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Cooperative Catalysis for the Highly Diastereo- and Enantioselective [4+3]-Cycloannulation of *ortho*-Quinone Methides and Carbonyl Ylides

Arun Suneja,[a] Henning Jakob Loui,[a] and Christoph Schneider*[a]

Dedicated to Professor Mark Lautens on the occasion of his 60th birthday

Abstract: We describe herein a highly diastereo- and enantioselective [4+3]-cycloannulation of *ortho*-quinone methides and carbonyl ylides to furnish functionalized, oxa-bridged dibenzooxacines with excellent yields and stereoselectivity in a single synthetic step. The combination of rhodium and chiral phosphoric acid catalysis working in concert to generate both transient intermediates in situ provides direct access to complex bicyclic products with two quaternary and one tertiary stereogenic centers. The products may be further functionalized into valuable and enantiomerically highly enriched building blocks.

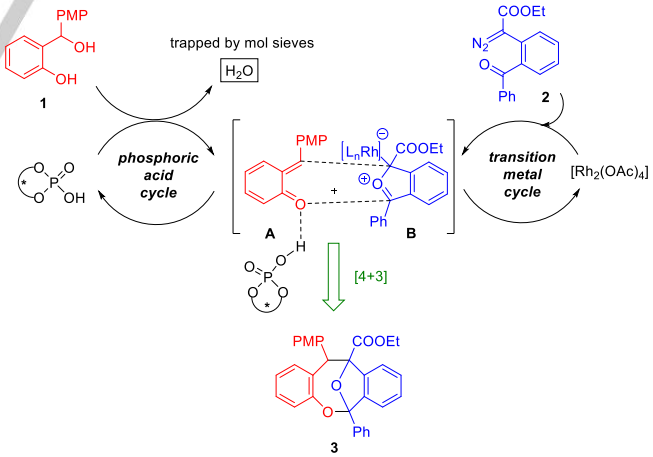
Oxa-bridged heterocyclic skeletons are ubiquitously present in numerous natural products and bioactive molecules.[1] Therefore, the development of new, efficient, and stereoselective synthetic methods towards their rapid construction are highly desirable. Extensive efforts have previously been directed at carbo-bridged bicyclic frameworks through Lewis-acid-catalyzed intramolecular Diels-Alder (IMDA) reactions, molecular rearrangements involving ring-opening/closure tandem process, free-radical reactions, and transition-metal catalyzed annulation reactions.[2] However, there still remains a high demand for the synthesis of oxa-bridged heterocycles.[3]

The combination of a transition metal catalyst and a Lewis acid or organocatalyst to activate two different substrates for a given reaction has attracted significant interest among synthetic organic chemists recently as it potentially enables highly efficient and/or unprecedented complex chemical transformations in a one-pot operation.[4] The success of this strategy relies upon the simultaneous activation of two reacting partners by two different catalysts that operate in concert in two distinct catalytic cycles.[4c] A prominent early example in this respect constitutes the work of Hu and Gong on cooperative Rh-/chiral phosphoric acid catalyzed multicomponent reactions of *α*-diazoesters, amines or alcohols, and imines which were converted into α-functionalized β-amino esters with excellent enantio- and diastereocontrol.[5] In another example, Terada et al. developed an elegant carbonyl ylide formation/reduction-sequence towards isochromanones under cooperative Rh-/chiral phosphoric acid catalysis.[6]

Carbonyl ylides generated from carbonyl compounds and a rhodium carbene complex are classically considered as highly reactive transient species and are widely employed in 1,3-dipolar cycloaddition reactions with a wide variety of 2π-systems.[7, 8] However, their reactivity with 4π-systems is still underexplored due to the challenges associated with entropy factors and strain aspects in the formation of seven-membered rings.[9, 10]

Ortho-quinone methides (*o*-QMs) feature a particularly reactive 4π-system and have increasingly been exploited as versatile synthetic intermediates for the construction of complex heterocycles.[11] In recent years, we and others have meticulously developed Brønsted acid-catalyzed reactions of *o*-QMs with a wide range of typically 2π-nucleophiles leading to a broad range of benzannulated oxygen heterocycles with good to excellent stereocontrol.[12, 13]

We now report the first cooperative, catalytic, enantioselective [4+3]-cycloannulations of *o*-QMs and carbonyl ylides to afford complex and enantiomerically highly enriched oxabicyclic dibenzooxacines. We envisioned that a chiral phosphoric acid would easily form a hydrogen-bonded *o*-QMs **A** starting from *ortho*-hydroxy benzylalcohol **1** in one catalytic cycle while in a second and separate catalytic cycle a carbonyl ylide **B** was generated via Rh-catalyzed decomposition of a α-diazoester **2** tethered to an aryl ketone (Scheme 1). The decisive question here was whether both transient intermediates **A** and **B** formed in only catalytic amounts would have the sufficient stability and lifetime to undergo the desired [4+3]-cycloannulation and provide the product **3** with good stereocontrol in the chiral environment provided by the phosphoric acid catalyst.



Scheme 1. Design plan for the reaction between *o*-QMs and carbonyl ylides via cooperative Rh-/phosphoric acid-catalysis.

Enantioselective [4+3]-cycloadditions of *o*-QMs have first been described independently by Scheidt and Ye under chiral NHC catalysis to produce benzoxopinones.[14a, b] Very recently, the first example of a phosphoric acid-catalyzed enantioselective reaction of *o*-QMs with 2-indolylmethanols as 1,3-dipoles toward indolylbenzoxepins has been established by Shi et al.[14c] An interesting study of the Lautens group described a purely Brønsted

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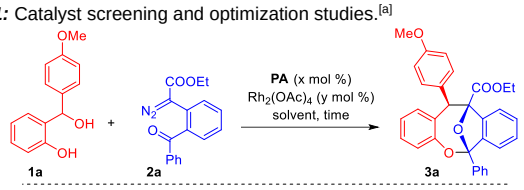
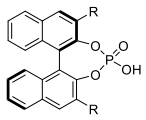
acid-catalyzed, diastereoselective synthesis of oxa-bridged oxazocines via cycloaddition with isomünchnones.[14e]

To test our hypothesis, we initiated our investigations with the model reaction between benzhydryl alcohol **1a** and α-diazoester **2a** in the presence of 5 mol% of $Rh_2(OAc)_4$ and chiral phosphoric acid **PA1** (10 mol%) in $CHCl_3$ at room temperature. We were delighted to obtain the desired product **3a** in 77% yield after 12 h with moderate diastereo- and enantioselectivity (Table 1, entry 1). Importantly, diazoester **2a** had to be added slowly for a period of 1 h using a syringe pump to avoid side reactions of the transient carbonyl ylide.

Table 1: Catalyst screening and optimization studies.[a]





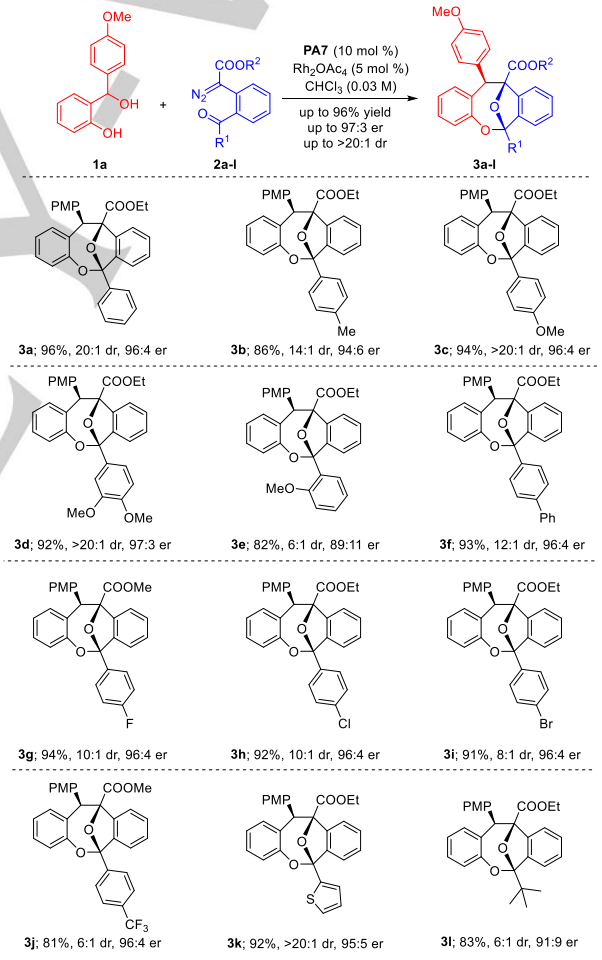
R = 3,5-$(CF_3)_2$-C_6H_3; **PA1**
R = 9-phenanthryl; **PA2**
R = 2,4,6-(^{i}Pr)$_3$-C_6H_2; **PA3**
R = 2,6-Me-4-^{t}Bu-C_6H_2; **PA4**
R = 2,4,6-Me-C_6H_2; **PA5**
R = 2,4,6-Et-C_6H_2; **PA6**
R = 2,3,4,5,6-Me-C_6; **PA7**

entry	PA	solvent	time [h]	3a (%)[b,c]	er[d]	dr[e]
1	**1**	$CHCl_3$	12	77	66:34	16:1
2	**2**	$CHCl_3$	12	71	82:18	20:1
3	**3**	$CHCl_3$	12	75	69:31	10:1
4	**4**	$CHCl_3$	12	79	83:17	20:1
5	**5**	$CHCl_3$	12	80	84:16	20:1
6	**6**	$CHCl_3$	12	73	88:12	20:1
7	**7**	$CHCl_3$	12	79	92:8	20:1
8	**7**	CH_2Cl_2	12	83	83:17	20:1
9	**7**	1,2-DCE	12	75	83:17	15:1
10	**7**	PhMe	48	58	85:15	8:1
11	**7**	CPME	48	trace	ND	ND
12[f]	**7**	$CHCl_3$	12	96	96:4	20:1

[a]Reactions were carried out with 0.10 mmol of **1a**, 0.11 mmol of **2a** and $Rh_2(OAc)_4$ (5 mol %) in the presence of catalyst **PA** (10 mol %) in $CHCl_3$ (3 mL). [b]Isolated yield of both diastereomers after chromatographic purification. [c]Decomposition accounts for remainder of mass balance. [d]Enantiomeric ratios (e.r.) were determined by chiral HPLC. [e]Diastereomeric ratios (d.r.) were determined from ^{1}H NMR of crude reaction mixture. [f] With 3 Å MS (35 mg).

Extensive screening of suitable chiral phosphoric acid catalysts[15] revealed that $Rh_2(OAc)_4$ (5 mol%) and 10 mol% of (*R*)-**PA7** provided the best combination, which afforded **3a** in 79% yield with 20:1-diastereoselectivity and with 92:8 e.r. (entry 7). A short study of reaction conditions revealed $CHCl_3$ to be the solvent of choice and that both chemical yield and enantioselectivity were further improved by using 3 Å molecular sieves (MS) as dehydrating agent. Thus, using these conditions **3a** was eventually obtained in 96% yield with 20:1-diastereoselectivity and with 96:4 e.r. (entry 12). Interestingly, lowering the catalyst loading of $Rh_2(OAc)_4$ and (*R*)-**PA7** did not deteriorate the enantiomeric ratio, but led to a decrease in the diastereoselectivity of the product (see the Supporting Information for more details).

With optimized conditions in hand, we set out to examine the substrate scope of the reaction. Initially, a series of *α*-diazoesters **2a-k** was tested with benzhydryl alcohol **1a** as model *ortho*-quinone methide precursor. Pleasingly, the reaction worked well with all substrates and afforded products **3a-k** in good to excellent yields and excellent enantioselectivities of up to 97:3 e.r. (Scheme 2). The diastereoselectivity appeared to be dependent on the electronic character of the aryl substituent with electronrich aryl groups generally giving rise to almost perfect selectivity. In particular, the thiophene-substituted diazoester **2k** gave rise to product **3k** with 92% yield as a single diastereomer and with 95:5 e.r. On the other hand, substrates **2g-j** carrying electron-poor substituents (such as halogen and CF_3-groups) furnished products **3g-j** with diminished diastereoselectivity, albeit in excellent yields and up to 96:4 e.r. *Ortho*-substituted aryl groups had a detrimental effect on both the diastereo- and enantioselectivity as documented for **3e** (6:1 d.r., 89:11 e.r.) most probably for steric reasons. Most importantly, this cycloannulation is not limited to aryl- and heteroaryl-substituted diazoketones but could be extended to an alkyl-substituted substrate as well. Thus, dibenzooxacine **3l** was obtained in high yield and stereoselectivity similar to the other products.



Scheme 2. Substrate scope for reactions of *ortho*-hydroxy benzhydryl alcohol **1a** with various *α*-diazoesters **2a-l**. [a]Reactions were carried out with 0.1 mmol of **1a**, 0.11 mmol of **2**, 3 Å MS (35 mg) and $Rh_2(OAc)_4$ (5 mol %) in the presence of catalyst **PA7** (10 mol %) in $CHCl_3$ (3 mL).

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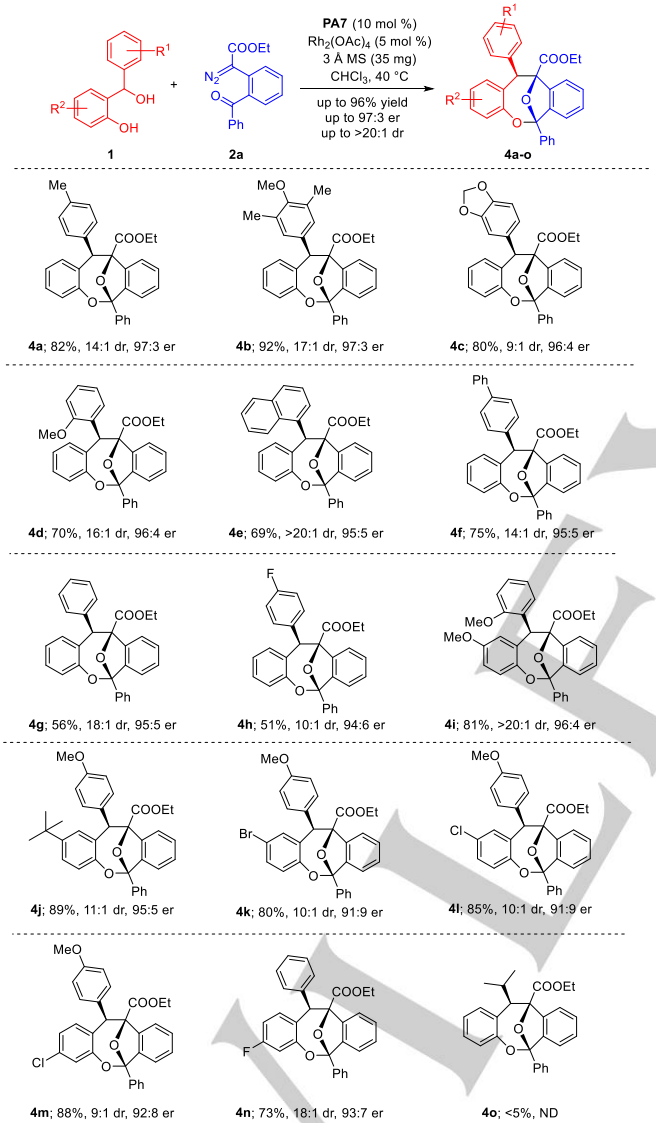
We then turned our attention to reactions of *α*-diazoester **2a** with various substituted *o*-hydroxy benzhydryl alcohols **1** as *ortho*-quinone methide precursors (Scheme 3). Gratifyingly, a broad variety of substrates with both electron-donating as well as electron-withdrawing in the *o*-QM component were readily converted into products **4a-n** at slightly elevated temperature. Yields ranged from moderate to excellent and the diastereo- and enantioselectivity was generally very high. Here again, a dependance of reaction outcome on the electronic character of the substrates was observed. Whereas electron-rich benzhydryl alcohols furnished products with very good yields (e.g. **4a-4f**), electron-poor substrates afforded products with only moderate chemical yield, albeit excellent enantioselectivity (e.g. **4g** and **4h**).



Scheme 3. Expansion of substrate scope for reaction of various *ortho*-hydroxy benzhydryl alcohol **1** with *α*-diazoester **2a**. [a]Reactions were carried out with 0.1 mmol of **1**, 0.11 mmol of **2a**, 3 Å MS (35 mg) and $Rh_2(OAc)_4$ (5 mol %) in the presence of catalyst **PA7** (10 mol %) in $CHCl_3$ (3 mL).

Structural variation in the quinone moiety was more readily tolerated irrespective of the electronic character. Thus, products **4j-4n** with alkyl and various halogen substituents were obtained with synthetically useful yields and very good diastereo- and enantioselectivity (Scheme 3). Unfortunately, the *i*Pr-substituted benzhydryl alcohol **1o** failed to deliver product **4o** because the transient *o*-QM generated in situ from **1o** apparently was too unstable to successfully engage the transient carbonyl ylide in the cycloannulation event. The X-ray structure analysis of the major diastereomer of product **3k** confirmed both the relative and absolute configuration which was assigned to all other products accordingly (Figure 1).[16, 17]

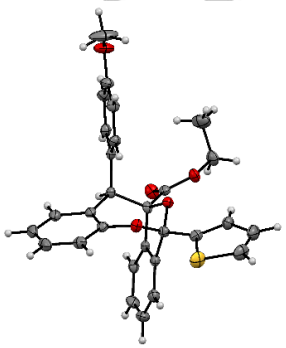
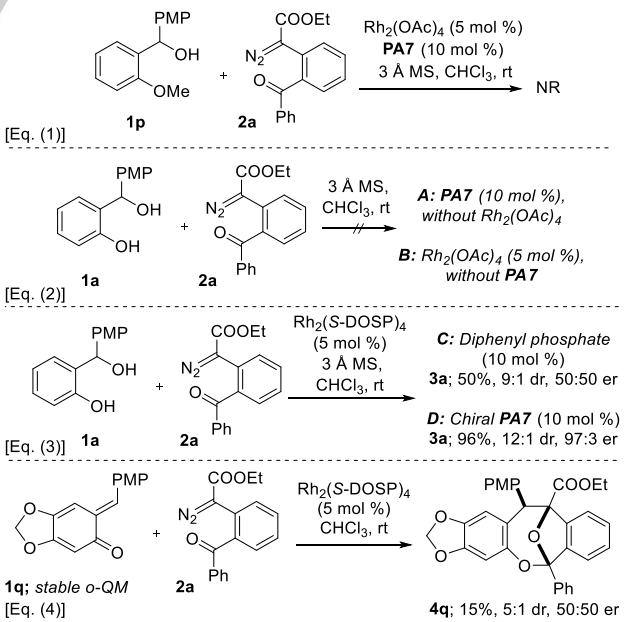


Figure 1: X-ray crystal structure of product **3k**.[16]

To gain more insight into the mechanism of this cycloannulation process some control experiments were conducted. Under the standard conditions *O*-methyl protected benzhydryl alcohol **1p** failed to react with **2a** underlining the importance of the *o*-QM structure for this reaction (Scheme 4, eq. 1). Furthermore, neither in the presence of the phosphoric acid alone with $Rh_2(OAc)_4$ absent (case A) nor in the presence of $Rh_2(OAc)_4$ alone with the phosphoric acid absent (case B) was a successful reaction observed (eq. 2). We therefore conclude that both catalysts actively participate in this reaction by generating both the *o*-QM and the carbonyl ylide as transient intermediates. These control experiments strongly support our initial reaction design of a cooperative catalytic activation of both nucleophile and electrophile in a one-pot process.



Scheme 4. Control experiments.

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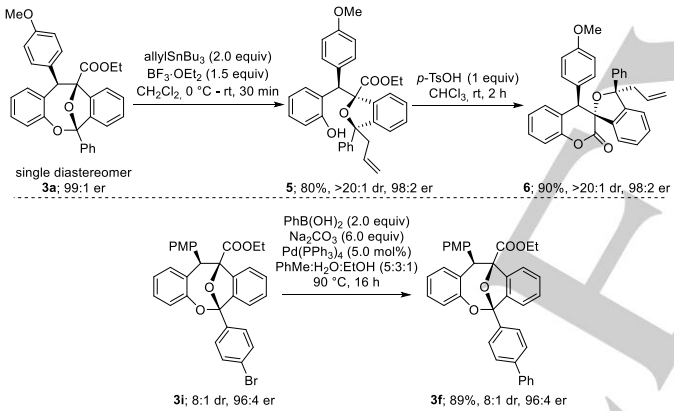
In order to further shine light on the origin of enantioselectivity we conducted reactions of **1a** and **2a** in the presence of a chiral rhodium catalyst and both an achiral and a chiral phosphoric acid (Scheme 4, eq. 3). Whereas the enantioselectivity of the latter reaction was virtually unchanged in comparison to the reaction with $Rh_2(OAc)_4$ reported above, no enantioselectivity was observed with diphenyl phosphate as Brønsted acid catalyst. Moreover, reaction of the stable *ortho*-quinone methide **1q** and **2a** in the presence of the chiral rhodium catalyst alone delivered dibenzooxacine **4q** in low yield and as a racemic mixture indicating once again the critical role of the chiral phosphoric acid for the enantioselectivity of the process (eq. 4).

Finally, we attempted some structural modifications of the products and identified the acetal moiety of **3a** as a good starting point for further synthetic elaborations. Under BF_3-activation the acetal was readily cleaved to the corresponding oxonium ion which was trapped with allyltributylstannane to furnish isobenzofuran **5** with good yield and complete diastereocontrol. Phenol **5** was then lactonized with *p*-TsOH to produce the highly congested spirocyclic dihydrocoumarin **6** again with good yield (Scheme 5). The product **6** was thus obtained in 72% yield over two steps as a single diastereomer and with 98:2 e.r. On the other hand, the oxa-bridged products **3** are sufficiently stable as to easily tolerate further post-modifications such as a Suzuki-Miyaura cross coupling reaction which proceeded in very good yield in the case of **3i**.



Scheme 5. Synthetic elaborations of oxa-bridged dibenzooxacines **3**.

In conclusion, we have developed a novel and highly stereoselective [4+3]-cycloannulation of transient carbonyl ylides with *in situ* generated *o*-QMs via cooperative Rh-/phosphoric acid catalysis. The reaction comprises the catalytic enantio- and diastereoselective synthesis of oxa-bridged heterocycles featuring two quaternary and one tertiary stereogenic centers in a one-pot operation. The benzannulated *O*-heterocycles were obtained in typically high yields (up to 96%) and excellent stereoselectivities (up to >20:1 d.r. and up to 97:3 e.r.). Moreover, the products may be successfully manipulated to access valuable synthetic building blocks. The striking feature of this process is the separate catalytic activation of nucleophile and electrophile with a chiral phosphoric acid enabling the formation of a transient hydrogen-bonded *ortho*-quinone methide and $Rh_2(OAc)_4$ delivering the transient carbonyl ylide in a one-pot operation. Further extensions of this process are currently underway in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric synthesis • carbonyl ylides • cycloannulation • *ortho*-quinone methides • cooperative catalysis

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[16] CCDC 1946746 (**3k**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[17] We assume a similar transition state assembly in this reaction as in previous examples of phosphoric acid-catalyzed reactions of *ortho*-quinone methides (see e. g. ref. 12j) based upon the identical absolute configuration of the products.

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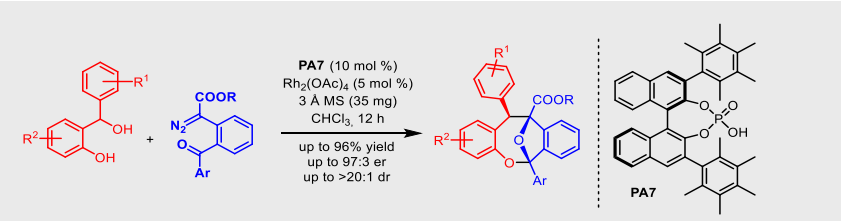

A combination of $Rh_2(OAc)_4$ and a chiral phosphoric acid catalyzed the highly diastereo- and enantioselective reaction of transient carbonyl ylides and *ortho*-quinone methides both in situ generated in cooperative catalytic cycles to afford a broad range of functionalized, oxa-bridged dibenzooxacines featuring two quaternary and one tertiary stereogenic centers.

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Cooperative Catalysis for the Highly Diastereo- and Enantioselective [4+3]-Cycloannulation of *ortho*-Quinone Methides and Carbonyl Ylides