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Directing Group Assisted Nucleophilic Substitution of Propargylic Alcohols via *o*-Quinone Methide Intermediates: Brønsted Acid Catalyzed, Highly Enantio- and Diastereoselective Synthesis of 7-Alkynyl-12a-acetamido-Substituted Benzoxanthenes

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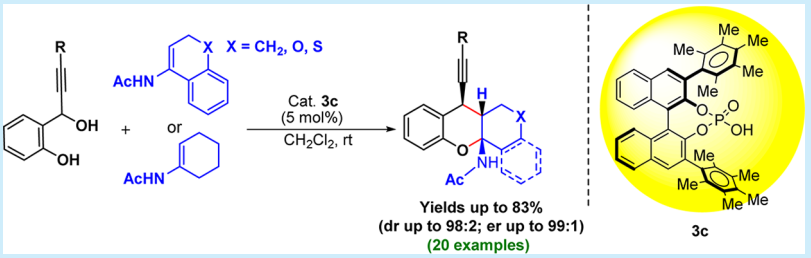
Supporting Information



ABSTRACT: BINOL-based, chiral phosphoric acids catalyze the substitution of 1-(*o*-hydroxyphenyl)propargylic alcohols with enamides to furnish 7-alkynyl-12a-acetamido-substituted benzo[*c*]xanthenes and related heterocycles in a one-pot operation with excellent diastereo- and enantioselectivity. Ambient reaction temperature, operationally simple reaction conditions, low catalyst loading, high yields, and excellent stereocontrol are attractive features of this process and make it a highly practical and versatile transformation.

Studies on the direct nucleophilic displacement of the hydroxyl group in propargylic alcohols are currently among the prime objectives in organic synthesis.[1] The highly versatile nature of the alkyne moiety makes such reactions highly attractive in organic synthesis. Fully or semisaturated products are easily obtained by catalytic hydrogenation, and various other functional groups are readily accessible by a range of known transformations of the alkynyl group.[2]

Accordingly, transition-metal-catalyzed propargylic substitution reactions have attracted a great deal of attention recently.[3] Gold-, ruthenium-, and copper-catalyzed processes have been disclosed by the groups of Campagne,[4] Toste,[5] Sheppard,[6] Nishibayashi,[7] Alexakis, and others, respectively.[8] In addition, Nishibayashi et al. have disclosed powerful ruthenium- and copper-catalyzed enantioselective alkylation and amination reactions of propargylic alcohols and derivatives thereof.[9] They have also developed cooperative ruthenium−prolinol ether- and ruthenium−copper-catalyzed asymmetric reactions of propargylic alcohols and esters.[10] Recently, Hu[11] and van Maarseeven[12] and co-workers have reported various copper-catalyzed, enantioselective substitution reactions of propargylic acetates as well. Nevertheless, there is a great demand for novel, enantioselective propargylic substitution reactions that are applicable to a broad substrate range.

Recently, our group has developed a series of highly efficient Brønsted acid catalyzed, enantioselective substitution reactions of *o*-hydroxybenzhydryl alcohols employing 1,3-dicarbonyl compounds, enamides, indoles, and naphthols as nucleophiles.[13] Pursuing this strategy, we have successfully established one-pot and high-yielding syntheses of various chromene- and xanthene-based oxygen heterocycles as well as triarylmethanes with excellent stereocontrol. These transformations proceeded through in situ generated *o*-quinone methides (*o*-QM) activated through the hydrogen-bonded chiral phosphoric acid catalyst.[14] *o*-QMs are highly reactive 1-oxabutadienes which have frequently been employed in the synthesis of natural products and bioactive molecules.[15] However, the transient nature of *o*-QM principally poses challenges to synthetic applications, and it was only recently that a range of catalytic, enantioselective processes have been successfully developed for *o*-QM chemistry including palladium, cinchona alkaloid, BINOL, Brønsted acid, and NHC catalyzed reactions.[16]

We report herein the Brønsted acid catalyzed, highly enantioselective substitution of 1-(*o*-hydroxyphenyl)propargylic alcohols **1** with enamides **2** which upon subsequent *N,O*-acetalization generate highly functionalized 7-alkynyl-12a-acetamido-substituted benzo[*c*]xanthenes **4** and related heterocycles carrying three contiguous chiral centers. The products were obtained in good yield and excellent diastereo- and enantioselectivity in a one-pot operation (Scheme 1b). The *o*-hydroxy group within **1** helps to form the highly reactive *o*-QM, which readily adds the enamide nucleophile in a conjugate

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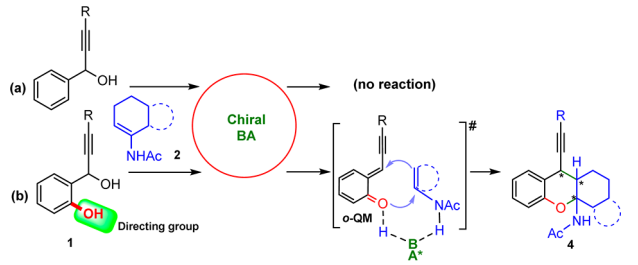
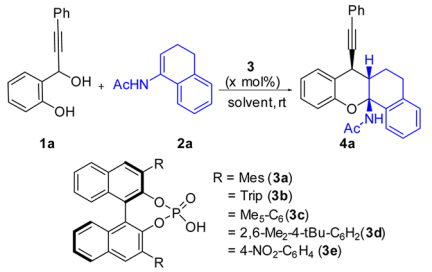
Scheme 1. Brønsted Acid Catalyzed Reaction of Propargylic Alcohols (A) without and (B) with Directing Group via *o*-QM



addition event. Accordingly, substrates lacking this *o*-hydroxy group or carrying a protected *o*-hydroxy group (e.g., OMe) do not react under these conditions (Scheme 1a).

We initiated our studies by investigating the reaction of 1-(*o*-hydroxyphenyl)-3-phenylpropargylic alcohol (**1a**) (1 equiv) with enamide **2a** (1 equiv) in CH_2Cl_2 in the presence of various chiral phosphoric acids **3a–e** (5 mol %) (Table 1). 7-Alkynyl-

Table 1. Optimization Studies[a–d]



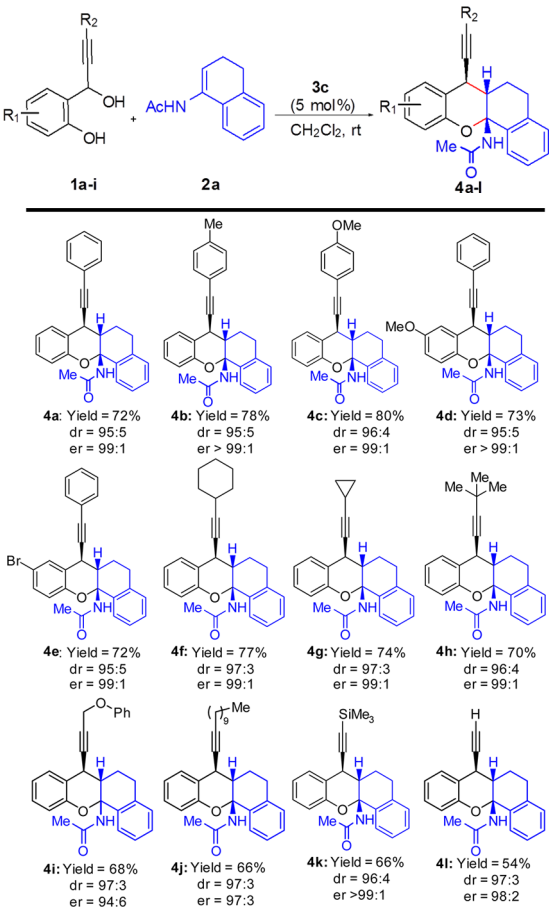
entry	cat.	solvent	time (h)	% yield[b]	dr[c]	er[d]
1	**3a**	CH_2Cl_2	8	64	>95:5	96:4
2	**3b**	CH_2Cl_2	16	50[c]	>95:5	99:1
3	**3c**	CH_2Cl_2	8	**72**	**>95:5**	**99:1**
4	**3d**	CH_2Cl_2	8	70	>95:5	98:2
5	**3e**	CH_2Cl_2	16	57	96:4	90:10

[a]All reactions were carried out with 0.23 mmol (1 equiv) of **1**, 0.23 mmol (1.0 equiv) of enamide **2a**, and 5 mol % of catalyst **3a–e** in 2 mL of CH_2Cl_2 at rt for 8–16 h. [b]Isolated yield of the product. [c]dr was determined through ^{1}H NMR analysis of the crude reaction mixture. [d]er was determined through chiral HPLC analysis (see the Supporting Information).

12a-acetamido-substituted benzo[*c*]xanthene **4a** was obtained as largely a single diastereomer in good to moderate yields in almost all cases studied within 8–16 h at room temperature. The results further revealed that *ortho*-disubstitution within the 3,3′-aryl substituents in the BINOL backbone of the Brønsted acid catalyst gave superior enantioselectivities. For example, with phosphoric acids **3a** and **3b** carrying mesityl and 2,4,6-triisopropyl phenyl groups as 3,3′-substituents, the product was obtained with excellent selectivity but only moderate yield (entries 1 and 2). Phosphoric acid **3d** gave rise to an improved yield while maintaining the excellent enantioselectivity observed before (entry 4). Phosphoric acid catalyst **3c** with pentamethylated 3,3′-phenyl groups was found to be the optimal catalyst for this reaction, which gave the highest enantioselectivity of 99:1 er in combination with excellent diastereoselectivity of >95:5 and good product yield of 72% (entry 3). Neither yield nor stereoselectivity of the reaction were affected through the use of molecular sieves.

To assess the applicability of this process, various 1-(*o*-hydroxyphenyl)propargylic alcohols **1a–l** were subsequently reacted with enamide **2a** under the above-optimized reaction conditions, and the results are summarized in Table 2. In all

Table 2. Substrate Scope[a–d]



[a]All reactions were carried out with 0.42 mmol (1 equiv) of **1**, 0.42 mmol (1.0 equiv) of enamide **2a**, and 5 mol % of catalyst **3c** in 4 mL of CH_2Cl_2 at rt for 8–36 h. [b]Isolated yield of the purified product. [c]dr was determined by ^{1}H NMR analysis of the crude reaction mixture. [d]er was determined through chiral HPLC analysis (see the Supporting Information).

cases studied, the reaction proceeded smoothly and was typically completed within 8–36 h at rt. Inspection of Table 2 reveals that the products were obtained typically in good yield and excellent diastereo- and enantioselectivity, irrespective of the substitution pattern within the alkynyl or the aryl group. A broad range of internal alkynes with various substituents like aromatic, carbocyclic, ethers, aliphatic, long-chain aliphatic, and TMS moieties were readily tolerated, delivering the products with excellent results as well. Even a terminal alkyne withstood the reaction conditions and furnished the desired product **4l** in moderate yield but with excellent diastereo- and enantioselectivity. A crystal structure of **4e** (Table 2) and **7** (Table 3) revealed the absolute configuration which was assigned to all other products as well (see the SI for details).[17]

In order to further broaden the scope of this reaction with respect to the enamide component, we employed some more carbocyclic as well as heterocyclic enamides in this process, all

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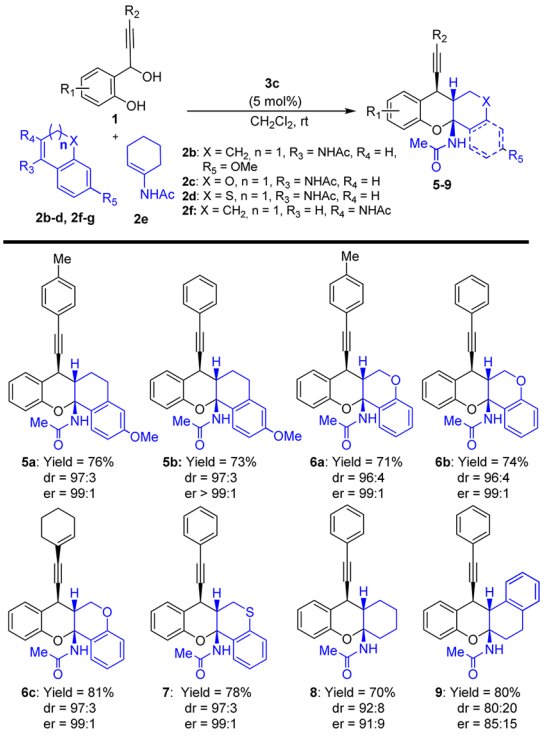
Table 3. Substrate Scope[a–d]



[a]All reactions were carried out with 0.42 mmol (1.0 equiv) of **1**, 0.42 mmol (1.0 equiv) of enamides **2b–f**, and 5 mol % of catalyst **3c** in 4 mL of CH_2Cl_2 at rt for 8–36 h. [b]Isolated yield of the purified product. [c]dr was determined by ^1H NMR analysis of the crude reaction mixture. [d]er was determined through chiral HPL analysis (see the Supporting Information).

of which delivered the desired products in good yield and excellent selectivity (Table 3).

Quite interestingly, using chromene- and thiochromene-based enamides **2c** and **2d** as nucleophiles furnished the corresponding alkynyl-substituted chromeno[4,3-*b*]chromenes **6a–c** and thiochromeno[4,3-*b*]chromene **7**, respectively, in good yield, exceptional diastereo- and enantiocontrol. Enamide **2e**, lacking the annulated aromatic ring, also conferred the addition product **8** in good yield, diastereoselectivity, and 88:12 er. With regioisomeric enamide **2f** as substrate, alkynylated benzo[*a*]xanthene **9** was successfully obtained, albeit with decreased selectivity. Acyclic enamides, however, currently give rise to only low enantioselectivity.[18]

The excellent results obtained with enamides **2a–f** encouraged us to further investigate *N*-acetylated enaminone **11** as a nucleophile. Under the optimized conditions, **11** underwent nucleophilc substitution with propargylic alcohols **1a** and **1h** followed by *N,O*-acetalization to yield the desired products **11a** and **11b**, respectively, in good yield and moderate selectivity (Scheme 2).

To further reveal the synthetic potential of this new process, some of the products were subsequently subjected to catalytic hydrogenation using 10% Pd/C to furnish 7-alkyl-12a-acetamido-substituted tetrahydrobenzo[*c*]xanthenes **12a–f** with facility (Table 4). This strategy offers an excellent method of accessing these products which otherwise would be inaccessible.

In summary, we have developed a highly enantioselective, Brønsted acid catalyzed propargylic alkylation of 1-(*o*-hydroxyphenyl)propargylic alcohols with enamides, a process

Scheme 2. Enaminone 10 as Nucleophile

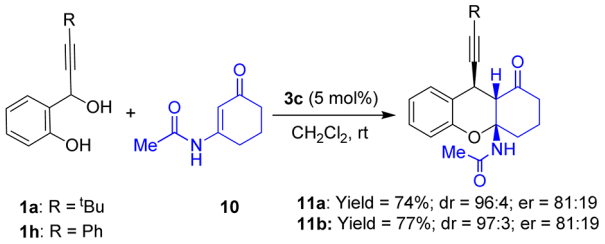
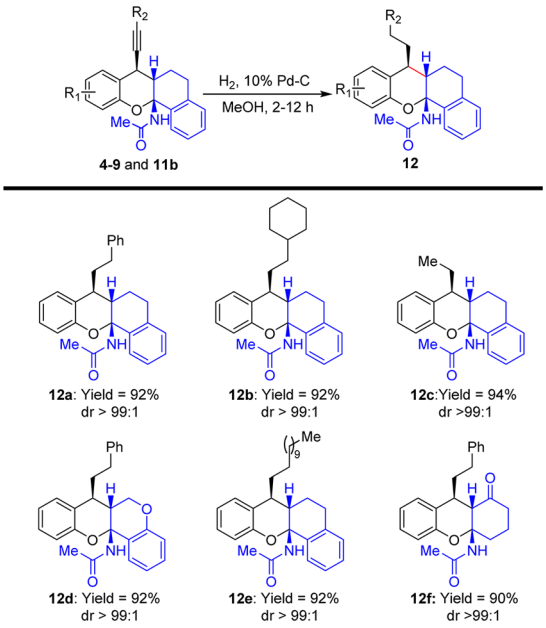


Table 4. Hydrogenation Reactions[a–c]



[a]All reactions were carried out with 0.42 mmol (1 equiv) of **4–9** and **12b**, 10 mg of Pd/C catalyst in 6 mL of CH_3OH at rt under positive pressure of H_2 for 2–12 h. [b]Isolated yield of the purified product. [c]dr was determined through ^1H NMR analysis of the product mixture.

which upon subsequent *N,O*-acetalization furnishes a broad range of 7-alkynyl-12a-acetamido-substituted benzo[*c*]-xanthenes and related heterocycles efficiently. The products can be easily converted into their highly valuable saturated analogues by catalytic hydrogenation. This study further emphasizes the efficacy of phosphoric acid catalyzed, enantioselective reactions of *o*-QMs and extends the scope of synthetic transformations involving enamide nucleophiles.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, spectral data for all new compounds, and crystallographic data and CIF information for **4e** and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) CCDC 1038657 and CCDC 1036085 contain the supplementary crystallographic data of **4e** and **7** for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre (CCDC) via www.ccdc.cam.ac.uk/data_request/cif. For details concerning the crystal structure of **4e** and **7**, see the Supporting Information as well.

(18) Reaction of the pinacolone-derived enamide with propargylic alcohol **1a** (R^1, R^2 = H) furnished the product in 74% yield, 96:4 dr, and 57:43 er.

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