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Enantioselective Dehydrative γ-Arylation of α-Indolyl Propargylic Alcohols with Phenols: Access to Chiral Tetrasubstituted Allenes and Naphthopyrans

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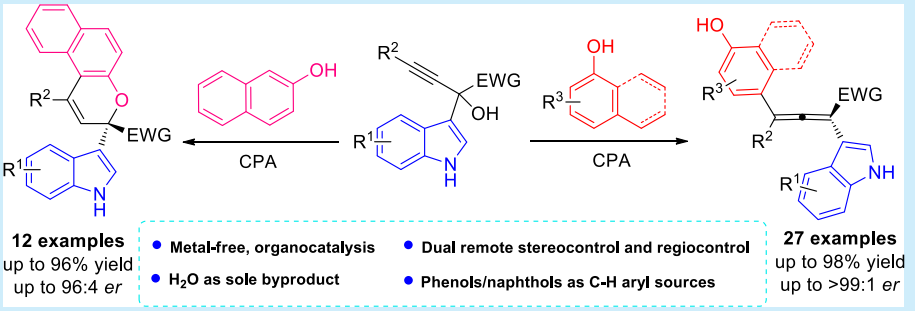

ABSTRACT: Herein, we report an enantioselective dehydrative γ-arylation of α-indolyl propargylic alcohols with phenols via organocatalysis, which provides efficient access to chiral tetrasubstituted allenes and naphthopyrans in high yields with excellent regio- and enantioselectivities under mild conditions. This method features the use of cheaply available naphthols/phenols as the C−H aryl source and liberating water as the sole byproduct. Control experiments suggest that the excellent enantioselectivity and remote regioselectivity stem from dual hydrogen-bonding interaction with the chiral phosphoric acid catalyst.

Axially chiral allenes are prevalent in many natural products, functional materials, and bioactive molecules and are used as chiral auxiliaries, ligands, and organocatalysts in asymmetric synthesis.[1] Moreover, allenes also serve as versatile synthons in various chemical transformations in organic synthesis.[2] Consequently, optically active allenes have long been recognized as attractive targets for synthetic chemists, and various elegant strategies have been developed,[3] which include central-to-axial chirality transfer,[4] kinetic resolution of racemic allenes,[5] and metal[6] and organocatalytic[7] asymmetric synthesis. However, most of these methods are focused on the synthesis of chiral 1,3-disubstituted or 1,1,3-trisubstituted allenes. In contrast, the synthesis of chiral tetrasubstituted allenes,[8] particularly (hetero)aryl-substituted allenes from readily available starting materials, remains challenging and has less been reported.

Propargylic alcohols and derivatives have been considered as ideal precursors for the construction of chiral allenes, including tetrasubstituted ones. The most classical approach to accessing chiral tetrasubstituted allenes relies on stereospecific formal S_N2' substitutions or sigmatropic rearrangements from enantiopure propargylic precursors catalyzed by metal catalysts.[3] In contrast, catalytic asymmetric synthesis of tetrasubstituted allenes from racemic propargylic precursors, especially propargylic alcohol, is undoubtedly more attractive but also more challenging. In 2017, the group of Sun has reported the organocatalytic synthesis of chiral tetrasubstituted allenes from racemic propargylic alcohols, which mechanistically involves asymmetric trapping of intermediate propargylic cations with nucleophilic β-diketones or thioacetic acid.[8g,h] More recently, Ma and co-workers have elegantly realized the efficient catalytic asymmetric formation of tetrasubstituted 2,3-allenoic acids from racemic propargylic alcohols via Pd-catalyzed kinetic resolution.[8c] Despite these advances, it is still desirable to develop new methods for synthesizing structurally diverse chiral tetrasubstituted allenes.

One the other hand, given the significance of chiral tetrasubstituted allenes bearing aryl substituents, a great deal of effort has been devoted to the asymmetric construction of these skeletons based on the arylative transformation of various propargylic precursors. In this context, the groups of Aggarwal[8a] and Studer[8b] have developed metal-catalyzed

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stereospecific synthesis of tetrasubstituted allenes via γ-arylation of enantioenriched propargylic boronic esters and carboxylic acids, respectively (Scheme 1a). However, this strategy suffers from the requirement of prefunctional starting materials and pre-established central chirality, which limits its application. Moreover, C−H functionalization reactions provide a straightforward approach for the facile transformation of readily available hydrocarbons.[9] In this regard, the groups of Ma,[9a,d] Glorius,[9b] and Sundararaju[9c] have reported the metal-catalyzed C−H bond allenylation of (hetero)arenes with propargylic precursors, affording tetrasubstituted allenes through a concerted metalation/deprotonation (CMD) process (Scheme 1b). Despite significant advances, these C−H allenylation reactions mainly furnish racemic tetrasubstituted allenic compounds, and the catalytic enantioselective version of such a transformation remains less explored. In addition, the covalent installation and removal of special directing groups were generally required.

Inspired by these pioneering studies and the recent progress on phenol-directed C−H functionalization reactions,[10] we envisioned that phenols might be directly used as the aryl sources to react with propargylic alcohols, thereby providing the possibility of developing a direct enantioselective dehydrative arylation strategy for the construction of chiral tetrasubstituted allenes (Scheme 1c). However, several challenges need to be considered: (1) overcoming the C/O chemoselectivity of the phenols, (2) obtaining high regioselectivity between the *ortho* and *para* positions of phenols, (3) achieving high regioselectivity at the C3 position versus the C1 position of propargylic alcohols, and (4) choosing an appropriate chiral catalytic system to efficiently control the chemo-, regio-, and enantioselectivities mentioned above. As a continuation of our interest in asymmetric organocatalysis,[11] we envisioned that synergistic hydrogen-bonding activation of both the phenols and the propargylic alcohols could address those challenges, thereby allowing the straightforward synthesis of chiral fully substituted allenes through an organocatalytic dehydrative C−H bond allenylation approach.[12]

To verify the feasibility of our hypothesis, α-indolyl-α-trifluoromethyl propargylic alcohol **1a** and 1-naphthol **2a** were chosen as the model substrates using chiral phosphoric acids as the catalysts (Table 1). Propargylic alcohol **1a** was chosen as the substrate due to their hydrogen-bonding interaction property of the indole moiety with the phosphoric acid catalyst.[13] Meanwhile, to the best of our knowledge, the formed chiral tetrasubstituted allenes bearing privileged indole and CF_3 moieties cannot be easily acquired by conventional methods[9b,14] and have not been accessed, which might open up opportunities for further bioactivity studies.[15] To our delight, when (*S*)-**A1** was employed as the catalyst, the reactions proceeded smoothly and afforded allene **3a** in 90% yield with 76:22 er (Table 1, entry 1). Remarkably, the C−H allenylation occurs at the *para* position rather than the *ortho* position of 1-naphthol. To improve the stereoselectivity, a series of chiral phosphoric acid catalysts were then examined (Table 1, entries 2−9). Fortunately, we found the spirocyclic phosphoric acid catalyst (*R*)-**B3** gave the best yield (96%) and enantioselectivity (97:3 er) (Table 1, entry 9). Next, the solvent effect was investigated, and a significant solvent effect

Scheme 1. Synthesis of (Chiral) Tetrasubstituted Allenes via γ-Arylation of Propargylic Compounds

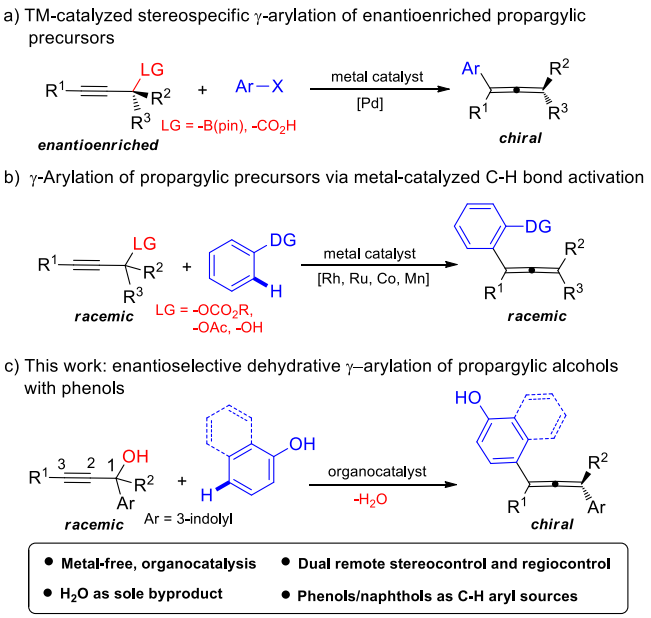
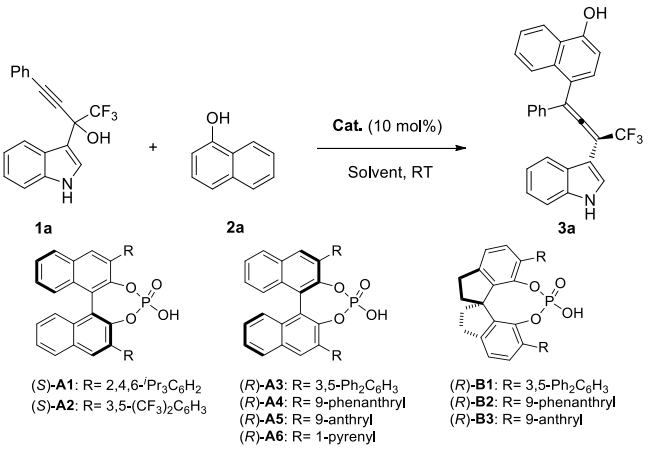


Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	time (h)	yield[b] (%)	er[c] (%)
1	(*S*)-**A1**	DCM	96	90	76:22
2	(*S*)-**A2**	DCM	12	96	60:40
3	(*R*)-**A3**	DCM	48	93	23:77
4	(*R*)-**A4**	DCM	72	93	37:63
5	(*R*)-**A5**	DCM	36	95	20:80
6	(*R*)-**A6**	DCM	48	94	23:77
7	(*R*)-**B1**	DCM	40	95	88:12
8	(*R*)-**B2**	DCM	32	86	95:5
9	(*R*)-**B3**	DCM	32	96	97:3
10	(*R*)-**B3**	DCE	72	93	97:3
11	(*R*)-**B3**	$CHCl_3$	72	93	96:4
12	(*R*)-**B3**	toluene	32	95	97:3
13	(*R*)-**B3**	THF	NR	–	–
14[d]	(*R*)-**B3**	DCM	28	96	98:2
15[d,e]	(*R*)-**B3**	DCM	56	96	>99:1

[a]Unless otherwise specified, all reactions were carried out with a catalyst (10 mol %), **1a** (0.10 mmol), and **2a** (0.12 mmol) in the indicated solvent (2.0 mL) at room temperature. [b]Isolated yield of **3a**. [c]Determined by chiral-phase HPLC analysis. [d]With 50 mg of 4 Å molecular sieves. [e]Reaction carried out at 0 °C.

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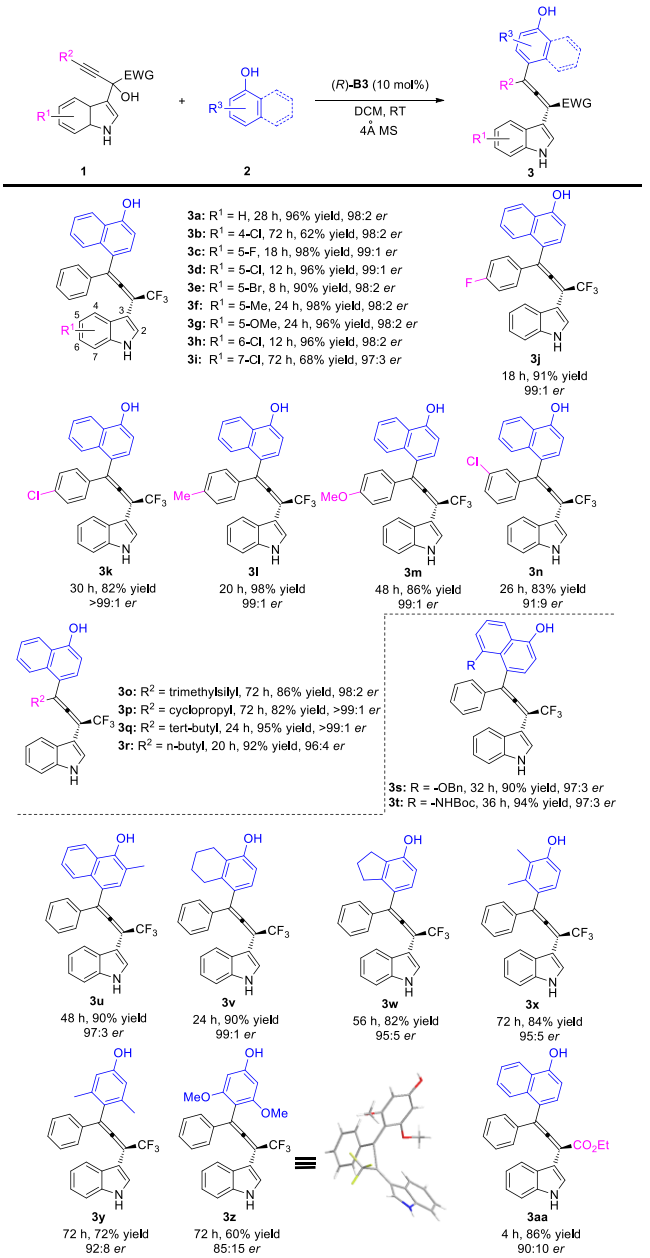
was observed (Table 1, entries 9−13). Compared with other solvents, such as 1,2-dichloroethane, chloroform, and toluene, DCM was the best choice for this reaction (Table 1, entry 9). When using THF as the solvent, the reaction could not take place (Table 1, entry 13). A higher enantioselectivity (98:2 er) was observed when 50 mg of 4 Å molecular sieves was added (Table 1, entry 14). When the reaction temperature was decreased to 0 °C with a prolonged reaction time, excellent enantioselectivity (>99:1 er) was achieved (Table 1, entry 15).

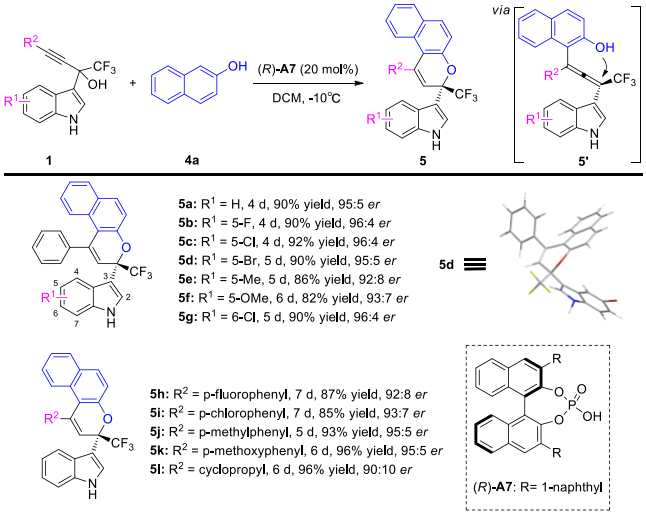
With optimal reaction conditions established (Table 1, entry 14), we next explored the scope of this reaction (Schemes 2 and 3). As illustrated in Scheme 2, we first investigated the substrate scope with respect to α-indolyl propargylic alcohols.

Scheme 2. Substrate Scope for the Synthesis of Chiral Tetrasubstituted Allenes[a]



[a]All reactions were carried out with (*R*)-**B3** (10 mol %), **1** (0.10 mmol), **2** (0.12 mmol), and 4 Å molecular sieves (50 mg), in DCM (2.0 mL) at room temperature. The isolated yield was determined after column chromatography. The er value was determined by chiral-phase HPLC analysis.

Scheme 3. Substrate Scope for the Synthesis of Naphthopyrans[a]



[a]All reactions were carried out with (*R*)-**A7** (20 mol %), **1** (0.05 mmol), and **4** (0.05 mmol) in DCM (0.5 mL) at −10 °C. The isolated yield was determined after column chromatography. The er value was determined by chiral-phase HPLC analysis.

The positions or electronic nature of the substituent on the indole ring appeared to have limited effects on the enantioselectivities, and the corresponding chiral tetrasubstituted allenes were afforded with 97:3−99:1 er (**3a**−**3i**). However, lower yields were observed for substrates bearing substituents at the C4 or C7 positions of the indole ring (**3b** and **3i**), probably due to the steric hindrance. Next, different substituents, including methyl, methoxyl, and halogens, on the phenyl ring of R^2 were all compatible, giving **3j**−**3n** in 82−98% yields with excellent stereocontrol. In addition, the R^2 group could be alkyl groups such as trimethylsilyl, cyclopropyl, *tert*-butyl, and *n*-butyl groups, delivering the corresponding products without significant effects on the results (**3o**−**3r**, 82−95% yields, 96:4 − >99:1 er). Moreover, α-naphthols bearing substituents could undergo effective transformations to furnish allenes **3s**−**3u** in high yields with excellent er. Subsequently, the generality and limitations of this method were further evaluated by changing from α-naphthols to less nucleophilic phenols. Electron-neutral and electron-rich phenols proved to be suitable aryl sources. Of note, 2,3-disubstituted phenols gave the desired products with yields and enantioselectivities that were better than those of 3,5-disubstituted phenols (**3v**−**3x**, 82−90% yields, 95:5−99:1 er; **3y** and **3z**, 60−72% yields, 85:15−92:8 er). In addition, when α-ester-substituted propargylic alcohol was subjected to the reaction, corresponding allene **3aa** was obtained in 86% yield with 90:10 er. The absolute configurations of allenes **3** were assigned by analogy to that of the literature,[12] and that of **3z** was determined unambiguously by X-ray crystallographic analysis.[16]

During the investigation of the γ-arylation reaction of α-indolyl propargylic alcohol **1** with 2-naphthol **4a** as the nucleophile, it was interesting to obtain an unexpected product naphthopyran **5a** (86% yield, 44:66 er, under the standard

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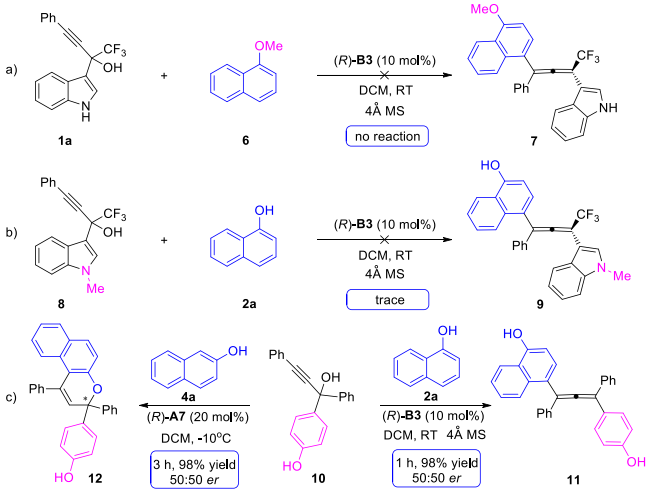
conditions in Scheme 2), which was probably formed through the intramolecular cyclization of allene intermediate **5′** (Scheme 3). It should be mentioned that the naphthopyran skeleton bearing a tetrasubstituted stereogenic center at the C3 position is a privileged heterocyclic structure present in many biologically active molecules and photochromic materials.[17] Encouraged by this fascinating result, we next turned our attention to improving the enantioselectivity of this reaction. After optimization of the reaction conditions (see the Supporting Information), naphthopyran **5a** could be afforded in 90% yield and 95:5 er when the reaction was performed at −10 °C with chiral phosphoric acid (*R*)-**A7** as the catalyst (Schemes 3 and 5a). Next, the scope of α-indolyl propargylic alcohols was explored with 2-naphthol **4a** as the nucleophile. As shown in Scheme 3, various α-indolyl propargylic alcohols **1** with electron-donating groups (-Me and -OMe) or electron-withdrawing groups (-F, -Cl, and -Br) at the 5 position of the indole ring produced the naphthopyrans in 82−92% yields with 92:8−96:4 er. Moreover, chloro substituents on the 5 or 6 position of the indole ring also did not obviously affect the reaction outcomes. In addition, various substituents, including *p*-fluorophenyl, *p*-chlorophenyl, *p*-methylphenyl, and *p*-methoxyphenyl, at R^2 were quite compatible, giving **5h**−**5k** in 85−96% yields with high enantioselectivities. R^2 could also be alkyl groups, such as the cyclopropyl group, efficiently producing corresponding product **5l** (96% yield, 90:10 er). The absolute stereochemistry of naphthopyrans **5** was assigned by analogy to that of **5d**, which was determined by X-ray crystallographic analysis[16] and comparison of the electronic circular dichroism (ECD) spectrum of **5d** and its calculated enantiomeric counterpart (for details, see the Supporting Information).

To explore the origins of the excellent stereocontrol and regiocontrol in this catalytic system, several control experiments were carried out (Scheme 4). When 1-methoxynaphthalene **6** was subjected to the standard conditions, desired product **7** was not observed and **1a** has only low conversion (Scheme 4a). Similarly, *N*-methyl-protected substrate **8** led to a trace amount of allene **9** (Scheme 4b). These results implied that the free OH and NH groups might simultaneously interact with the chiral phosphoric acid catalysts via dual hydrogen-bonding interactions. Moreover, when the indole moiety of the substrate is switched to the *p*-hydroxyphenyl group, substrate **10** could react smoothly with 1-naphthol and 2-naphthol under the standard conditions, delivering corresponding products **11** and **12** in racemic form, albeit with excellent yields. Although propargylic alcohol **10** has been successfully employed as a substrate by Sun and co-workers in the synthesis of chiral tetrasubstituted allenes,[8g] it is not applicable to the current γ-arylation transformation, suggesting that the α-indolyl moiety of the propargylic alcohol is crucial for the stereocontrol of this transformation.

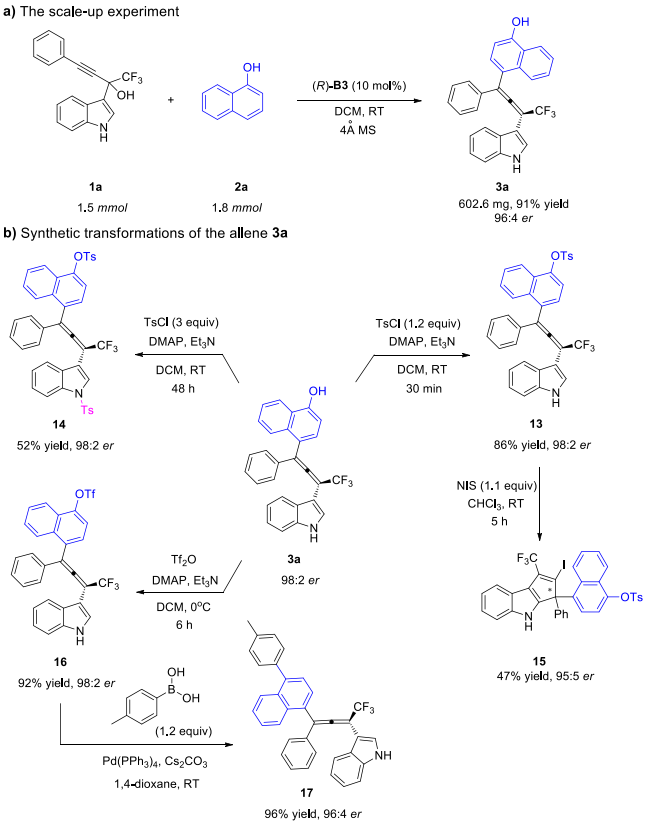
Under standard reaction conditions, a scale-up experiment (Scheme 5a) was carried out and **3a** could be obtained without obviously sacrificing the yield or enantioselectivity. Furthermore, to explore the utility of the products, we carried out the derivatization of product **3a** (Scheme 5). The hydroxy group and the amino group of **3a** could be selectively or simultaneously transformed into triflate or *p*-toluenesulfonic acid ester in good yield and without a loss of enantiomeric purity, which provides possibilities for further functionalization. The cyclization of **3a** to 2-iodine-3,4-dihydrocyclopenta-[*b*]-indole **15** was successfully realized in the presence of NIS. In addition, a possible reaction mechanism was proposed for this reaction as shown in the Supporting Information.

In conclusion, we have developed the enantioselective dehydrative γ-arylation of propargylic alcohols with phenols/naphthols catalyzed by chiral phosphoric acids. A wide range of tetrasubstituted allenes and naphthopyrans were afforded in high yields with excellent enantioselectivities (39 examples, ≤98% yield and >99:1 er) under mild reaction conditions. It is noteworthy that the incorporation of an α-indolyl moiety into

Scheme 4. Control Experiments



Scheme 5. Scale-up Experiment and Synthetic Transformations of Allene 3a



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propargylic alcohol substrates is the key to the success of this protocol, which allows readily available phenols to be used as the C−H aryl source, and enables dual remote functionalization of two reaction components. Further synthetic applications of this strategy are ongoing in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02386.

Full experimental procedures, spectroscopic characterizations, and NMR and HPLC spectra (PDF)

Accession Codes

CCDC 2010785 and 2010790 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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Notes

The authors declare no competing financial interest.

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