Organocatalysis

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Organocatalytic Intramolecular [4+2] Cycloaddition between In Situ Generated Vinylidene *ortho*-Quinone Methides and Benzofurans

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Abstract: *Described herein is the enantioselective construction of oxygen-containing [5-6-5] tricyclic heterocycles by an organocatalyzed asymmetric [4+2] cycloaddition of vinylidene ortho-quinone methides and benzofurans. According to this methodology, a series of oxygen-containing [5-6-5] tricyclic heterocycles with various functional groups were synthesized in excellent enantio- and diastereoselectivities (>99% ee, >20:1 d.r.). Furthermore, the deuterium-labeling experiments and high-resolution mass spectroscopy demonstrated that a vinylidene ortho-quinone methide intermediate was involved and possibly resulted from a prototropic rearrangement of 2-ethynylphenol. Remarkably, a catalyst loading as low as 0.1 mol%, and a gram-scale synthesis were achieved for this transformation.*

Tricyclic and polycyclic heterocycles are common motifs in natural and synthetic products with pharmaceutical and agrochemical utility.[1] In particular, the oxygen-containing fused structure with either the characteristic [6-6-5] or [6-5-5] tricyclic system is found as part of the core of various naturally occurring molecules with a variety of biological activities (Figure 1).[2] For example, phomactin A[3] is a specific platelet activating factor (PAF) antagonist, which inhibits the PAF-induced platelet aggregation. Therefore, efficient synthetic methods to these core structures have been extensively explored. The widely applied approaches for constructing tricyclic heterocyclic skeletons involve either building each ring independently or constructing two rings in a single step. An ideal way to build a tricyclic skeleton would be to build the three rings in one step from readily available starting materials, thus making it step and atom economical.

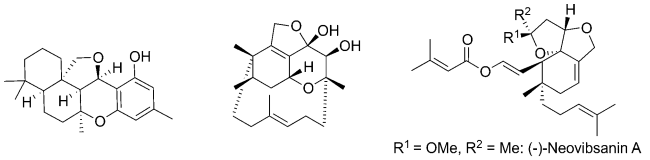
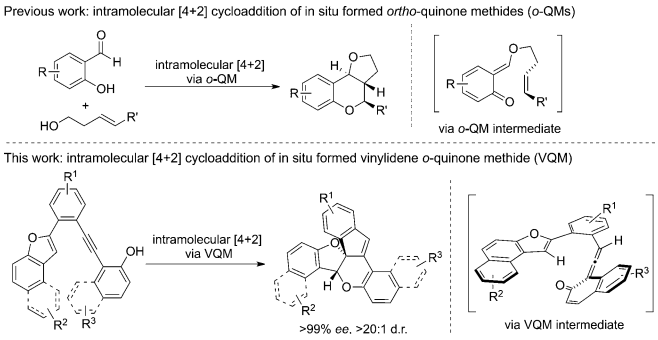


Figure 1. Natural products containing tricyclic structures.

In the past decades, organocatalytic [4+2] cycloadditions[4] were one of the most widely used synthetic methods for the synthesis of simple and complex ring systems. Among the reported examples, asymmetric [4+2] cycloaddition between *ortho*-quinone methides (*o*-QMs)[5] and olefins represents one of the most direct and expedient approaches for constructing oxygen-containing heterocycles. Great achievements in the field of intermolecular [4+2] cycloadditions were made by the groups of Sun,[6] Rueping,[7] Shi[8] et al.[9] Recently, List and co-workers[10] reported the first imidodiphosphoric acid-catalyzed[11] intramolecular [4+2] cycloaddition of in situ generated *o*-QMs (Scheme 1). Compared with



Scheme 1. Asymmetric intramolecular [4+2] cycloaddition of vinylidene *ortho*-quinone methide (VQM).

the wide application of *o*-QMs in asymmetric synthesis, vinylidene *ortho*-quinone methide (VQM),[12] a variant of *o*-QMs, has been seldom explored. The highly active VQM intermediate can be generated through a prototropic rearrangement (tautomerization) of 2-(phenylethynyl)phenol under basic conditions.[13] Therefore, it is assumed that if an electron-rich dienophile exits in the same molecule, an intramolecular, formal, inverse electron-demand hetero-Diels–Alder cycloaddition may occur (Scheme 1). Herein, we report the first asymmetric intramolecular [4+2] cycloaddition of VQM, derived from 2-ethynylphenol derivatives, with benzofuran.[14] It provides facile access to valuable chiral [5-6-5] tricyclic derivatives with contiguous quarternary and tertiary stereogenic centers.

To prove our hypothesis, we selected **1a** as the model substrate to evaluate the catalysts and search for the optimal reaction conditions (Table 1). Encouraged by the success of cinchona alkaloids and cinchona-alkaloid-derived urea catalysts in asymmetric catalysis,[15] we first screened a class of cinchona alkaloids and cinchona-alkaloid-derived thioureas and squaramide organocatalysts. To our delight, when the

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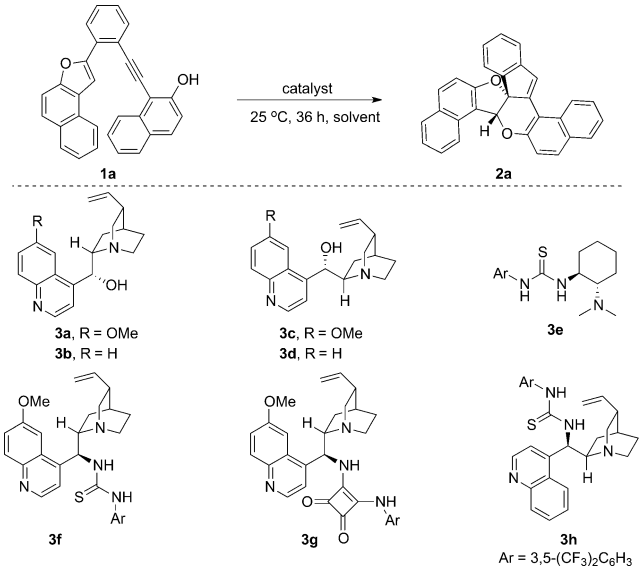
Table 1: Optimization of reaction conditions.[a]



Entry	Catalyst	Solvent	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	3a	$CHCl_3$	72	>20:1	77 (−)
2	3b	$CHCl_3$	85	>20:1	73 (−)
3	3c	$CHCl_3$	75	>20:1	73 (+)
4	3d	$CHCl_3$	93	>20:1	72 (+)
5	3e	$CHCl_3$	85	>20:1	96 (+)
6	3f	$CHCl_3$	98	>20:1	>99 (+)
7	3g	$CHCl_3$	96	>20:1	89 (+)
8	3h	$CHCl_3$	70	>20:1	97 (−)
9	3f	THF	15	>20:1	6 (+)
10	3f	toluene	53	>20:1	93 (+)
11	3f	CH_2Cl_2	77	>20:1	97 (+)
12	3f	CH_2ClCH_2Cl	62	>20:1	96 (+)

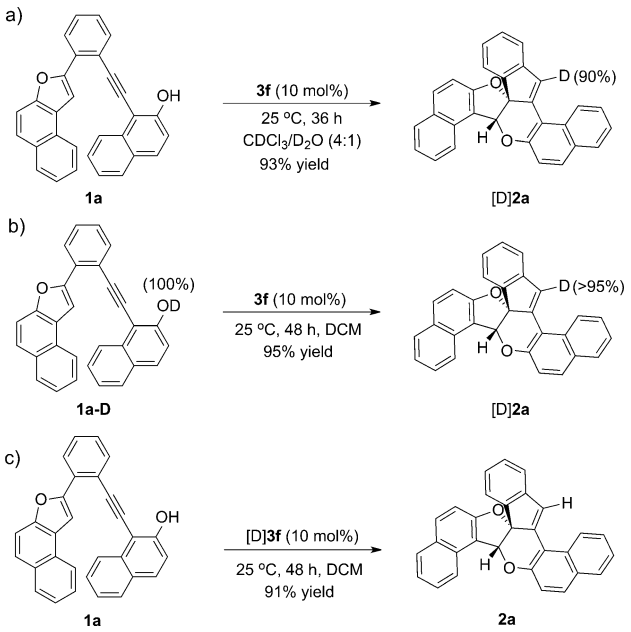
[a] Reaction conditions: 1a (0.05 mmol) and catalyst (10 mol%) in solvent (1.0 mL) at 25 °C for 36 h, unless otherwise specified. [b] Yields of isolated products. [c] Diastereomeric ratio (d.r.) was determined by ^{1}H NMR spectroscopy. [d] The *ee* value was determined by HPLC analysis. THF = tetrahydrofuran.

reaction was conducted with the quinine **3a** (10 mol%) as the catalyst in $CHCl_3$ at 25 °C, the desired product **2a** was obtained in 72% yield with 77% *ee* (entry 1). The quinidine **3c** gave the desired **2a** with a slightly poorer enantioselectivity (entry 3). Although the cinchonine-type catalysts **3b** and **3d** were led to excellent yields, moderate *ee* values were obtained (entries 2 and 4). Gratifyingly, with the thiourea catalyst **3e**, which had been used extensively as a privileged bifunctional organocatalyst, the desired product could be isolated in 85% yield and 96% *ee* (entry 5). This result suggested that the hydrogen bonding of the catalyst was crucial for achieving high enantioselectivity. Therefore, several other hydrogen-bonding catalysts were evaluated, including the thioureas **3f** and **3h**, and the squaramide **3g**. Eventually, **3f** was found to be the most effective catalyst for this transformation in terms of the stereoselectivity (>99% *ee*), diastereomeric ratio (>20:1 d.r.), and yield (98% yield). With the best catalyst in hand, we then evaluated the solvent effect on this reaction. Among the tested solvents, $CHCl_3$ exhibited the best performance (entries 6, and 9–12).

With the identified optimized reaction conditions (Table 1, entry 6), the scope of the [4+2] cycloaddition of the 2-ethynylphenol derivatives with benzofuran substrates was investigated to expand the structural diversity of the [5-6-5] tricyclic derivatives.

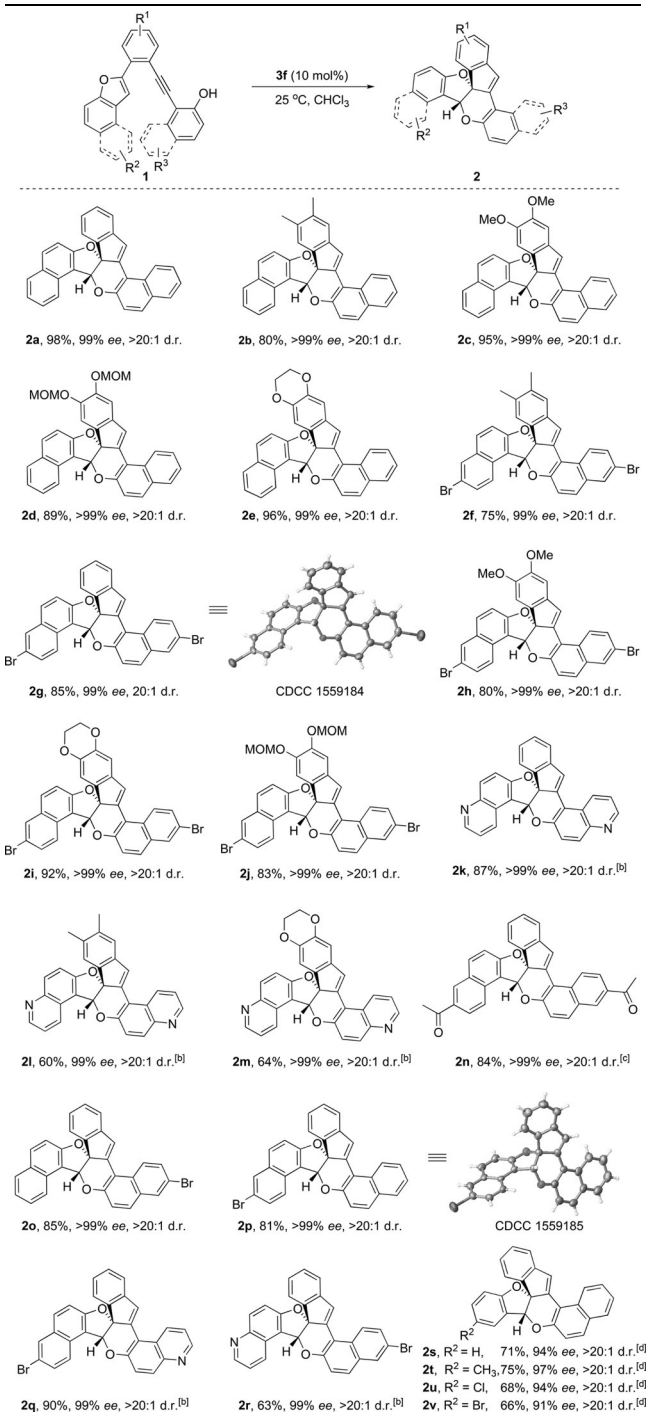
First, the substrates with substituents on the 2-aryl moiety were examined. The methyl, methoxy, methoxymethoxy, and ethylene glycolyl groups were perfectly compatible with the reaction conditions and the corresponding products were obtained with 80–96% yields and up to greater than 99% *ee* (**2b–e**, Table 2). Subsequently, the substituents at the alkynyl and naphtho[2,1-*b*]furan moieties of **1** were further evaluated. For example, substrates with a bromo group on the rings of the naphtho[2,1-*b*]furan and naphthalen-2-ol moieties successfully delivered to the desired products with excellent enantio- and diastereoselectivities (>99% *ee*, >20:1 d.r.; **2f–j**). Moreover, the substrates with quinolyl groups on the furan and alkynyl moieties also uneventfully gave the desired product with perfect enantioselectivities (**2k–m**). Substrates with different groups incorporated into the furan and alkynyl motifs were tested in this reaction and gave the corresponding products with up to more than 99% *ee* (**2o–r**). At last, when the substrates with benzofuran containing different substituents were employed, the corresponding products were obtained with excellent enantioselectivities and moderate yields (**2s–v**). The structure and absolute configuration of **2** were additionally confirmed by X-ray crystallographic studies on the products **2g** and **2p** (see the Supporting Information).

To gain insight into the mechanism of this methodology, several control experiments were carried out (Scheme 2). First, the formal [4+2] cycloaddition of **1a** was conducted in the presence of D_2O and [D]**2a**, in which the deuterium was incorporated at C3 of the 1H-indene, was obtained in 90% (Scheme 2a). The high deuterium incorporation might be ascribed to the almost complete H–D exchange between the



Scheme 2. Deuterium-labeling experiments. DCM = dichloromethane.

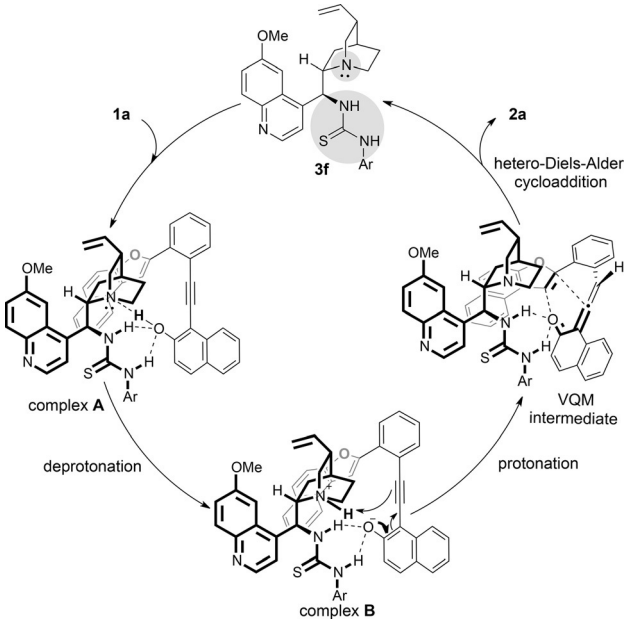
Table 2: Substrate scope.[a]



[a] Reaction conditions: 1 (0.05 mmol) and 3 f (10 mol%) in $CHCl_3$ (1.0 mL) at 25 8C for 36 h, unless otherwise specified. [b] Run at 40 8C for 48 h, 0.025 M. [c] Run at 25 8C for 6 days. [d] Run at 25 8C for 72 h. For sepicted crystal structures the thermal ellipsoids are shown at 50% probability.[17]

hydroxy group of **1a** and D_2O in $CDCl_3$. Subsequently, the O-deuterated naphthol-containing substrate was subjected to this reaction and greater than 95% yield of deuterated product was obtained (Scheme 2b). In addition, when the reaction was performed using [D]**3f** as the catalyst, [D]**2a** was not detected. These observations clearly reveal that the source of the hydrogen atom on C3 of the 1H-indene originates from the hydroxy group of **1a**.

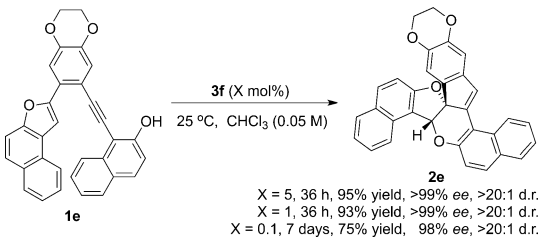
Based on these observations and previously reported mechanisms,[13b] a plausible catalytic cycle is depicted in Scheme 3. The initial step is the formation of the complex **A**



Scheme 3. Plausible catalytic cycle.

between the substrate and catalyst by hydrogen-bonding. The following deprotonation of the naphthol moiety by the quinuclidine base would result in the complex **B** which would undergo a prototropic rearrangement (tautomerization) to furnish the VQM intermediate. Mechanistically, the LUMO energy of the VQM intermediate, which serves as a diene, will be lowered by hydrogen bonding to the thiourea moiety. Subsequently, a formal inverse electron-demand hetero-Diels–Alder cycloaddition of this VQM with benzofuran, driven by both rearomatization and strain release, furnishes the desired product **2a**.

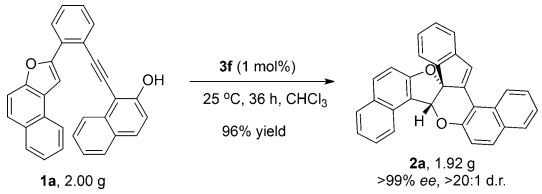
To investigate the efficiency of this process, the effect of catalyst loading[16] has also been explored (Scheme 4). To our delight, when the catalyst loading was decreased to 1 mol%, the chemical yield and enantioselectivity was almost unchanged. When 0.1 mol% of the catalyst was used, the



Scheme 4. The effect of catalyst loading. Reactions were performed on a 0.5 mmol scale.

yield of this reaction was decreased to 75% and the enantioselectivity was maintained (98% *ee*).

To further explore the potential synthetic practicality of this transformation, a gram-scale reaction of **1a** was carried out with **3f** (1 mol%) as the catalyst under the optimal reaction conditions. As expected, **2a** was obtained successfully in 96% yield with greater than 99% *ee* (Scheme 5).



Scheme 5. Gram-scale reaction.

In summary, we have demonstrated an enantioselective construction of oxygen-containing [5-6-5] tricyclic heterocycles by an organocatalytic [4+2] cycloaddition of VQM and benzofuran, and a series of oxygen-containing [5-6-5] tricyclic heterocycles with various functional groups were synthesized in good to excellent yields with up to more than 99% *ee* under mild reaction conditions. In addition, the reaction could be easily scaled up to gram-scale (2.0 g). Moreover, preliminary mechanistic studies demonstrated that a VQM intermediate was involved and possibly resulted from a prototropic rearrangement of 2-ethynylphenol. Further detailed mechanistic studies and applications of this reaction are currently in progress in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: cycloaddition · heterocycles · organocatalysis · polycycles · rearrangements

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[1] For selected reviews, see: a) G. Mehta, A. Srikrishna, *Chem. Rev.* **1997**, *97*, 671–719; b) R. A. Craig, B. M. Stoltz, *Chem. Rev.* **2017**, *117*, 7878–7909.

[2] For selected reviews, see: a) Y.-M. Shi, W.-L. Xiao, J.-X. Pu, H.-D. Sun, *Nat. Prod. Rep.* **2015**, *32*, 367–410; b) J. W. Blunt, B. R. Copp, R. A. Keyzers, M. H. G. Munro, M. R. Prinsep, *Nat. Prod. Rep.* **2017**, *34*, 235–294.

[3] a) X. Zhu, N. M. Muñoz, K. P. Kim, H. Sano, W. Cho, A. R. Leff, *J. Immunol.* **1999**, *163*, 3423–3429; b) P. J. Mohr, R. L. Halcomb, *J. Am. Chem. Soc.* **2003**, *125*, 1712–1713; c) W. P. D. Goldring, G. Pattenden, *Acc. Chem. Res.* **2006**, *39*, 354–361; d) Y. Tang, K. P. Cole, G. S. Buchanan, G. Li, R. P. Hsung, *Org. Lett.* **2009**, *11*, 1591–1594; e) G. Du, W. Bao, J. Huang, S. Huang, H. Yue, W. Yang, L. Zhu, Z. Liang, C.-S. Lee, *Org. Lett.* **2015**, *17*, 2062–2065.

[4] For selected reviews, see: a) E. J. Corey, *Angew. Chem. Int. Ed.* **2002**, *41*, 1650–1667; *Angew. Chem.* **2002**, *114*, 1724–1741; b) K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem. Int. Ed.* **2002**, *41*, 1668–1698; *Angew. Chem.* **2002**, *114*, 1742–1773; c) S. Mukherjee, J. W. Yang, S. Hoffmann, B. List, *Chem. Rev.* **2007**, *107*, 5471–5569; d) A. Moyano, R. Rios, *Chem. Rev.* **2011**, *111*, 4703–4832; e) J.-L. Li, T.-Y. Liu, Y.-C. Chen, *Acc. Chem. Res.* **2012**, *45*, 1491–1500; For selected examples, see: f) K. Juhl, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2003**, *42*, 1498–1501; *Angew. Chem.* **2003**, *115*, 1536–1539; g) T. Akiyama, H. Morita, K. Fuchibe, *J. Am. Chem. Soc.* **2006**, *128*, 13070–13071; h) M. He, G. J. Uc, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 15088–15089; i) B. Han, J.-L. Li, C. Ma, S.-J. Zhang, Y.-C. Chen, *Angew. Chem. Int. Ed.* **2008**, *47*, 9971–9974; *Angew. Chem.* **2008**, *120*, 10119–10122; j) B. Han, Z.-Q. He, J.-L. Li, R. Li, K. Jiang, T.-Y. Liu, Y.-C. Chen, *Angew. Chem. Int. Ed.* **2009**, *48*, 5474–5477; *Angew. Chem.* **2009**, *121*, 5582–5585; k) J.-L. Li, T.-R. Kang, S.-L. Zhou, R. Li, L. Wu, Y.-C. Chen, *Angew. Chem. Int. Ed.* **2010**, *49*, 6418–6420; *Angew. Chem.* **2010**, *122*, 6562–6564; l) Ł. Albrecht, G. Dickmeiss, C. F. Weise, C. Rodríguez-Escrich, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2012**, *51*, 13109–13113; *Angew. Chem.* **2012**, *124*, 13286–13290; m) P. Hu, J. Hu, J. Jiao, X. Tong, *Angew. Chem. Int. Ed.* **2013**, *52*, 5319–5322; *Angew. Chem.* **2013**, *125*, 5427–5430; n) C. Min, C.-T. Lin, D. Seidel, *Angew. Chem. Int. Ed.* **2015**, *54*, 6608–6612; *Angew. Chem.* **2015**, *127*, 6708–6712; o) N. Brindani, G. Rassu, L. Dell'Amico, V. Zambrano, L. Pinna, C. Curti, A. Sartori, L. Battistini, G. Casiraghi, G. Pelosi, D. Greco, F. Zanardi, *Angew. Chem. Int. Ed.* **2015**, *54*, 7386–7390; *Angew. Chem.* **2015**, *127*, 7494–7498; p) W. Yao, X. Dou, Y. Lu, *J. Am. Chem. Soc.* **2015**, *137*, 54–57.

[5] For selected book and reviews on *o*-QMs, see: a) Y. Chiang, A. J. Kresge, Y. Zhu, *Pure Appl. Chem.* **2000**, *72*, 2299–2308; b) H. Amouri, J. Le Bras, *Acc. Chem. Res.* **2002**, *35*, 501–510; c) R. W. Van De Water, T. R. R. Pettus, *Tetrahedron* **2002**, *58*, 5367–5405; d) *Quinone Methides* (Ed.: S. E. Rokita), Wiley-VCH, New York, **2009**; e) S. B. Ferreira, F. de C. da Silva, A. C. Pinto, D. T. G. Gonzaga, V. F. Ferreira, *J. Heterocycl. Chem.* **2009**, *46*, 1080–1097; f) T. P. Pathak, M. S. Sigman, *J. Org. Chem.* **2011**, *76*, 9210–9215; g) N. J. Willis, C. D. Bray, *Chem. Eur. J.* **2012**, *18*, 9160–9173; h) W.-J. Bai, J. G. David, Z.-G. Feng, M. G. Weaver, K.-L. Wu, T. R. R. Pettus, *Acc. Chem. Res.* **2014**, *47*, 3655–3664; i) L. Caruana, M. Fochi, L. Bernardi, *Molecules* **2015**, *20*, 11733–11764; j) Z. Wang, J. Sun, *Synthesis* **2015**, *47*, 3629–3644; k) A. A. Jaworski, K. A. Scheidt, *J. Org. Chem.* **2016**, *81*, 10145–10153.

[6] a) Z. Wang, F. Ai, Z. Wang, W. Zhao, G. Zhu, Z. Lin, J. Sun, *J. Am. Chem. Soc.* **2015**, *137*, 383–389; b) Z. Lai, Z. Wang, J. Sun, *Org. Lett.* **2015**, *17*, 6058–6061; c) W. Zhao, Z. Wang, B. Chu, J. Sun, *Angew. Chem. Int. Ed.* **2015**, *54*, 1910–1913; *Angew. Chem.* **2015**, *127*, 1930–1933; d) Z. Wang, J. Sun, *Org. Lett.* **2017**, *19*, 2334–2337.

[7] a) C.-C. Hsiao, H.-H. Liao, M. Rueping, *Angew. Chem. Int. Ed.* **2014**, *53*, 13258–13263; *Angew. Chem.* **2014**, *126*, 13474–13479; b) C.-C. Hsiao, S. Raja, H.-H. Liao, I. Atodiresei, M. Rueping, *Angew. Chem. Int. Ed.* **2015**, *54*, 5762–5765; *Angew. Chem.* **2015**, *127*, 5854–5857.

[8] a) R.-Y. Zhu, C.-S. Wang, J. Zheng, F. Shi, S.-J. Tu, *J. Org. Chem.* **2014**, *79*, 9305–9312; b) J.-J. Zhao, S.-B. Sun, S.-H. He, Q. Wu, F.

