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

Arun Suneja, Henning Jakob Loui, and Christoph Schneider*

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 dibenzo[oxacinocines 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 enantioselectively highly enriched building blocks.

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

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 since it potentially enables highly efficient and/or unprecedented complex chemical transformations in a one-pot operation. 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. A prominent early example is the work of Hu, Gong, and co-workers on cooperative Rh/chiral phosphoric acid catalyzed multicomponent reactions of α-diazoesters, alcohols, and imines, which were converted into α-hydroxy β-amino esters with excellent enantio- and diastereoselectivity.[10] In another example, Terada et al. developed an elegant carbonyl ylide formation/reduction sequence towards isochromanones under cooperative Rh/chiral phosphoric acid catalysis.[9]

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 Bronsted 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 stereosecontrol.[12,13]

We now report the first cooperative, catalytic, enantioselective [4+3]-cycloannulation of o-QMs and carbonyl ylides to afford complex and enantioselectively highly enriched oxabicyclic dibenzo[oxacinocines. We envisioned that a chiral phosphoric acid would easily form hydrogen-bonded o-QM A starting from ortho-hydroxy benzylalcohol I in one catalytic cycle, while in a second and separate catalytic cycle, carbonyl ylide B would be generated through 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 very low amounts would have sufficient stability and lifetime to undergo the desired [4+3]-cycloannulation and provide the product 3 with good stereosecontrol in the chiral environment provided by the phosphoric acid catalyst.

Enantioselective [4+3]-cycloadditions of o-QMs were first described independently by the groups of Scheidt and Ye under chiral NHC catalysis to produce benzoazopinones.[14a, b] Very recently, the first example of a phosphoric acid catalyzed enantioselective reaction of o-QMs with 2-indolylmethanols as 2-indole ylides toward indolylbenzoxepines was established by Shi et al.[14c] An interesting study by the Lautens group described a purely Bronsted acid catalyzed
diastereoselective synthesis of oxo-bridged oxazocines through cycloaddition with isomünchnones. 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 Rh₂(OAc)₃ and chiral phosphoric acid PA1 (10 mol %) in CHCl₃ at room temperature. We were delighted to obtain the desired product 3a in 77% yield after 12 h with moderate diastereo- and enantioselectivity (Scheme 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.

Extensive screening of suitable chiral phosphoric acid catalysts revealed that Rh₂(OAc)₃ (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 CHCl₃ 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. When 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 Rh₂(OAc)₃ and (R)-PA7 did not decrease the enaniomeric 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 a model ortho-quinone methide precursor. Pleasingly, the reaction worked well with all substrates and afforded products 3a-k in good to excellent yields and with excellent enantioselectivity of up to 97:3 e.r. (Scheme 2). The diastereoselectivity appeared to be dependent on the electronic character of the aryl substituent, with electron-rich aryl groups generally giving rise to almost perfect selectivity. In particular, the thiophene-substituted diazoester 2k gave rise to product 3k in 92% yield as a single diastereomer and with 95:5 e.r. On the other hand, substrates 2g-j, which carry electron-poor substituents (such as halogen and CF₃ 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 shown for 3e (6:1 d.r., 89:11 e.r.), probably for steric reasons. Most importantly, this cycloaddition is not limited to aryl- and heteroaryl-substituted diazoketones but could be extended to an alkyl-substituted substrate as well, since dibenzoxacine 3l was obtained in high yield and stereoselectivity similar to the other products.

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 and electron-withdrawing substituents 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 were generally very high. Here again, a dependence 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 substituents afforded products with only moderate chemical yield, albeit excellent enantioselectivity (e.g., 4g and 4h).

Structural variation of the quinone moiety was more readily tolerated irrespective of the electronic character, and 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 iPr-substituted benzhydryl alcohol 1o failed to deliver product 4o because the transient o-QM generated in situ from 1o was apparently 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] 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, thereby 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 Rh2(OAc)4 absent (case A) nor in the presence of Rh2(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 2.** Substrate scope for reactions of ortho-hydroxy benzhydryl alcohol 1a with various α-diazoesters (2a–l). Reactions were carried out with 0.1 mmol of 1a, 0.11 mmol of 2, 3 Å MS (35 mg) and Rh2(OAc)4 (5 mol%) in the presence of catalyst PA7 (10 mol%) in CHCl3 (3 mL).

**Scheme 3.** Expansion of substrate scope for the reaction of ortho-hydroxy benzhydryl alcohols 1 with α-diazoester 2a. Reactions were carried out with 0.1 mmol of 1, 0.11 mmol of 2a, 3 Å MS (35 mg) and Rh2(OAc)4 (5 mol%) in the presence of catalyst PA7 (10 mol%) in CHCl3 (3 mL).

**Figure 1.** X-ray crystal structure of product 3k.[16]
In order to further shine light on the origin of the 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 Rh₂(OAc)₄ reported above, no enantioselectivity was observed with diphenyl phosphate as a Brønsted acid catalyst. Moreover, reaction of the stable ortho-quinone methide 1q and 2a in the presence of the chiral rhodium catalyst alone delivered dibenzoazocine 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 BF₃ activation, the acetal was readily cleaved to the corresponding oxonium ion, which was trapped with allylttributylstannane to furnish isobenzofuran 5 with good yield and complete diastereoregion. Phenol 5 was then lactonized with p-TsOH to produce the highly congested spiroyclic dihydrocoumarin 6, again with good yield (Scheme 5). Product 6 was obtained in 72% yield over two steps as a single diastereomer and with 98:2 e.r. On the other hand, the oxad-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.

In conclusion, we have developed a novel and highly stereoselective [4+3]-cycloannulation of transient carbonyl ylides with in situ generated o-QMs through cooperative Rh/phosphoric acid catalysis. The reaction enables the catalytic enantio- and diastereoselective synthesis of oxad-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 stereoselectivity (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 Rh₂(OAc)₄ delivering the transient carbonyl ylide in a one-pot operation. Further extensions of this process are currently underway in our laboratory.

Acknowledgements

This work was generously supported by the Deutsche Forschungsgemeinschaft (SCHN 441/11-2) and through gifts of chemicals from BASF and Evonik. We thank Dr. M. Schlegel for helpful discussions and Dr. P. Lönecke (both University of Leipzig) for solving the X-ray crystal structure.

Conflict of interest

The authors declare no conflict of interest.

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

How to cite: Angew. Chem. Int. Ed. 2020, 59, 5536–5540
Angew. Chem. 2020, 132, 5580–5585

[1] a) Y. Li, M. Dai, Angew. Chem. Int. Ed. 2017, 56, 11624; Angew. Chem. 2017, 129, 11782; b) R. C. Jadulco, C. D. Pond, R. M. Van Wagoner, M. Koch, O. G. Gideon, T. K. Matainaho, P. Piskaut, L. R. Barrows, J. Nat. Prod. 2014, 77, 183.
[2] a) W. Zhao, Chem. Rev. 2010, 110, 1706; b) Z. Yin, Y. He, P. Chiu, Chem. Soc. Rev. 2018, 47, 8881.
[3] a) J. Zhang, Z. Liao, L. Chen, S. Zhu, Chem. Eur. J. 2019, 25, 9405; b) J. Zhang, Z. Liao, L. Chen, H. Jiang, S. Zhu, Chem. Commun. 2019, 55, 7382.
[4] Selected reviews: a) M. H. Wang, K. A. Scheidt, Angew. Chem. Int. Ed. 2016, 55, 14912; Angew. Chem. 2016, 128, 15134; b) S. Afewerki, A. Cordova, Chem. Rev. 2016, 116, 13512; c) Y. Deng, S. Kumar, H. Wang, Chem. Commun. 2014, 50, 4272; d) H. Pellissier, Tetrahedron 2013, 69, 7171; e) X. Guo, W. Hu, Acc. Chem. Res. 2013, 46, 2427; f) Z. Du, Z. Shao, Chem. Soc. Rev.
From our group: a) R. Ukis, C. Schneider, Angew. Chem. Int. Ed. 2012, 51, 2043; b) Q. Wu, T. R. R. Pettus, J. Org. Chem. 2013, 78, 7703; c) L. P. Yang, L. Z. Gong, J. Am. Chem. Soc. 2008, 130, 7782.

From other groups: a) F. Jiang, K.-W. Chen, P. Wu, Y.-C. Zhang, J. Am. Chem. Soc. 2017, 139, 9839; c) A. G. Smith, H. M. L. Davies, J. Am. Chem. Soc. 2012, 134, 18241; d) X. Hong, S. France, A. Padwa, Tetrahedron 2007, 63, 5962; e) M. P. Doyle, M. A. McKervey, T. Wulff, Chem. Commun. 2016, 52, 8607; f) Z. Lai, J. Sun, Synlett 2016, 27, 555; m) J.-J. Zhao, Y.-C. Zhang, M.-M. Xu, M. Tang, F. Shi, J. Org. Chem. 2015, 80, 10016; n) G. C. Tsui, L. Liu, B. List, Angew. Chem. Int. Ed. 2015, 54, 7703; Angew. Chem. 2015, 127, 7814; o) H. Hu, Y. Liu, J. Guo, L. Lin, Y. Xu, X. Liu, X. Feng, Chem. Commun. 2015, 51, 3835; p) W. Zhao, Z. Wang, B. Chu, J. Sun, Angew. Chem. Int. Ed. 2015, 54, 2010; Angew. Chem. 2015, 127, 1930; q) J.-J. Zhao, S.-B. Sun, S.-H. He, Q. Wu, F. Shi, Angew. Chem. Int. Ed. 2015, 54, 5460; Angew. Chem. 2015, 127, 5550; r) Z. Wang, F. Ai, Z. Wang, W. Zhao, G. Zhu, Z. Lin, J. Sun, J. Am. Chem. Soc. 2015, 137, 383; s) C.-C. Hsiao, S. Raja, H.-H. Liao, I. Atodiresei, M. Rueping, Angew. Chem. Int. Ed. 2015, 54, 5762; Angew. Chem. 2015, 127, 5854; t) Z. Lai, Z. Wang, J. Sun, Org. Lett. 2015, 17, 6058; u) C.-C. Hsiao, H.-H. Liao, M. Rueping, Angew. Chem. Int. Ed. 2014, 53, 13258; Angew. Chem. 2014, 126, 13474; v) M. Rueping, U. Uria, M. Y. Lin, I. Atodiresei, J. Am. Chem. Soc. 2011, 133, 3732; w) D. Wileke, E. Herdewick, T. Bach, Synlett 2011, 1235.

[14] Recent enantioselective [4+3]-cycloannulations of α-OMs: with chiral NH catalysis: a) J. Izquierdo, A. Orue, K. A. Scheidt, J. Am. Chem. Soc. 2013, 135, 10634; b) H. Lv, W.-Q. Jia, L.-H. Sun, S. Ye, Angew. Chem. Int. Ed. 2013, 52, 8607; Angew. Chem. 2013, 125, 8769; with chiral phosphoric acid catalysis: c) M. Sun, C. Ma, S.-J. Zhou, S.-F. Lou, J. Xiao, Y. Jiao, F. Shi, Angew. Chem. Int. Ed. 2019, 58, 8705; Angew. Chem. 2019, 131, 8795; catalytic, non-enantioselective reactions see: d) J.-Y. Du, Y.-H. Ma, F.-X. Meng, R.-R. Zhang, R.-N. Wang, H.-L. Shi, Q. Wang, Y.-X. Fan, H.-L. Huang, J.-C. Cui, C.-L. Ma, Org. Lett. 2019, 21, 465; e) H. Lam, Z. Qureshi, M. Wegmann, M. Lautens, Angew. Chem. Int. Ed. 2018, 57, 16185; Angew. Chem. 2018, 130, 16417; f) a related process not involving α-OMs that appeared during the revision of this manuscript see: C. R. Xu, K. X. Wang, D. W. Li, L. L. Lin, X. M. Feng, Angew. Chem. Int. Ed. 2019, 58, 18438; Angew. Chem. 2019, 138, 18609; g) G.-J. Mei, Z.-Q. Zhu, J.-J. Zhao, C.-Y. Bian, J. Chen, R.-W. Chen, F. Shi, Chem. Commun. 2017, 53, 2768; h) J. Xu, S. Yuan, J. Peng, M. Miao, Z. Chen, H. Ren, Org. Biomol. Chem. 2017, 15, 7515.

[15] Selected reviews: a) F. E. Heldt, D. Grau, S. B. Tsoyoeva, Molecules 2015, 20, 16103; b) D. Parmar, E. Sugiono, S. Raja, M. Rueping, Chem. Rev. 2014, 114, 9047; c) A. A. Desai, W. D. Wulff, Synthesis 2010, 3670; d) D. Kampen, C. M. Reisinger, B. List, Top. Curr. Chem. 2010, 291, 395; e) A. Zamfir, S. Schenker, M. Freund, S. B. Tsoyoeva, Org. Biomol. Chem. 2010, 8, 5262; f) M. Terada, Synthesis 2010, 12, 1929; g) T. Akiyama, Chem. Rev. 2007, 107, 5744.

[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 Ref. [12]) for example based upon the identical absolute configuration of the products.