3 equiv	DCE	81
8	$TiCl_4$	4 equiv	DCE	95
9	$TiCl_4$	4 equiv	DCM	78
10	$TiCl_4$	4 equiv	THF	trace
11[d]	$TiCl_4$	4 equiv	DCE	68
12[e]	$TiCl_4$	4 equiv	DCM	42

[a]Reaction conditions: **1a** (0.2 mmol), Lewis acid (20 mol %), solvent (1 mL), 4 Å powder molecular sieves (20 mg), run at −20 °C under argon for 8 h. [b]Isolated yields. [c]Without molecular sieves. [d]Run at −10 °C. [e]Run at −78 °C.

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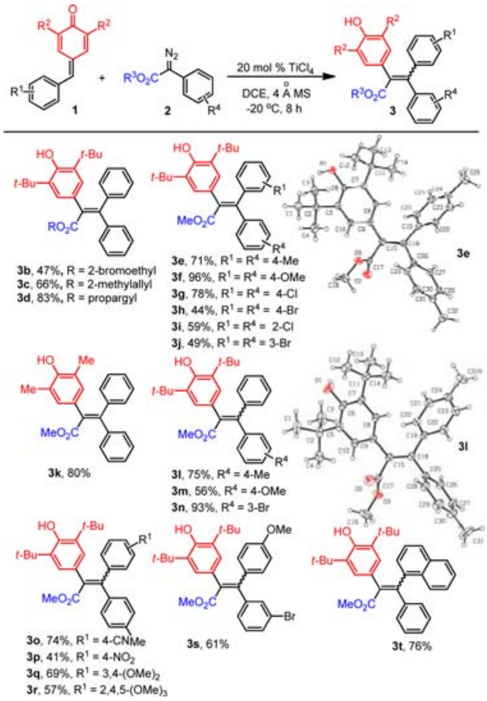
structure to be tetrasubstituted alkene.[14] Moreover, we were interested to find that the two phenyl rings were cleaved from their original *p*-QMs and diazo skeleton, indicating an unprecedented metathesis reaction in this process. Next, a variety of Lewis acids were screened to optimize the reaction conditions. It was found that BF_3-Et_2O, $SnCl_4$, and $Cu(OTf)_2$ were inferior (entries 3−5). The amount of diazoester **2a** was then increased and could improve the yield dramatically (entries 6 and 7). When the amount was increased to 4 equiv, the yield could be ultimately improved to 95% (entry 8). A survey of the solvents showed that DCM was effective but led to a lower yield, while the use of THF resulted in trace product formation (entries 9 and 10). Additionally, either increasing the temperature to −10 °C or decreasing the temperature to −78 °C would diminish the yield (entries 11 and 12).

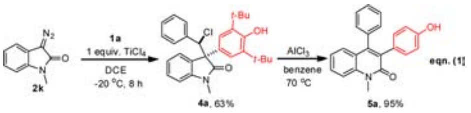
With the optimized reaction conditions in hand, we set out to explore the generality of this process (Scheme 1). Various *tert*-butyl-tethered *p*-QMs and diazoesters with the same aromatic ring substitution were subject to the reaction and proceeded well to furnish the tetrasubstituted alkenes. In these cases, the same aromatic ring substitution excluded the formation of *E*/*Z* isomers. Variation of the ester to 2-bromoethyl, 2-methylallyl, and propargyl would lead to the corresponding functional products, albeit in a slightly lower yield (**3b**−**3d**), and those functional groups would offer the opportunity for further derivation. A variety of substituted *p*-QMs and diazoesters with substitution, such as methyl, methoxy, chloro, or bromo, were also applicable in this metathesis process to produce the tetrasubstituted alkenes (**3e**−**3j**) in moderate to excellent yields. Furthermore, the single-crystal X-ray analysis of **3e** confirmed the structure again.[15] In addition, when the methyl-tethered *p*-QM **1h** was subject to the reaction, the process could proceed smoothly to furnish product **3k** in good yield. Mechanistically, when the aromatic ring substitutions of *p*-QMs and diazoester were differential, this process was expected to furnish a mixture of *E*/*Z* isomers. Indeed, a variety of *p*-QMs and diazoesters with differential aromatic rings were subject to the reaction, and this metathesis process furnished inseparable *E*/*Z* isomers of alkenes. For example, the reaction of *p*-QM **1a** (with a phenyl ring) and diazoester **2e** (with a 4-tolyl ring) afforded alkene **3l** as a mixture, and the single-crystal X-ray analysis disclosed the structure of *E*/*Z* isomers.[16] Therefore, the combinations of *p*-QMs and diazoesters enable the formation of diverse tetrasubstituted alkene formation (**3m**−**3t**). The functional groups, such as cyano, nitro, and naphthanyl, were compatible in this process.

Scheme 1. Scope of the Metathesis Reaction toward Tetrasubstituted Alkenes[a]



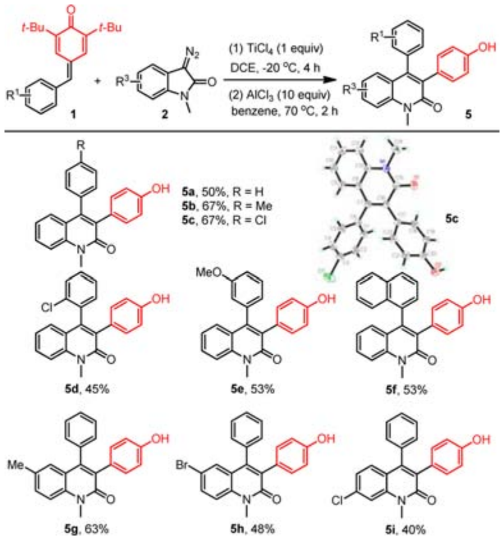
[a]Reaction conditions: **1** (0.2 mmol), **2** (0.8 mmol), $TiCl_4$ (0.2 mmol), DCE (2 mL), run at −20 °C under argon for 8 h; yields refer to isolated products.

Interestingly, variation of diazoester to diazo-oxindole **2k** to react with **1a** under standard reaction conditions delivered trace alkene product. The next optimization found that when the amount of $TiCl_4$ was increased to 1 equiv and the molecular sieves were removed, an unprecedented reaction would occur between *p*-QMs and diazo-oxindole for accessing product **4a** in 63% yield (eq 1). The structure was confirmed by X-ray analysis, and a chloro atom was found to be incorporated on the benzyl group, which should originate from $TiCl_4$.[17] The next attempt of $AlCl_3$-promoted de-*tert*-butylation led to a rearrangement to funrnish quinolinone product **5a**.



Next, we were pleased to find that the two steps could be merged as a one-pot metathesis reaction toward C−C double bond formation for quinolinone synthesis (Scheme 2). Various substituted *p*-QMs were subjected to this process to furnish the quinolinones in moderate yields. Notably, the functional groups were well-tolerated in this protocol, such as chloro and bromo,

Scheme 2. Scope of the Metathesis Reaction toward Quinolinones[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.8 mmol), $TiCl_4$ (0.2 mmol), DCE (2 mL), run at −20 °C under argon for 4 h, then run at 70 °C in benzene for 2 h; yields refer to isolated products.

thus offering an opportunity for further application. The structure of compound **5c** was confirmed by X-ray analysis.[18] Moreover, the substituted diazo-oxindoles were also found to be applicable in this process to furnish the desired phenol-containing quinolinone products. Due to the wealth of quinolinones in pharmaceuticals, this method represents a distinct approach to these compounds.[19,20]

To unravel the synthetic utility, we conducted a gram-scale reaction. For example, a gram-scale reaction was conducted for **1a** and **2a** according to the procedure, and 1.58 g of **3a** could be furnished in 89.4% yield and could be applied to synthesis of the desired molecules (see Supporting Information). Meanwhile, 0.7 g of **5c** could be formed in 65% yield (see Supporting Information).

To gain insight into the reaction mechanism, the ^{13}C-labeling reactions were conducted (Figure 1). The ^{13}C-**1a** was synthesized and subjected to reaction with **2a** and **2k** to generate ^{13}C-**3a** and ^{13}C-**5a**. For ^{13}C-**3a**, the CNMR analysis shows that the labeling carbon was cleaved with quinone and tethered with two phenyl rings. With respect to ^{13}C-**4a**, the labeling carbon is found to be the methylene carbon tethering a chloro atom and placed at the 4-position of the quinolinone moiety of ^{13}C-**5a**.

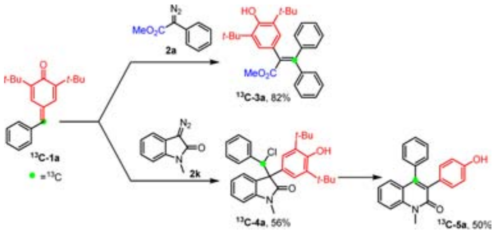


Figure 1. ^{13}C-labeling reaction.

Based on these experiments, a plausible reaction mechanism is depicted in Figure 2. Initially, the *p*-QM **1** was activated by $TiCl_4$ to form cationic intermediate **A**, which was trapped by diazo compound **2** to give cyclopropanation intermediate **B** with nitrogen extrusion. The quinone moiety is further activated by $TiCl_4$ for cyclopropane fragmentation to deliver cationic species **C**. At this stage, a divergent transformation occurs. For those diazoesters derived from **C**, the aromatic ring originates from diazoesters undergoing migration to form **D**, and the following hydrogen elimination transformed **D** to tetrasubstituted alkene skeleton **E**. Finally, protonation of **E** furnishes the product (**3** or **4**) and regenerates $TiCl_4$. Thus, this catalytic cycle constitutes a metathesis process. With respect to the intermediate **C** that originated from diazo-oxindoles, a direct chloride addition to the benzyl cation gives **F** and the following protonation furnishes **4**. When **4** is treated with $AlCl_3$, the de-*tert*-butylation and dechlorination occur simultaneously to form cationic **G**, which undergoes a sequential ring expansion to form quinolinones **5** with C−C double bond formation. Thus, the whole process constitutes a metathesis reaction formation.

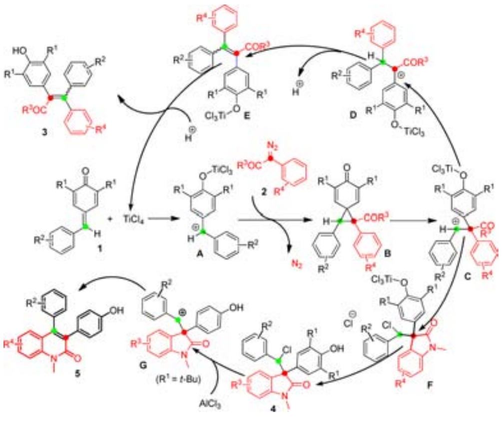


Figure 2. Proposed mechanism.

In conclusion, a metathesis reaction of *p*-QMs and diazo compounds was developed toward C−C double bond formation. The protocol could deliver tetrasubstituted alkenes and quinolinones, while the process could also be scaled up. Furthermore, ^{13}C-labeling reactions were conducted to elucidate a possible reaction mechanism.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02365.

Full experimental procedures, characterization data, and NMR data (PDF)
Crystallographic data for **3a** (CIF)
Crystallographic data for **3e** (CIF)
Crystallographic data for **3l** (CIF)
Crystallographic data for **4a** (CIF)
Crystallographic data for **5c** (CIF)

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Notes

The authors declare no competing financial interest.

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(14) **3a**: CCDC 1449198.

(15) **3e**: CCDC 1470628.

(16) **3l**: CCDC 1470629.

(17) **4a**: CCDC 1454863.

(18) **5c**: CCDC 1491659.

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