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Merging Oxidative Dearomatization and Aminocatalysis: One-Pot Enantioselective Synthesis of Tricyclic Architectures

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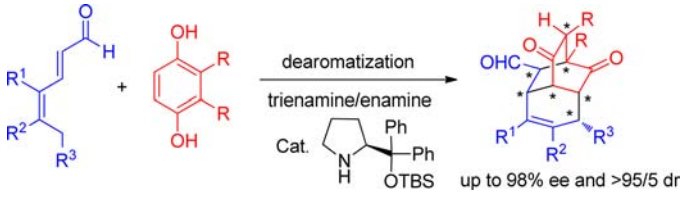
ABSTRACT



The combination of oxidative dearomatization and trienamine/enamine activation in a single vessel is described. Under these conditions, a three-bond forming process generates functionalized tricyclic architectures with up to six contiguous stereocenters with excellent stereoselectivities from readily available planar substrates.

The construction of nonaromatic polycyclic architectures represents an important synthetic challenge due to their presence in a myriad of molecules of biological interest. Despite great strides in this field, the straightforward formation of functionalized sp^3-rich cyclic architectures from simple substrates remains an unmet need in synthesis while such methodologies are highly desired to meet the challenge of drug discovery.[1] Among the array of potential substrates, the transformation of aromatic structures is a focal point for extensive research efforts in light of the large number of biologically active molecules which are derived from or contain aromatic units.[2] In particular, the combination of an oxidative dearomatization reaction and asymmetric organocatalyzed desymmetrization processes represents an attractive way for complexity-building synthesis.[3,4] In an important contribution to this field, the Gaunt group has reported an elegant one-pot strategy for the preparation of highly functionalized enantioenriched cyclic compounds based on oxidative dearomatization of a para-substituted phenol and an amine-catalyzed intramolecular enantioselective Michael reaction.[5] Following on from this work, only a few reports have succeeded in the combination of oxidative dearomatizations and asymmetric organocatalyzed functionalizations in a single vessel.[5,6] Most of them involve an oxidative dearomatization with an organocatalytic intramolecular functionalization which represents a limitation to reaching a vast array of diverse and complex cyclic optically active structures.

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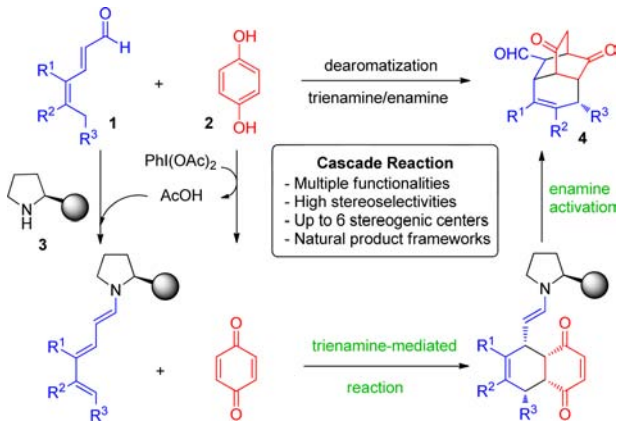
As part of our ongoing research into the development of organocatalytic one-pot transformations,[7] we wish to report herein the implementation of a new one-pot strategy that directly converts hydroquinone derivatives into enantioenriched tricyclic architectures through oxidative dearomatization and an amine-catalyzed Diels–Alder/Michael cascade reaction (Scheme 1). The strategy depicted herein lies in the use of planar molecules that are deprived of architectural complexity for which activation strategies would change their reactivity to enable the construction of tridimensional polycyclic compounds. The Diels–Alder cycloaddition was chosen as an embodiment of this strategy and required initiation by HOMO-raising of dienals **1** through trienamine activation and dearomatization of the hydroquinone **2**.[8,9]

Scheme 1. Dearomatization and Trienamine/Enamine Activation



By analogy to previous works on trienamine-mediated Diels–Alder cycloaddition, it was anticipated that the *endo* product will be obtained under these conditions with exquisite control of regio- and stereoselectivity.[10] At this stage, we hypothesized that the Diels–Alder adduct bearing an enamine side chain should lead to the tricyclic compound **4** through an intramolecular Michael addition.[11] To the best of our knowledge, only one example reported by Jørgensen and Chen in 2011 described the combination of trienamine and enamine activations in a single flask.[10a] The one-pot dearomatization/trienamine/enamine sequence would generate enantioenriched sp^3-rich tricyclic motifs for which the straightforward preparation is a considerable synthetic challenge. In addition, the tricyclic ring system is encountered in various natural products isolated from plants and microorganisms. Valerianannoid A,[12] Penicillone A,[13] and Atropurpuran[14] are selected examples of natural products (Figure 1).

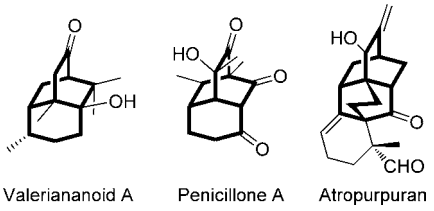


Figure 1. Tricyclic motif and natural products.

As conceptualized in Scheme 1, we sought to develop a strategy involving an oxidant and an aminocatalyst in a single vessel. (Diacetoxyiodo)benzene was targeted as an attractive oxidant due to its favorable safety profile, low toxicity, ease of handling, and applications in a wide range of transformations.[15] In addition, this oxidant has already been used in asymmetric transformations combining aminocatalysis and oxidative dearomatization.[16] Central to the implementation of the one-pot strategy is the double role of (diacetoxyiodo)benzene. Preliminary results have shown that $PhI(OAc)_2$ enables oxidation of hydroquinone into benzoquinone, and the acetic acid byproduct of this reaction is internally recycled to act as a cocatalyst in the trienamine/enamine transformation.[17,18] In light of the ability of diarylprolinol silyl ether catalysts to promote trienamine activation,[19] we investigated the reaction of dienal **1a**, hydroquinone **2**, and $PhI(OAc)_2$ in the presence of 10 mol % of bulky catalysts such as **3** under various reaction conditions (Table 1). The optimal ratio of

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(11) At this stage, 5-*exo-trig* Michael addition could not be ruled out even if 6-*endo-trig* Michael addition led to less strained tricyclic compounds. See DFT calculations in the Supporting Information for further details.

(12) Ming, D. S.; Yu, D. Q.; Yang, Y. Y.; He, C. H. *Tetrahedron Lett.* **1997**, *38*, 5205.

(13) Liu, W.; Gu, Q.; Zhu, W.; Cui, C.; Fan, G.; Zhu, T.; Liu, H.; Fang, Y. *Tetrahedron Lett.* **2005**, *46*, 4993.

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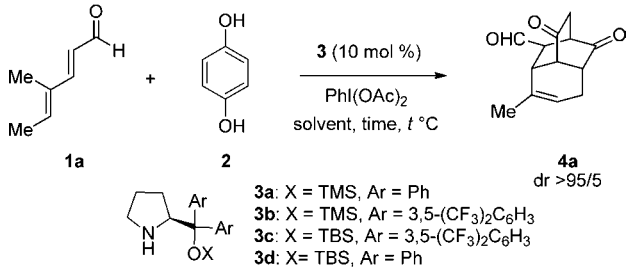
(15) For the use of hypervalent iodine reagents in total synthesis, see: (a) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235. (b) Silva, L. F.; Olofsson, B. *Nat. Prod. Rep.* **2011**, *28*, 1722.

(16) González, D. F.; Benfatti, F.; Waser, J. *ChemCatChem* **2012**, *4*, 955.

(17) For the influence of acidic conditions on the reaction, see Supporting Information.

Table 1. Reaction Optimization[a]



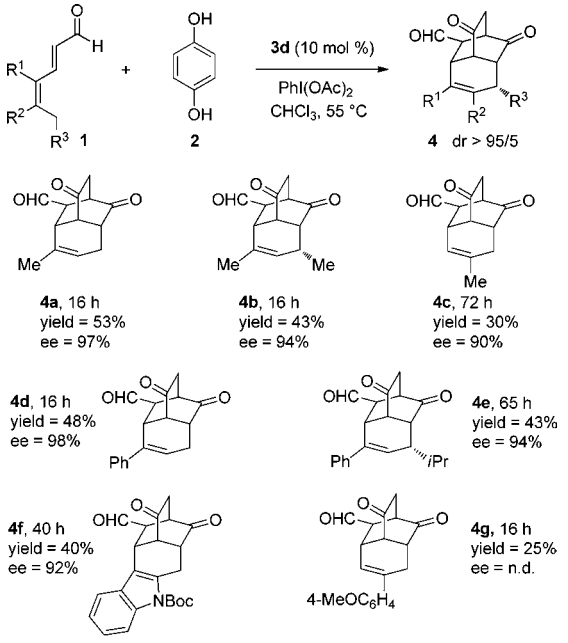
entry	3	solvent	conditions	% yield	% ee[b]
1	**3a**	$CHCl_3$	55 °C, 4 h	52	90
2[c]	**3a**	$CHCl_3$	55 °C, 4 h	30	89
3	**3a**	$CHCl_3$	rt, 48 h	n.r.	n.d.
4	**3a**	CH_3CN	55 °C, 4 h	14	80
5	**3a**	toluene	55 °C, 4 h	20	86
6	**3a**	$ClCH_2CH_2Cl$	55 °C, 4 h	41	90
7	**3b**	$CHCl_3$	55 °C, 4 h	<10	n.d.
8	**3c**	$CHCl_3$	55 °C, 4 h	<10	n.d.
9	**3d**	$CHCl_3$	55 °C, 4 h	43	97
10	**3d**	$CHCl_3$	55 °C, 16 h	53	97

[a] Reactions were performed on 0.5 mmol scale using 1 equiv of **1a**, 1.5 equiv of **2**, and 1.4 equiv of $PhI(OAc)_2$ unless otherwise noted. Diastereomeric ratios were determined by ^1H NMR analysis of the crude. n.r. = no reaction. n.d. = not determined. [b] Enantiomeric excesses were determined by chiral HPLC. [c] In this case 1.5 equiv of **1a**, 1 equiv of **2**, and 1.05 equiv of $PhI(OAc)_2$ were used.

substrates for the reaction turned out to be 1:1.5 for **1a:2** in the presence of 1.4 equiv of $PhI(OAc)_2$ (entries 1 and 2). The reaction at 55 °C for 4 h in $CHCl_3$ gave rise to the tricyclic compound **4a** in 52% yield with 90% ee after purification by flash chromatography, while no reaction occurred at room temperature (entry 3). It is important to note that only one diastereoisomer was detected under the conditions described in this survey and full analyses were carried out to unambiguously confirm the structure of **4a**.[20] To assess the influence of the reaction media, various solvents were screened (entries 4–6). The use of acetonitrile or toluene proved to be detrimental to the reaction, while performing the transformation in chlorinated solvents led to the best results in terms of both selectivity and reactivity (entries 1 and 6). By using the reaction conditions reported in entry 1 ($CHCl_3$, 55 °C, 4 h), various diarylprolinol silyl ether catalysts **3** were investigated (entries 7–9). The use of 3,5-$(CF_3)_2C_6H_3$-derived catalysts **3b** and **3c** shut down the reaction while **3d** possessing a bulkier TBS group gave interesting results by producing **4a** in 43% yield and 97% ee (entries 7–9). The best result was obtained by reacting **1a** and hydroquinone in the presence of 10 mol % of **3d** for 16 h at 55 °C (entry 10). Under these conditions, the tricyclic compound **4a** was obtained with an excellent stereoselection (97% ee) in 53% yield, corresponding to an average yield of 80% per bond formed.

Having established the optimal reaction conditions, our interest then focused on the scope and limitations of the dearomatization/trienamine/enamine sequence involving a focused selection of dienals **1** and hydroquinone **2** in the presence of **3d** as a catalyst (Scheme 2).

Scheme 2. Substrate Scope



Excellent levels of enantioselection were obtained for all substrates regardless of the steric and electronic features of the aldehyde substituents. Gratifyingly, compounds **4a**–**4c** were produced in moderate-to-good yields. The use of 2,4-dienals with a 4-phenyl group did not influence the reaction outcome. Indole-derived dienal was amenable to the reaction providing access to the polycyclic structure **4f** in 40% yield with 92% ee. The reaction with an aldehyde bearing a 5-anisyl group gave rise to the unstable product **4g** in 25% yield. It is important to note that appropriate electron-donating substituents on the dienal are required for the success of the reaction because 2,4-heptanedienal (**1**, $R^1 = R^2 = H$, $R^3 = Me$) turned out to be inert under the reaction conditions.[21]

(18) For examples of strategies using waste as a cocatalyst or catalyst, see: (a) Alaimo, P. J.; O'Brien, R., III; Johnson, A. W.; Slauson, S. R.; O'Bien, J. M.; Tyson, E. L.; Marshall, A.-L.; Ottinger, C. E.; Chacon, J. G.; Wallace, L.; Paulino, C. Y.; Connell, S. *Org. Lett.* **2008**, *10*, 5111. (b) Yang, B.-L.; Weng, Z.-T.; Yang, S.-J.; Tian, S.-K. *Chem.—Eur. J.* **2010**, *16*, 718. (c) Cao, J.-J.; Zhou, F.; Zhou, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 4976. (d) Gao, M.; Yang, Y.; Wu, Y.-D.; Deng, C.; Shu, W.-M.; Zhang, D.-X.; Cao, L.-P.; She, N.-F.; Wu, A.-X. *Org. Lett.* **2010**, *12*, 4026. (e) Zhu, Y.-P.; Gao, Q.-H.; Lian, M.; Yuan, J. J.; Liu, M.-C.; Zhao, Q.; Yang, Y.; Wu, A.-X. *Chem. Commun.* **2011**, *47*, 12700. (f) Yang, Y.; Gao, M.; Shu, W.-M.; Wu, L.-M.; Zhang, D.-X.; Wu, A.-X. *Org. Biomol. Chem.* **2013**, *11*, 1226. (g) Chen, L.; Shi, T.-D.; Zhou, J. *Chem.— Asian J.* **2013**, *8*, 556.

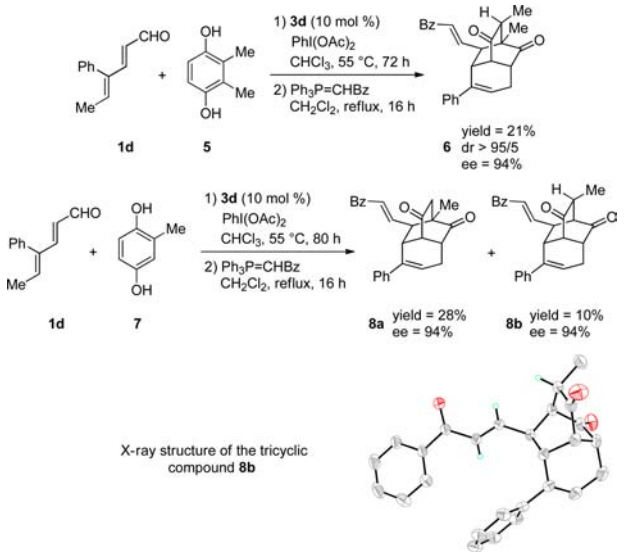
(19) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248.

(20) See Supporting Information for further details.

(21) For similar results in trienamine-mediated Diels–Alder, see: Jia, Z.-J.; Zhou, Q.; Zhou, Q.-Q.; Chen, P.-Q.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2011**, *50*, 8638.

In order to further highlight the applicability of the methodology, the reaction of **1b** and **2** was performed on gram scale providing access to **4b** in 40% yield (1.2 g) with identical enantiomeric excess (ee = 94%) as reported in Scheme 2. To lend further credence to the strategy merging dearomatization and asymmetric aminocatalysis, the synthetic sequence was extended to 2,3-dimethylhydroquinone **5** for which the corresponding benzoquinone is not commercially available (Scheme 3).[22]

Scheme 3. Application to Substituted Hydroquinones **5** and **7**

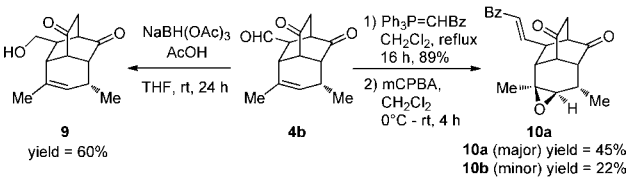


Treatment of dienal **1d** with 2,3-dimethylhydroquinone **5** under optimized conditions followed by chemoselective Wittig olefination gave rise to the desired tricyclic compound **6** that incorporates a quaternary stereogenic center in 21% overall yield with excellent stereocontrol. As shown in Scheme 3, the unsymmetrical methylhydroquinone **7** was also investigated, and **8a** and **8b** were respectively obtained in 28% and 10% yield. The relative configuration was assigned by X-ray analysis of the derivative **8b**.

Additional to providing a tricyclic architecture, compounds **4** contain a set of useful functional groups such as aldehyde, ketone, and alkene for further orthogonal transformations. Besides Wittig olefination of the aldehyde function as depicted in Scheme 3, chemoselective reduction

(22) 2,3-Dimethyl-1,4-benzoquinone is not commercially available in major chemical companies.

Scheme 4. Transformations of Products



of **4b** with 2.5 equiv of $NaBH(OAc)_3$ in the presence of acetic acid afforded the alcohol **9** in 60% yield (Scheme 4).

Functionalization of the alkene was carried out by masking the aldehydic function *via* Wittig reaction followed by epoxidation at room temperature for 4 h in the presence of *meta*-chloroperbenzoic acid. Under these conditions, the epoxides **10a** and **10b** were obtained in 67% yield as a separable mixture of two diastereoisomers for which stereochemistry has been determined by NOESY experiments.

In summary, we have developed a novel one-pot three-bond forming sequence from readily available planar substrates aiming at preparing functionalized tricyclic architectures with up to six contiguous stereogenic centers. A noteworthy feature of this transformation is the excellent level of stereoselectivity for the trienamine/enamine cascade reaction. In addition, the tricyclic target compounds include multiple orthogonal functionalities which can undergo various chemoselective transformations. In the future, the combination of polycyclic structures and high functional density brought by the substituents of the hydroquinone derivatives and dienals paves the way for applications in the synthesis of natural products, while the rapid and efficient construction of structural diversity and complexity offered by our strategy should find applications in Diversity Oriented Synthesis.

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Supporting Information Available. Experimental procedures and compound characterization data including NMR spectra and relevant HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.