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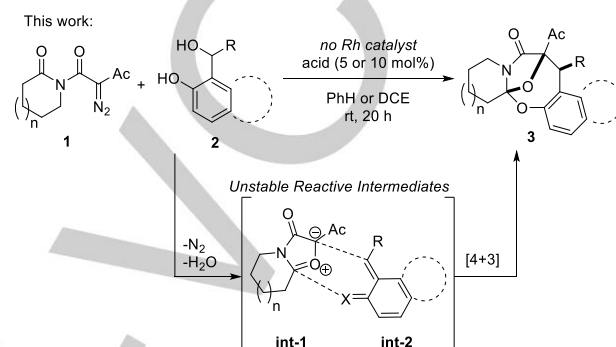
Transition Metal-Free [4+3]-Cycloaddition of *ortho*-Quinone Methides and Isomünchnones: Catalytic and Diastereoselective Assembly of Oxa-bridged Oxazocine Scaffolds

Heather Lam, Zafar Qureshi, Marcus Wegmann, and Mark Lautens*

Abstract: Cycloadditions are powerful processes to synthesize complex polycyclic scaffolds. Herein, we disclose a [4+3]-cycloaddition between an in situ generated *ortho*-quinone methide and an isomünchnone to yield oxa-bridged oxazocine cores, generating N₂ and H₂O as the sole by-product. Using only catalytic amounts of camphorsulfonic acid, it is possible to generate both reactive intermediates in one step, eliminating the need for rhodium catalysts generally employed for isomünchnone formation. Spectroscopic data and X-ray crystallography indicate the formation of the *syn* diastereomer, with the main side-product arising from a hydrate participating in a competing [4+2]-cycloaddition pathway.

Highly-functionalized polycyclic oxazocines are known to have a range of biologically relevant functions.^[1] However, bridged oxazocines have not been well documented in the literature.^[2] Herein, we report a facile method towards novel oxa-bridged oxazocine scaffolds through the acid-catalyzed in situ formation of *ortho*-quinone methides (*o*-QM) and isomünchnones. Although [4+2]-cycloadditions of *o*-QMs and [3+2]-cycloadditions of isomünchnones are well documented in the synthesis of common heterocycles, [4+3]-cycloadditions of *o*-QM and isomünchnones have yet to be explored.^[3] We envisioned that with mild conditions, either a rhodium- or acid catalyzed formation of isomünchnone **int-1** from diazoimide **1** could occur alongside the acid-catalyzed formation of the *o*-QM **int-2** generating only N₂ and H₂O as by-products. The reactive intermediates **int-1** and **int-2** would subsequently react in a [4+3]-cycloaddition to form a complex polycyclic scaffold (Scheme 1).

We commenced our studies by investigating the reactivity with a stable *o*-QM. Though the isomünchnones formed from **1a** are not isolable, some electron-rich *o*-QMs such as **2a** can be isolated as an orange solid at room temperature. As a proof of concept for the [4+3]-cycloaddition, we applied the standard Rh₂(OAc)₄ catalyzed diazo decomposition conditions to a mixture of **1a** with a stable *o*-QM **2a** (Table 1). Under these conditions, the reaction proceeded to give the desired cycloadduct product **3a** in 28% isolated yield (entry 1). Using 5 mol% (+)-camphorsulfonic acid (CSA) allowed us to obtain a similar result with a slightly elevated yield of **3a** (entry 2). In the absence of catalyst, **1a** could be recovered near quantitatively, whilst **2a** had mostly decomposed (entry 3). The relative



Scheme 1. General [4+3]-cycloaddition reaction between in situ generated isomünchnone with an *ortho*-quinone methide.

Table 1: [4+3]-cycloaddition between **1a** with a stable *o*-QM **2a**.^[a]

Entry	Catalyst	x mol%	3a [%] ^[b]	1a [%] ^[b]	2a [%] ^[b]
1	Rh ₂ (OAc) ₄	1	28	5	-
2	(+)-CSA	5	37	-	-
3	none	-	-	99	24 ^[c]

[a] Reaction conditions: **1a** (0.2 mmol, 1.0 equiv), **2a** (0.2 mmol, 1.0 equiv), Rh₂(OAc)₄ (x mol%) or (+)-CSA (x mol%), PhH (5 mL), 20 h. [b] ¹H NMR yields shown using 1,3,5-trimethoxybenzene as an internal standard. [c] **2a** in solution forms dimers over time.

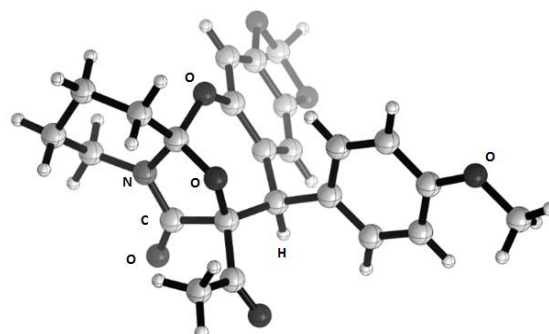
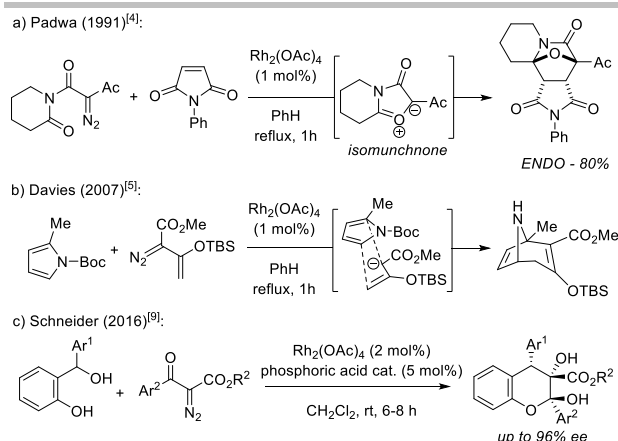


Figure 1. X-ray crystal structure of **3a**.

stereochemistry of **3a** was determined by X-ray crystallography, which indicated the *syn* diastereomer had formed, wherein the bridging oxygen atom is on the same face as the aryl group (Figure 1).^[4]

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Scheme 2. Literature precedent for the [4+3]-cycloaddition

It is known that the transition-metal catalyzed decomposition of diazo compounds generates a metal carbenoid, which can undergo diverse chemical reactions.^[5] Specifically, reactions between metal carbenes and 2π -systems have been thoroughly studied, often serving as a facile method to access bridged polycyclic scaffolds through [3+2]-cycloadditions.^[6] In the past two decades, Padwa and co-workers have extensively explored the utility of *in situ* generated isomünchnones made by diazoimide decomposition through the formation of a rhodium-carbene species (Scheme 2a).^[7] The neighboring carbonyl oxygen cyclizes onto the rhodium-carbene to form a five- or six-membered isomünchnone. The resulting isomünchnone often undergoes [3+2]-cycloadditions with dipolarophiles, in either an inter- or intramolecular fashion, to form complex polycyclic structures.

There are also reactions between metal-carbenes generated from vinyldiazoacetates and 4π -systems, exemplified by the work of Davies and co-workers. They have applied [4+3]-cycloadditions to the synthesis of tropanes, and the total synthesis of (-)-5-epi-vibsanin E, (+)-barekoxide and (-)-barekol (Scheme 2b).^[8]

Though alkenes are the most commonly encountered dipolarophiles for isomünchnones, 4π -systems have yet to be explored including *o*-QMs. *o*-QMs are useful building blocks in organic synthesis, and can be made through various methods.^[9] Since the diazo-decomposition reactions are generally performed at room or below-room temperature, we were interested in using mild conditions for the *in situ* generation of *o*-QMs. Schneider and Rueping demonstrated that chalcones could be synthesized from a [4+2]-cycloaddition between an *o*-QM and a 1,3-diketone.^[10] Additionally, Schneider established that it is possible to react *in situ*-generated *o*-QM with oxonium ylides to synthesize highly functionalized chromans.^[11] This sequence involved the phosphoric acid-catalyzed generation of the *o*-QM and the Rh-catalyzed decomposition of a diazoketone (Scheme 2c).

With the large body of work pertaining to transition metal-catalyzed decompositions of diazoalkanes, acid-catalyzed methods offer an inexpensive alternative.^[12] Johnston and co-workers demonstrated that the decomposition of diazoalkanes can be achieved using Brønsted acids to yield similar products as their metal-catalyzed counterparts.^[13] The full potential of this approach has yet to be delineated. We now report that Brønsted acid-catalysis can serve as an alternate route to accessing the desired isomünchnones formed from diazoimides, without the need for rhodium catalysts.

Table 2: Optimization of acid-catalyzed [4+3] cycloaddition between *in situ* generated isomünchnones with *ortho*-quinone methides.^[a]

A1: R = H
A2: R = 3,5- CF_3 -phenyl
A3: R = 4- NO_2 -phenyl
A4: R = Me_3 -phenyl

Entry	Cat.	x mol%	1a:2b	solvent	3b[%] ^[b]	3b'[%] ^[b]
1	(+)-CSA	5	1:1	PhH	60(58)	24
2	A1	5	1:1	PhH	20(18)	n.d.
3	A2	5	1:1	PhH	35(31) ^[f]	n.d.
4	A3	5	1:1	PhH	40(38) ^[g]	n.d.
5	A4	5	1:1	PhH	15(12) ^[h]	n.d.
6	<i>p</i> -TsOH	5	1:1	PhH	45(41)	n.d.
7	MsOH	5	1:1	PhH	56(50)	n.d.
8 ^[c]	none	-	1:1	PhH	n.r.	n.r.
9	(+)-CSA	5	2:1	PhH	69(64)	19
10 ^[d]	(+)-CSA	5	2:1	PhH	<5	0
11 ^[d]	(+)-CSA	20	2:1	PhH	50	17
12	(+)-CSA	20	2:1	PhH	67(60)	21
13 ^[e]	(+)-CSA	20	2:1	1,2-DCE	74(78)	21

[a] **1a**, **2b**, catalyst (x mol%) were added to a 2 dram vial equipped with a stir bar and dissolved in solvent, which was dried over 4Å MS (5 ml). The mixture was stirred for 10 h. 1,3,5-trimethoxybenzene was added as an internal standard for ^1H NMR yield. [b] ^1H NMR yields shown using 1,3,5-trimethoxybenzene as an internal standard. Isolated yields in brackets. Racemic mixtures were obtained unless otherwise stated. [c] Starting materials isolated. [d] Powdered 4Å MS (5 mg) added. [e] Same result achieved with (±)-CSA or (-)-CSA. [f] 4% ee. [g] 14% ee. [h] 15% ee. n.r., no reaction; n.d., not determined.

We tested conditions for the combination of **1a** and **2b**, a naphthyl-based *o*-QM precursor (Table 2). Aside from the desired product **3b**, we also observed the formation of an unprecedented cycloadduct **3b'**, a hydrate of the isomünchnone formed from a competing formal [4+2]-cycloaddition, in the presence of the H_2O generated from the *o*-QM decomposition.^[14] Though enantiomerically pure (+)-CSA was used, only racemic products were obtained. Attempts to transfer chirality from chiral phosphoric acids, **A1-4**, significantly lowered the yield of the desired product, but revealed that up to 15% enantiomeric excess could be achieved

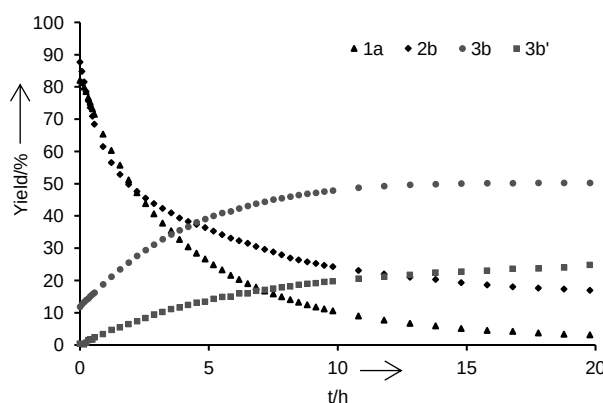
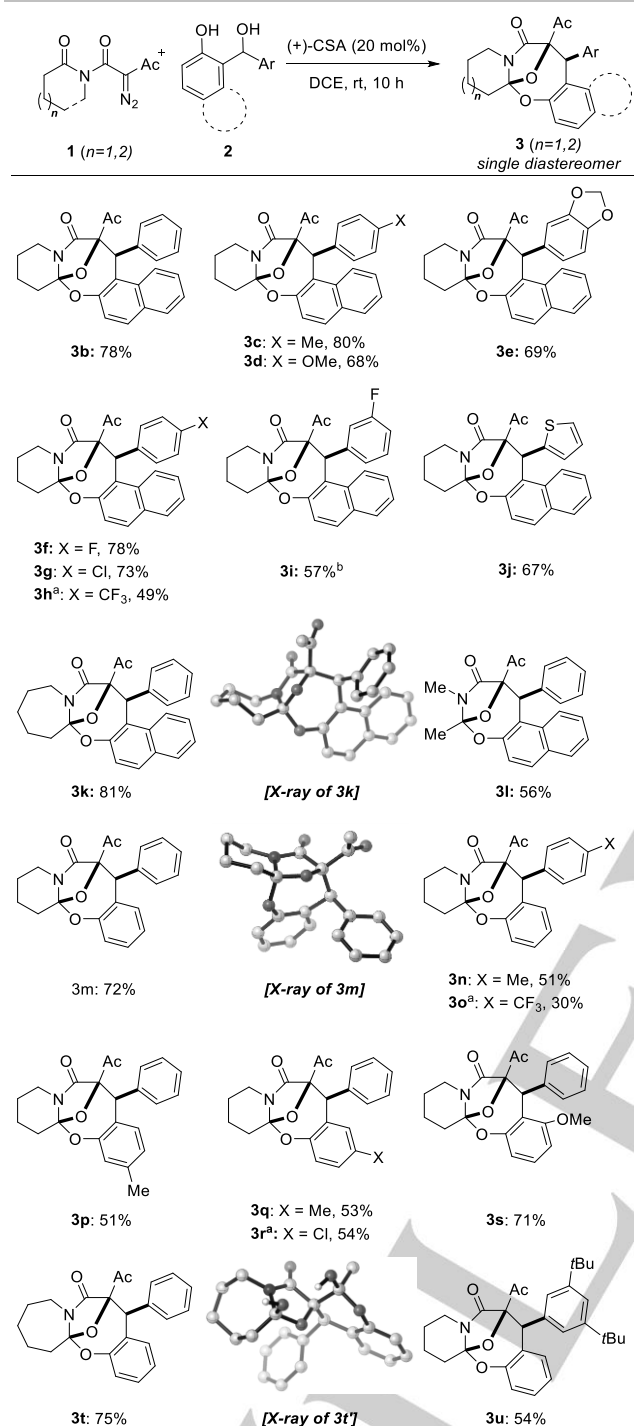


Figure 2. ^1H NMR monitoring of the reaction. Reaction conditions: **1a** (1.0 equiv), **2b** (1.0 equiv), (+)-CSA (5 mol%) and 1,3,5-trimethoxybenzene (3 mg) was added to a 2 dram vial equipped with a stir bar, dissolved in CD_2Cl_2 (0.05 M) and stirred 1 min. 1 mL of the mixture was used for study.

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Scheme 2. Substrate scope of the acid-catalyzed cycloaddition of diazomide **1** and naphthol *o*-QM precursors **2**. Reaction conditions: 0.4 mmol (2.0 equiv) diazomide **1**, 0.2 mmol (1.0 equiv) *ortho*-hydroxybenzhydrol **2**, and (+)-CSA (5 mol%), DCE (4 mL), RT, 10h. Isolated yields shown. Yield of byproduct shown in brackets. [a] Heated to 40 °C. [b] Run at 0.2 M.

using catalyst **A4** (entries 2-5). Other sulfonic acids, such as *p*-TsOH and MsOH, did not improve the yield of the reaction (entries 6-7). To further our understanding of the decomposition pathway, a ¹H NMR study under standard reaction conditions was undertaken (Table 2, entry 1, Figure 2). Our observations revealed that during the reaction, **1a** was converted to the isomünchnone faster than **2b** converted to the *o*-QM. Both products formed at the outset, with **3b**

forming faster than **3b'**. Taking into account the relative rates of decomposition of the starting materials, we concluded that increasing the ratio of **1a** to **2b** would improve the overall yield of the reaction. Consequently, the use of two equivalents of **1a** resulted in an increase in yield of **3b** (entry 9). Our attempts to suppress the formation of **3b'** through the addition of 4 Å MS lowered the yield of **3b** even when higher loadings of catalyst were used (entry 8-12). The use of drying agents such as MgSO₄ or Na₂SO₄ did not affect the yield of either product. After a screen of various solvents, we found that using 1,2-DCE further improved the yield of **3b** to 78% (entry 13).

The substrate scope of the reaction was investigated with various diazomides **1** and *o*-QM precursors **2** leading to products in generally good yields as single diastereomers (Scheme 2). Electron-donating groups were well tolerated on the aryl ring furnishing products **3c**–**3e** in good yields. Electron-withdrawing halogen groups or a CF₃-group at the *para*- position were tolerated and gave **3f**–**3h**. When the halogen was located at the *meta*- position, there was a significant decrease in yield (**3i**). *ortho*-Substituents inhibited the reaction. The aryl group could be replaced by a heteroaromatic ring such as thiophene to give **3j**. However, when the aryl group was replaced by a pyridyl ring, the reaction failed. A seven-membered lactam-based diazomide could be incorporated to afford **3k** in excellent yields, the structure of which was confirmed by X-ray crystallography. Using an acyclic diazomide, it was possible to obtain the desired cycloadduct **3l**.

We also explored the phenol-based *o*-QM precursors. The yields were generally lower than the naphthol analogues. This outcome may be due to faster decomposition of the *o*-QM precursor or the *o*-QM, in comparison to the diazomide. The parent unsubstituted *o*-QM precursor reacted to afford a good yield of the desired cycloadduct **3m**. Electron-donating and withdrawing groups were tolerated at the *para* position of the aryl ring and the quinone ring (**3n**–**r**, **u**) with decreased yields. Interestingly, placing an *ortho*-methoxy group on the quinone ring gave good yields of the cycloadduct **3s**. Using the seven-membered diazomide, we could obtain **3t** and was able to confirm the structure of the side-product **3t'** through X-ray crystallography (Figure 6).

Based on the stereochemistry of the isolated diastereomer, possible transition states are shown in Figure 3. We cannot say if the reaction is stepwise or concerted. If the reaction is concerted, the product could arise from a compact transition state between the *E*-*o*-QM and the isomünchnone or through an extended transition state between the *Z*-*o*-QM and the isomünchnone.

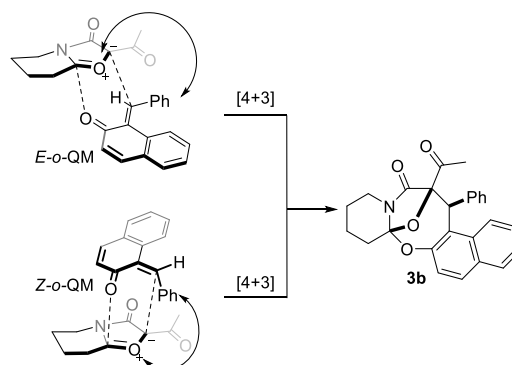


Figure 3. Possible transition states between the reactive intermediates of [4+3]-cycloaddition for the formation of *syn* product **3b**.

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In summary, we have developed a reaction between two non-isolable reactive intermediates, *o*-QMs and isomünchnones, using a simple and economical acid catalyst under mild conditions to generate new oxa-bridged oxazocine scaffolds. The results of the ¹H NMR study highlight the importance of the relative rates of decomposition of the starting materials. Both naphthol and phenol based *o*-QMs could participate in the reaction. The products are obtained as a single diastereomer and arise from a formal [4+3]-cycloaddition with good yields. Efforts to understand the reaction mechanism using DFT calculations and studies toward the enantioselective version of the reaction are underway.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: acid catalysis • cycloaddition • diastereoselective • diazo compounds • *ortho*-quinone methide • ylides

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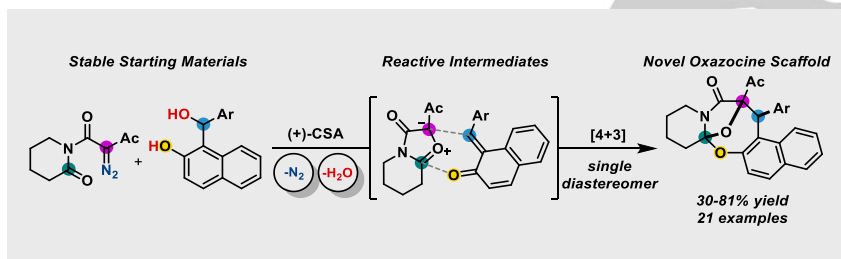
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