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Chiral Phosphoric-Acid-Catalyzed Cascade Prins Cyclization

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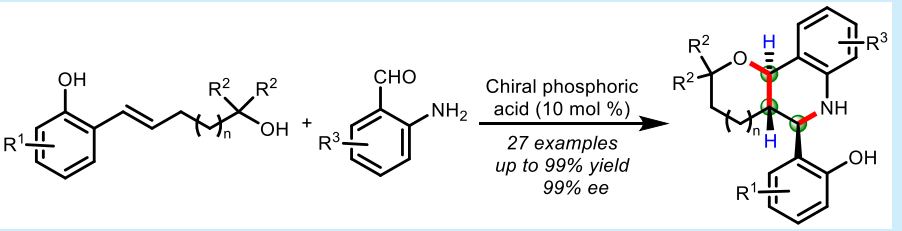
Supporting Information



ABSTRACT: Asymmetric Prins cyclization of in situ generated quinone methides and *o*-aminobenzaldehyde has been developed with chiral phosphoric acid as an efficient catalyst. This unconventional method provides a facile access to diverse functionalized trans-fused pyrano-/furo-tetrahydroquinoline derivatives in excellent yield and with excellent diastereo- and enantioselectivities (up to 99% yield and 99% ee). Mechanistic studies suggested that the three adjacent tertiary stereocenters were constructed through the sequential formation of C−O, C−C, and C−N bonds.

The Prins cyclization is an elegant method for the synthesis of various oxygenated heterocycles[1] and is a key reaction in many natural product syntheses.[2] Tremendous progress has been developed by using strong Brønsted acids or Lewis acids as catalysts.[3] However, the asymmetric variants of Prins cyclization have lagged far behind.[2,4,5] The reason may be due to the fact that it is difficult to control the carbenium intermediate. Lalli and van de Weghe developed the first asymmetric Prins cyclization, affording up to 60% ee by using a dual bis-phosphoric acid and a CuCl catalytic system.[4] Recently, List and coworkers developed a confined chiral imidodiphosphoric acid (IDP) for the asymmetric Prins reactions. Highly enantio-enriched *trans*-tetrahydrofurans were prepared by using a strong chiral acid with an extreme steric demand as the catalyst (Scheme 1a).[6] Moreover, employing the same catalyst, they reported the asymmetric synthesis of *trans*-tetrahydropyrans (THPs) with an *o*-quinone methide (*o*-QM) intermediate, probably via a [4 + 2] cycloaddition other than the previous Prins cyclization.[7] On the basis of previous research on the dearomative cycloaddition reaction involving *o*-QM intermediates,[8] together with our recent work[9] of vinylphenols/naphthols catalyzed by chiral phosphoric acids (CPAs), we envisioned that this asymmetric transformation could be improved if the substrate contains an electron-rich double bond enhanced by the *o*-hydroxyphenyl group, wherein a relative stable *o*-QM intermediate will be generated (Scheme 1b). Meanwhile, this may compensate for the weak acidity of CPA required for the Prins cyclization, and the selectivity could be promoted via the interaction between CPA and substrates/intermediates.

Chiral tetrahydroquinolines (THQs) are key nitrogen heterocyclic skeletons of many natural products and biologically active molecules.[10] Among them, ring-fused THQs are more unique and attractive because of their potential utilization in pharmaceuticals[11] as well as their enormous challenges in methodology, wherein three adjacent tertiary stereocenters are formed. To date, many catalytic systems have been developed through aza-Diels−Alder (DA) or Povarov reactions of imine intermediates and cycloolefins,[12] and a few asymmetric examples have been reported by Sundararajan,[13] Jacobsen,[14] Akiyama,[15] Feng,[16] Gong,[17] and Masson and Zhu.[18] Notably, only cis-fused THQs were obtained, resulting from the stereospecificity of the DA reaction.[19] To the best of our knowledge, there has been no facile access to corresponding chiral trans-fused THQ products. It remains a significant challenge to develop an unparalleled approach for trans-fused enantioenriched THQs.

We noted that an insightful investigation of the mechanism indicates that the diastereoselectivity (trans vs cis) of the Prins cyclization is dependent on the substrates and corresponding six-membered or five-membered transition states.[6b,20] Thus we assumed a one-pot cascade process to access trans-fused THQs: Trans-fused oxygenated heterocycles could be obtained in the Prins cyclization and then delivered to the chiral THQs

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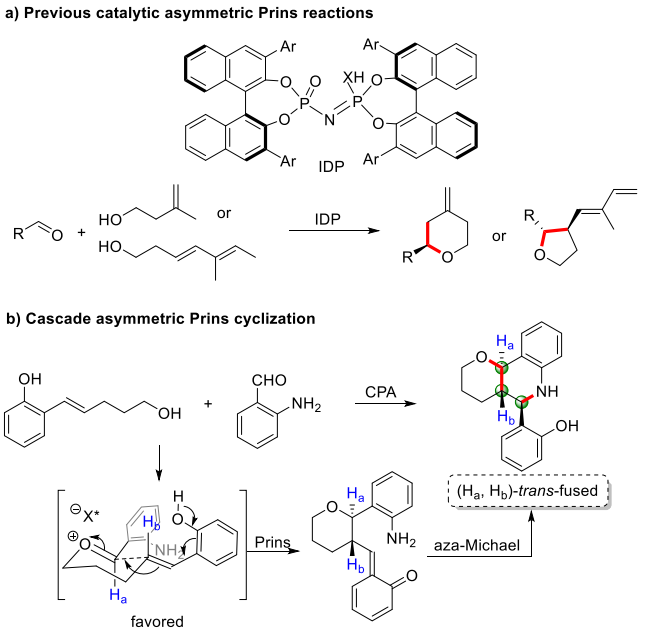
Scheme 1. Previous Asymmetric Prins Reactions and Cascade Prins Cyclization

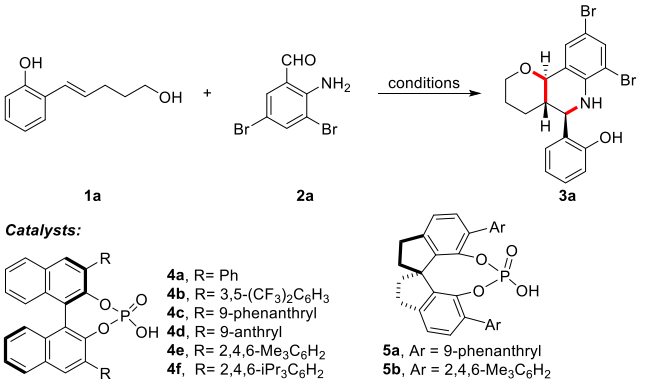


by sequential cyclization (Scheme 1b). The challenge associated with this hypothesis is the control of diastereo-/enantioselectivities in the Prins cyclization, which could be enabled by the design and utility of the advantaged six-membered transition state. Indeed, along with the formation of C−O, C−C, and C−N bonds, the trans-fused pyrano-/furo-THQ derivatives were obtained in excellent yield and with excellent diastereo- and enantioselectivities (up to 99% yield and 99% ee).

Considering the reactivity, hydroxyvinylphenol **1a** and 2-amino-3,5-dibromobenzaldehyde (**2a**) were chosen as the model substrates because the double bond in **1a** is more electronegative and the carbonyl group in **2a** is more electropositive. The initial result was consistent with our hypothesis. Trans-fused THQ **3a** was obtained as a single diastereoisomer in moderate yield (46%) by using 10 mol % diphenyl phosphate (**DPP**) as the catalyst in dichloromethane at room temperature. Encouraged by this result, we turned to screening of CPAs for the asymmetric transformation (Table 1). Simple BINOL-based CPA **4a** gave the desired product in low yield and with low ee (Table 1, entry 1), whereas the enantioselectivity and yield were obviously improved with bulky CPAs (Table 1, entries 2−6). To our delight, the key breakthrough was ultimately achieved when SPINOL-based CPA **5a** was employed (Table 1, entry 7). Excellent diastereoselectivity and enantioselectivity were observed, whereas the yield was still far from satisfying (entries 7 and 8). Then, a series of extensive surveys of solvents, substrate ratios, and temperatures was performed. It was found that the best result was given in 98% yield with 98% ee when adjusting the ratio of **1a**/**2a** to 1.2:1 at 40 °C for 24 h (Table 1, entry 15). Lower catalyst loading dramatically decreased the yield (Table 1, entry 16).

With the optimized conditions in hand, a series of substituted **1** was first examined (Scheme 2). In most reactions, both electron-donating groups and electron-withdrawing groups of **1** were well-tolerated, and the corresponding THQs were obtained in excellent yield (90−98%) and with

Table 1. Optimization of the Reaction Conditions[a]



entry	cat	solvent	T (°C)	t (h)	yield (%)[b]	ee (%)[c]
1	**4a**	CH_2Cl_2	rt	60	27	−21
2	**4b**	CH_2Cl_2	rt	60	37	−51
3	**4c**	CH_2Cl_2	rt	60	64	−58
4	**4d**	CH_2Cl_2	rt	60	49	−77
5	**4e**	CH_2Cl_2	rt	60	44	−81
6	**4f**	CH_2Cl_2	rt	60	52	−87
7	**5a**	CH_2Cl_2	rt	60	68	98
8	**5b**	CH_2Cl_2	rt	60	54	98
9	**5b**	DCE	rt	60	23	98
10	**5b**	toluene	rt	60	22	89
11	**5b**	MeCN	rt	60	11	45
12	**5b**	hexane	rt	60	4	53
13	**5b**	THF	rt	60	NA	NA
14[d]	**5b**	CH_2Cl_2	rt	48	93	98
15[d]	**5b**	CH_2Cl_2	40	24	98	98
16[d,e]	**5b**	CH_2Cl_2	40	36	37	98

[a]Reactions were carried out with **1a** (0.10 mmol), **2a** (0.12 mmol), and catalyst (10 mol %) in solvent (1.0 mL) under N_2. No other diastereoisomers were observed. [b]Isolated yield. [c]Determined by chiral HPLC. [d]0.12 mmol of **1a** and 0.10 mmol of **2a** were used. [e]5 mol % of **5b** was used.

excellent enantioselectivities (90−99% ee). Even the THQ **3g**, bearing a strong electron-withdrawing group, was obtained in 98% yield and with 98% ee. By contrast, the yields were obviously decreased when chloro (**3h**) and methyl (**3j**) were installed at the meta position of the phenyl ring. Notably, products containing multi halogens, such as **3b**, **3c**, **3d**, **3h**, and **3i**, were potential intermediates for the construction of more complex THQs via metal-catalyzed cross-coupling reactions. The difference in the reactivity of the halogens made these intermediates more diverse in synthesis. Furthermore, the challenging tertiary alcohol was investigated, which was more difficult for dehydration with aldehyde than primary alcohol. Compound **3k** was afforded in low yield (37%) but with excellent enantioselectivity (93% ee) under the standard conditions, and a 93% yield with 90% ee was obtained when the reaction was carried out at 60 °C. The absolute configuration of **3** was assigned on the basis of the X-ray crystallographic structure of ent-**3a**, **3b**, **3c**, **3d**, and **3g**.[21] To evaluate the practicality of this catalytic process, we carried out the scale-up reaction of **1a** and **2a**. As a result, the desired product **3a** was successfully obtained in 95% yield with 98% ee (Scheme 2).

Afterward, the derivatives of **2** were investigated (Scheme 3). For the 3-monosubstituted *o*-aminobenzaldehyde, different functional groups were well compatible in nearly quantitative

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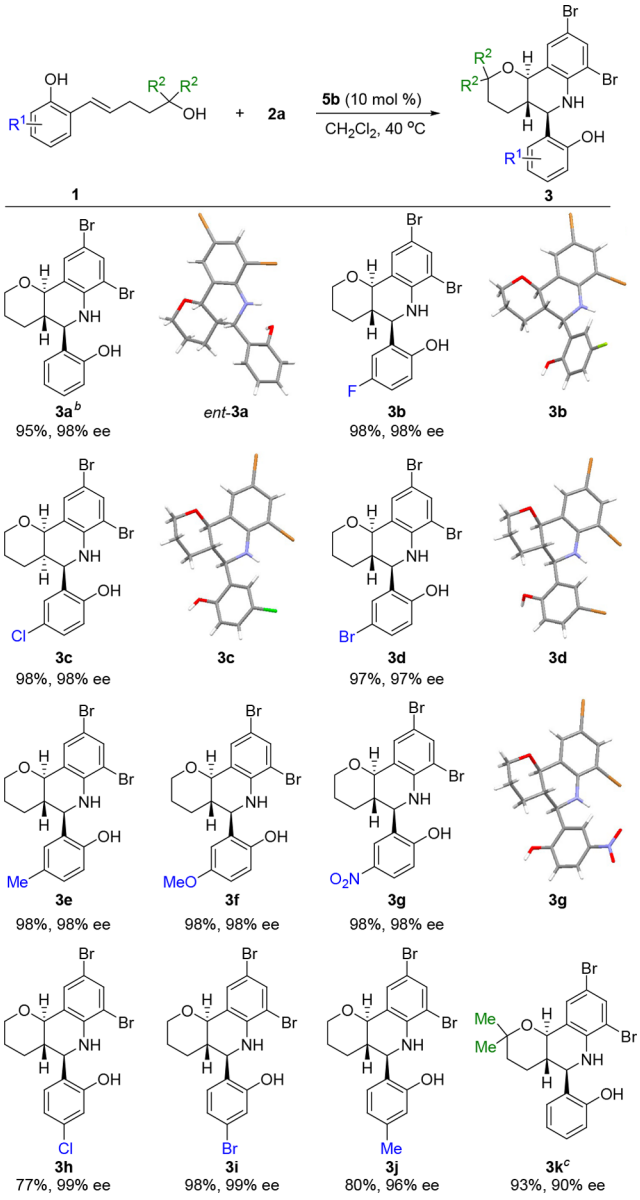
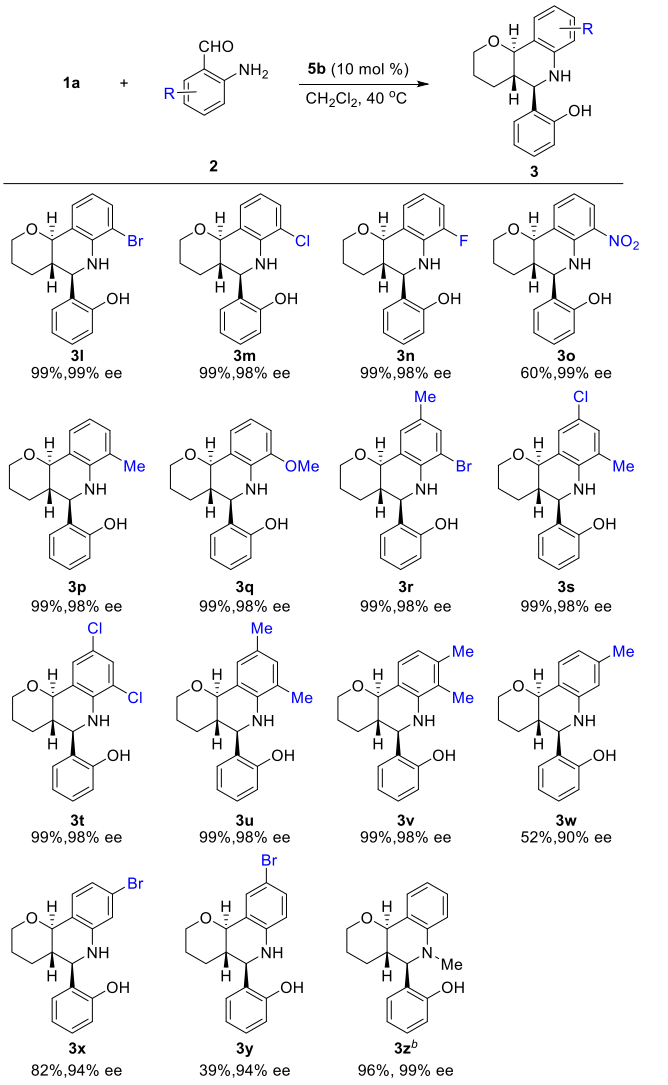
Scheme 2. Scope of 1a Derivatives[a]



[a]Reactions were carried out with **1** (0.12 mmol), **2a** (0.10 mmol), and **5b** (10 mol %) in CH_2Cl_2 (1.0 mL) under N_2 for 24 h. Yields refer to isolated products. [b]300 mg (1.08 mmol) of **2a** was used. [c]At 60 °C.

Scheme 3. Scope of 2a Derivatives[a]



[a]Reactions were carried out with **1a** (0.12 mmol), **2** (0.10 mmol), and **5b** (10 mol %) in CH_2Cl_2 (1.0 mL) under N_2 for 24 h. Yields refer to isolated products. [b]At 60 °C.

yield and with excellent enantioselectivities (all >98% ee), including bromo (**3l**), chloro (**3m**), fluoro (**3n**), methyl (**3p**), and methoxy (**3q**). The additional substituents on the five-position had no influence on the yields and enantioselectivities (**3r**–**u**). By contrast, the 3-nitro group (**3o**) led to excellent enantioselectivity (98% ee), albeit with a moderate yield. 4-Methyl *o*-aminobenzaldehyde afforded a lower yield and ee than 3,4-dimethyl *o*-aminobenzaldehyde (**3v** vs **3w**). For the further investigation, 4-bromo, 5-bromo, 6-bromo/-methyl, and unsubstituted *o*-aminobenzaldehyde were used as comparisons with 3-bromo *o*-aminobenzaldehyde. A slight decrease in the yield was observed for **3x**, but a dramatic decrease was observed for **3y**. No desired products were detected with 6-bromo/-methyl *o*-aminobenzaldehydes under the optimal conditions. The tremendous difference resulting from positions was probably due to the steric and electronic effects of substituents. In addition, *N*-methyl *o*-aminobenzaldehyde provided the target product **3z** in 96% yield and with 99% ee at 60 °C.

To gain insight into the mechanism, several control experiments were designed and carried out. Several derivatives of **1a** were subjected to the reaction under standard conditions. Methylation of the phenol of **1a** leads to no reaction, indicating that the process was possibly involved with *o*-QM intermediates (Scheme 4a). When a mixture of **1a** (*Z*/*E* 1:1) was used in the reaction under standard conditions, **3a** was obtained in 50% yield with 98% ee, and the *Z*-**1a** was recovered in nearly quantitative yield (Scheme 4b). This result was consistent with our hypothesis that the six-membered chair transition state from *Z*-**1a** was disfavored owing to the steric interactions with axial protons. Probably for the same reason, **5** was afforded moderate diastereoselectivity when **4** was used instead of **1a** (Scheme 4c). In addition, the treatment of excess **1** (2.4 equiv) with 4-cyanobenzaldehyde **2aa** returned product **6** in good yield, the structure of which was further determined by the X-ray analysis of its derivative **7d** (Scheme 4d).[21]

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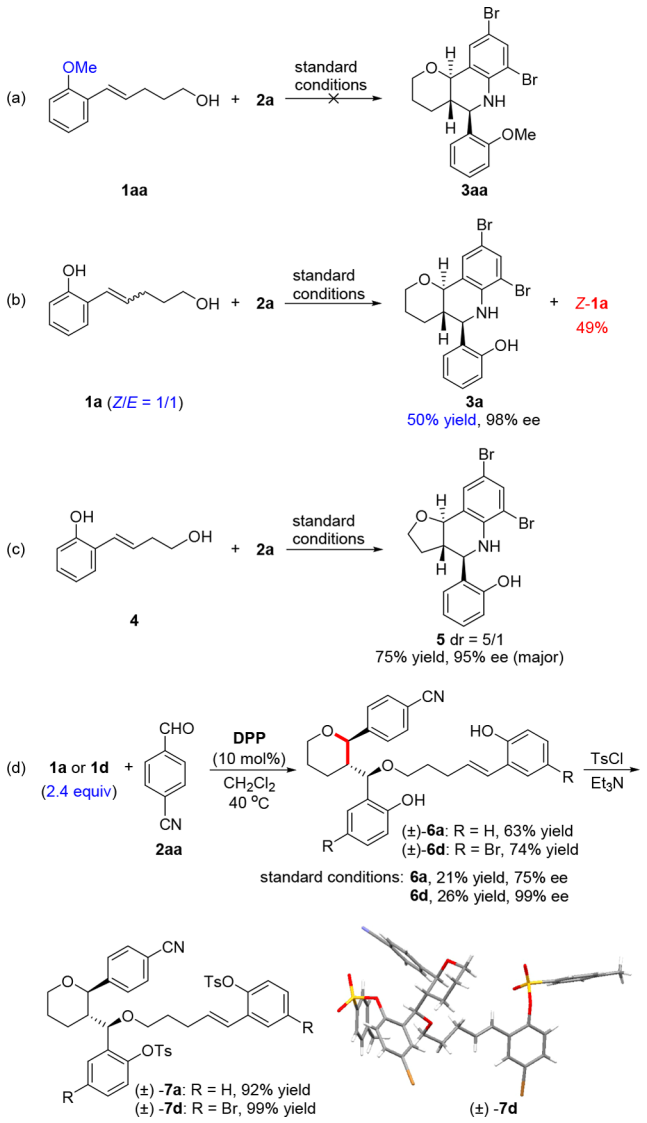
Scheme 4. Control Experiments



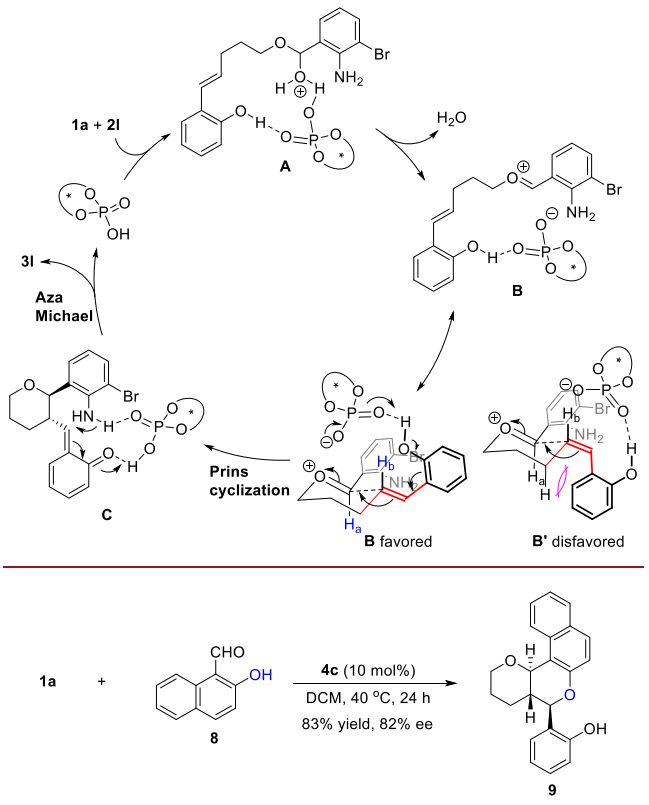
Moreover, enantioenriched **6a** and **6d** were obtained with good to excellent enantioselectivities under the optimal reaction conditions, albeit in lower yield. The capture of product **6** supported the stepwise pathway involved in the Prins cyclization.

Therefore, a plausible mechanism is proposed in Scheme 5. At the beginning, complex **A** is generated via the acid-catalyzed addition of hydroxyl to aldehyde **2l**; subsequently, the release of water forms an oxocarbenium ion **B** through the interaction with CPA. Then, the asymmetric Prins cyclization occurs via the dearomatization of phenol through the favored six-membered chair transition state, wherein H_a and H_b are located at the axial position. The disfavored transition state **B′** will be generated if *Z*-**1** is used in this reaction. Finally an aza-Michael reaction of intermediate **C** will afford the desired trans-fused **3l** and complete the catalytic cycle.

We have also attempted to apply the protocol in the reaction with salicylaldehyde derivative **8**, and preliminary studies have showed that the desired product **9** can be prepared in good yield and with excellent ee.

In summary, we reported an unprecedented example of a chiral phosphoric-acid-catalyzed asymmetric Prins cyclization

Scheme 5. Proposed Mechanism



reaction involving *o*-QM intermediates. As we expected, the Prins reaction probably proceeded through a favored six-membered chair transition state with low energy. The trans-fused THQ derivatives bearing three adjacent tertiary stereocenters were prepared in excellent yield and with excellent diastereo-/enantioselectivities through cascade Prins cyclizations and the aza-Michael reaction. Control experiments suggested that the dearomatization of phenol plays an important role in the transformation. Further investigations into the mechanism, development, and application of such cascade reactions are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02714.

Experimental details and spectroscopic and analytical data for new compounds (PDF)

Accession Codes

CCDC 1937551, 1937553−1937555, 1937717, and 1938892 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(21) See the Supporting Information.

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