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Silver(I)-Catalyzed Regioselective Construction of Highly Substituted α-Naphthols and Its Application toward Expeditious Synthesis of Lignan Natural Products

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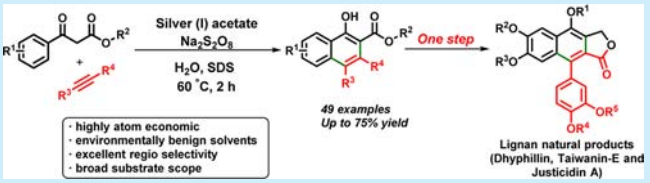
Supporting Information

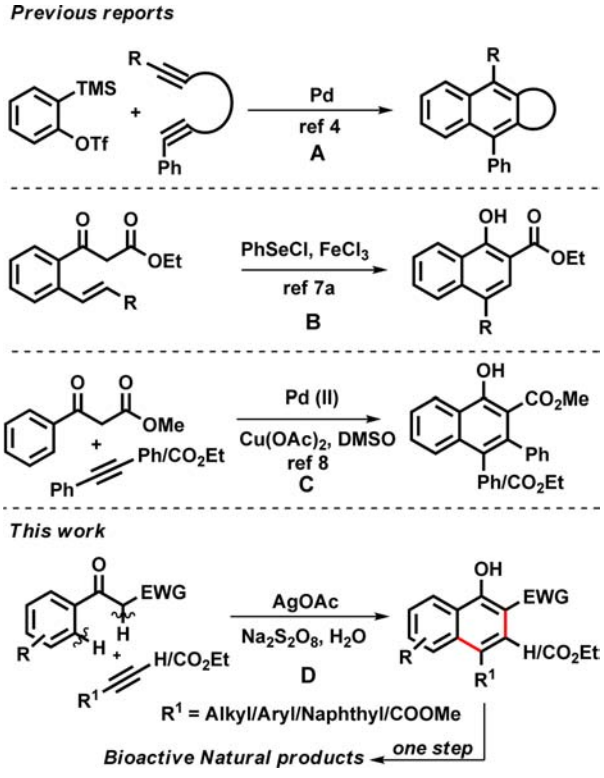
ABSTRACT: A novel route has been developed for regioselective synthesis of highly substituted α-naphthols, binaphthols, and anthracenol through silver(I) catalyzed $C(sp^3)-H/C(sp)-H$, $C(sp^2)-H/C(sp)-H$ functionalization of β-ketoesters and alkynes, respectively, in a single step using water as a solvent. This protocol exhibited broad substrate scope and paved the way for synthesis of anticancer arylnaphthalene lignan natural products such as diphyllin, taiwanin E, and justicidin A with excellent selectivity.



Selective synthesis of polysubstituted naphthalene derivatives has attracted organic as well as medicinal chemists, since these compounds have been found in many pharmaceuticals and biologically significant natural products.[1] In particular, α-naphthol tethered with an aromatic ring at the fourth position (aryl naphthol) has played a vital role in anticancer, antiviral, and V-ATPase inhibitory activity.[2] Apart from medicinal interest, these compounds have also been useful in asymmetric synthesis as a chiral source.[3] Numerous efforts have been made for the synthesis of substituted naphthalene and its derivatives, which includes transition-metal-catalyzed cycloaddition (mainly 2 + 2 + 2) reactions of prefunctionalized substrates (Scheme 1, A),[4] inter- and intramolecular Diels–Alder reactions,[5] and Lewis acid catalyzed annulations.[6] Recently, Wirth et al. (Scheme 1, B)[7a] and Yu et al.[7b] synthesized the 4-arylnaphthols through a radical mediated transformation from prefunctionalized precursors. Similarly, Wang and co-workers synthesized the poly substituted α-naphthols through the palladium catalyzed oxidative annulation (Scheme 1, C).[8] However, most of these existing approaches are inadequate for the synthesis of naphthalene-embedded bioactive lignan natural products. As a consequence, a practical, atom-economical, and regioselective construction of such compounds from easily accessible substrates is indispensable and exciting.

As a part of our drug development program, we reported a few novel and efficient methods for the generation of bioactive molecule libraries.[9] In continuation of these efforts, herein we disclose (Scheme 1, D) an innovative protocol for the regioselective synthesis of highly functionalized α-naphthols, binaphthols, and anthracenol in the presence of AgOAc and sodium persulfate in water as a solvent using mild and environmentally benign reaction conditions. Further, the current protocol has been successfully applied for the synthesis of biologically active lignan natural products such as diphyllin (**4**), taiwanin E (**5**), and justicidin A (**6**).

Scheme 1. Approaches for Polysubstituted Naphthalenes



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Our preliminary investigation started with a reaction between ethyl benzoyl acetate **1a** and phenylacetylene **2a** in water with 20 mol % of silver(I) nitrate ($AgNO_3$) as catalyst and potassium persulfate ($K_2S_2O_8$) as an oxidant at 60 °C, which resulted in 50% conversion of reactants and isolation of the desired arylnaphthol product **3aa** in 25% yield. The low yield of the reaction was attributed to poor solubility of reactants in aqueous medium. To address this concern, the reaction was carried out in a combination of aqueous organic solvents such as H_2O/MeCN, H_2O/DMF, H_2O/DMSO, H_2O/THF, and H_2O/DCE and in nonaqueous organic solvents. Surprisingly, in all of these attempts no product was isolated (see the Supporting Information). In a subsequent attempt, we introduced the sodium dodecyl sulfate (SDS) as a surfactant to improve the solubility of reactants. Pleasingly, the yield was improved to 40%. Increasing the catalyst loading from 20 to 30 mol % was also helpful to further improve the yield of **3aa** to 48%. We then turned our attention to screen other silver salts such as AgOAc, Ag_2CO_3, and AgO. Among them, AgOAc produced a better yield of **3aa** (55%) along with the elimination of the homocoupled (Glaser−Hay coupling) product of **2a** and also the regioisomer of **3aa**. Further improvement of yield of **3aa** from 55% to 65% was achieved upon using $Na_2S_2O_8$ as an oxidant instead of $K_2S_2O_8$. Unfortunately, other oxidants such as $(NH4)_2S_2O_8$, $KHSO_5$, $PhI(OAc)_2$, and TBHP were not able to produce the desired product **3aa**. The 2D-NMR data of **3ba** and the X-ray crystal structure of **3ac** unambiguously confirmed the regioselectivity.

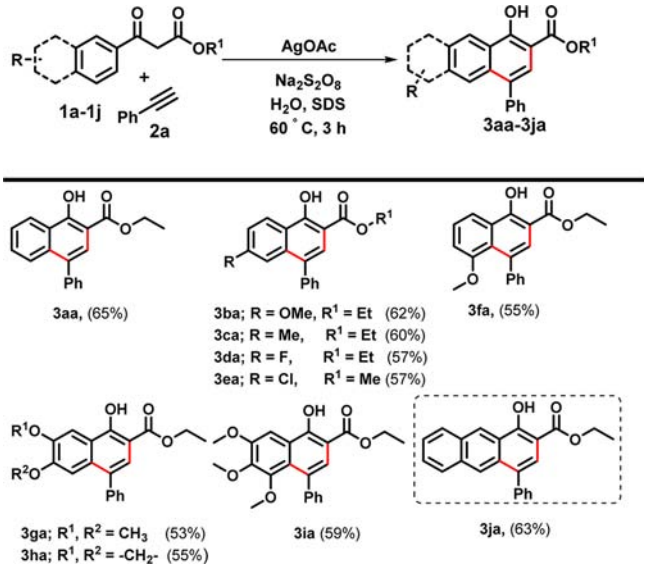
With the optimized conditions in hand, we used substrates with various substitutions on the aromatic ring of β-ketoesters for the synthesis of diverse α-naphthols (Scheme 2).

Initially, we examined electron-rich β-ketoesters such as **1b**, **1c**, and **1f**, which successfully furnished the desired products **3ba**, **3ca**, and **3fa** in good yields. Halo-substituted aromatic β-ketoesters **1d** and **1e** produced the corresponding α-naphthols **3da** and **3ea** in good yields (Scheme 2). Sterically crowded substrates such as disubstituted (**1g** and **1h**) and trisubstituted (**1i**) aromatic β-ketoesters also smoothly afforded the substituted α-naphthols **3ga**, **3ha**, and **3ia**, respectively, in good yields. A polycyclic anthracen-1-ol **3ja** was also successfully synthesized in good yields from naphthyl-β-ketoester (**1j**). In contrast to electron-rich β-ketoesters, electron-poor nitro-substituted β-ketoester (ethyl 3-(4-nitrophenyl)-3-oxopropanoate) failed to give the desired α-naphthol. It is noteworthy to mention here that reactants **1a−j** exclusively gave only one isomer of **3aa−ja**. Reaction between **1f** and **2a** cyclization transpired at the ortho position to the methoxy substitution of **1f** to give regioisomer **3fa**, and in the case of 3,4-disubstituted β-ketoesters (**1g** and **1h**), despite the strong electronic effect at the second position of the aromatic ring, cyclization occurred very selectively at the fourth position to furnish the desired α-naphthols **3ga** and **3ha** in good yields. This may be attributed to the associated steric factors.

After successful utilization of various β-ketoesters (**1a−j**) for the synthesis of polysubstituted α-naphthols, we next treated a variety of aromatic and aliphatic terminal alkynes (**2b−t**) under the optimized conditions for the synthesis of corresponding α-naphthols as depicted in Scheme 3.

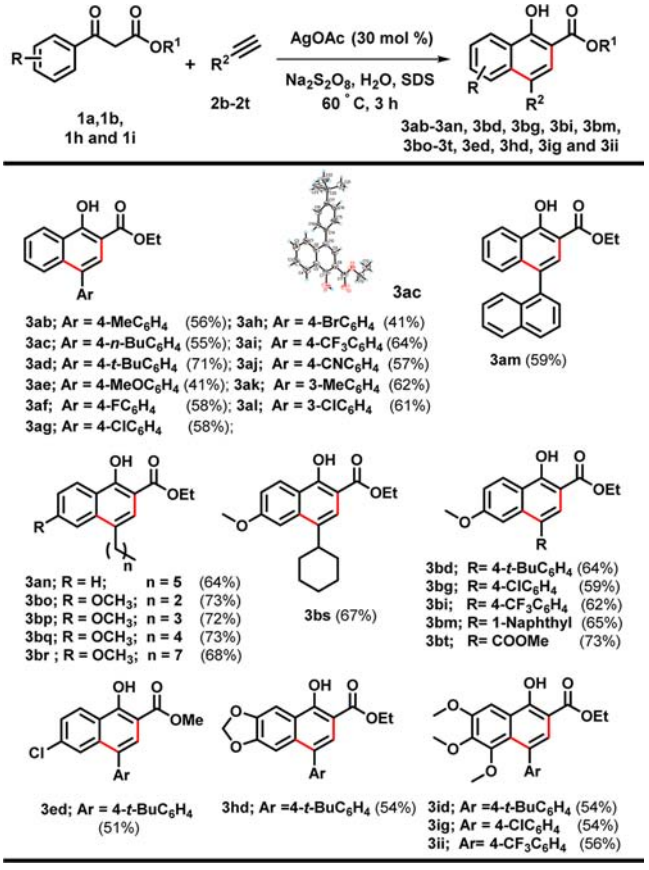
Alkyl-substituted (at the fourth position) aromatic terminal alkynes **2b−d** smoothly produced the respective α-naphthols **3ab−ad** in good yields, whereas electron-rich substituted alkyne **2e** gave a moderate yield of **3ae** (41%). Except **2h**, all other halo-substituted aromatic terminal alkynes **2f,g** and highly electron-deficient aryl terminal alkynes **2i** and **2j** furnished the

Scheme 2. Substrate Scope of β-Ketoesters for the Synthesis of α-Naphthol Derivatives[a]



[a]Conditions: 1 mmol of **1a−j**, 1.2 mmol of **2a**, 30 mol % of AgOAc, 1 mmol of $Na_2S_2O_8$, and 20 mol % of SDS in 4 mL of water at 60 °C for 3 h.

Scheme 3. Substrate Scope of Terminal Alkynes for the Synthesis of Aryl- and Alkylnaphthol Derivatives



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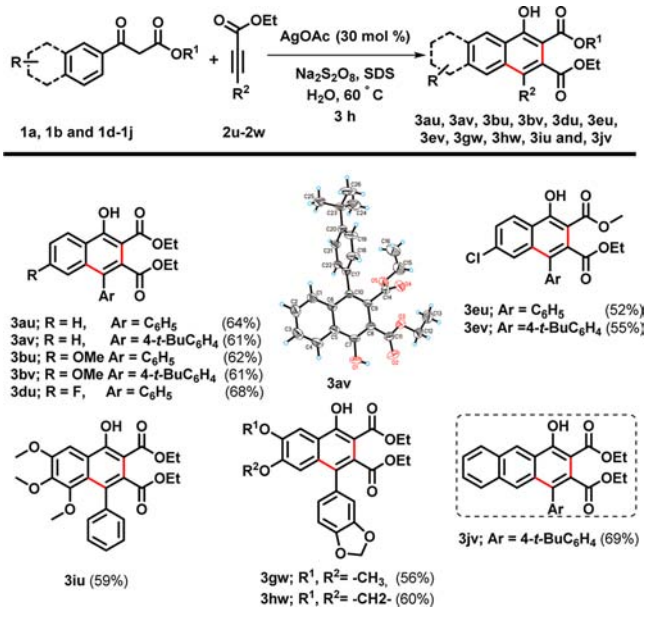
respective substituted α-naphthols **3af**–**aj** in good yields. Interestingly, our protocol was also successful in synthesizing a binaphthol class of compounds. In view of the importance of such motifs, naphthylacetylene (**2m**) was treated with β-ketoesters **1a** and **1b** using optimized reaction conditions to obtain **3am** and **3bm** in good yields (59 and 65%). Alkyl-substituted α-naphthol motifs exhibit potent biological activities, and direct synthesis of these compounds is a highly challenging task for synthetic chemists. We therefore planned to explore our method to synthesize such naphthols by replacing the aromatic terminal alkynes with aliphatic terminal alkynes (**2n**–**s**). When aliphatic acetylenes **2n**–**s** were treated with β-ketoesters **1a** and **1b**, the corresponding aliphatic α-naphthols **3an** and **3bo**–**br** and cyclohexyl-containing naphthol **3bs** were obtained in good to excellent yields in a single step (Scheme 3). Mono- (**1b** and **1e**), di- (**1h**), and trisubstituted β-ketoesters (**1i**) gave α-naphthols (**3bd**, **3bg**, **3bi**, **3bm**, **3bt**, **3ed**, **3ha**, **3id**, **3ij**, and **3ii**) in good yields (51%–73%) upon reaction with various substituted alkynes (**2a**, **2d**, **2g**, **2i**, **2m**, and **2t**).

Further, we studied the scope of 1,2-diarylalkynes, which could give 3,4-diaryl-α-naphthol derivatives. When we attempted a reaction with diphenylacetylene, unfortunately, the starting material was isolated as such, and no traces of product were detected. Considering the inertness of the diarylacetylene, we picked up an activated internal alkyne, i.e., ethyl phenylpropiolate. Delightedly, the reaction of **1a** with **2u** not only proceeded smoothly but also furnished the 1,2,3,4-tetrasubstituted highly functionalized naphthalene **3au** in 64% yield with high regioselectivity. The interesting regioselectivity prompted us to pave a pathway toward the construction of the arylnaphthalene lignan natural products **4**–**6**. Before attempting the synthesis of lignan natural products (**4**–**6**), we evaluated the generality of this new protocol with different β-ketoesters (**1a**,**b**,**d**–**j**) and a few aryl propiolates (**2u**–**w**), which led to the generation of a 4-aryl-1-naphthol skeleton (**3au**, **3av**, **3bu**, **3bv**, **3du**, **3eu**, **3ev**, **3gw**, **3hw**, and **3iu**) and a 4-aryl-1-anthracenol skeleton (**3jv**) having two consecutive ester functionalities with excellent regioselectivity (Scheme 4).

Scheme 4. Substrate Scope of Propiolates for the Synthesis of Poly Substituted Arylnaphthol Derivatives

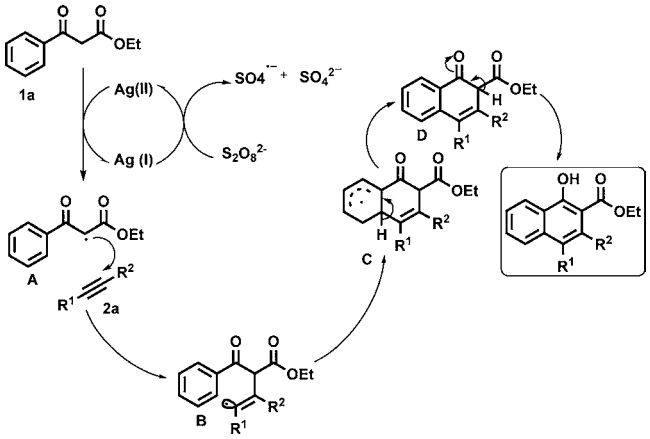


Moderate yields of the products in a few cases were due to the competitive homo-dimerization of β-ketoesters (5–10%). The structure of compound **3av** was unambiguously confirmed by single-crystal X-ray analysis.

Our literature search indicated that Ag(I) and the persulfate system follows the reaction through the radical pathway.[10] To verify whether the present method is also yielding the product via a radical mechanism, we conducted a few control experiments (see the Supporting Information) in the presence of radical scavengers such as TEMPO (2,2,6,6-tetramethylpiperidin-1-yloxy) and BHT (butylated hydroxytoluene). Progress of the reaction was almost halted from the product formation indicating involvement of radical intermediates, which is in line with the literature precedents.

On the basis of control experiments and previous reports,[10] we proposed a possible reaction pathway as shown in Scheme 5. Initially, in the presence of silver(I) salts, persulfate anion

Scheme 5. Possible Reaction Pathway for the Construction of Polysubstituted Arylnaphthols



disproportionates into the sulfate dianion and sulfate radical anion to produce active Ag(II) species. This Ag(II) oxidizes substrate **1a** to generate the highly stabilized radical **A**,[10b] which on subsequent addition to the alkyne (**2a**) furnishes the vinyl radical **B**. Selective formation of **B** may probably be due to the stabilization of radical by tethered aryl/alkyl groups.[11] Intramolecular cyclization of **B** produces the cyclic radial intermediate **C**, which might be immediately converted to **D** followed by aromatization (enol formation) to furnish the desired product.

To show the potential application of the current method, we embarked on the synthesis of biologically significant arylnaphthalene containing lignan natural products[12] such as diphyllin (**4**), taiwanin E (**5**), and justicidin A (**6**). Diphyllin (**4**) was isolated from many traditional medicinal plants.[13] Taiwanin E (**5**) and justicidin A (**6**) were isolated from the heartwood of the Japanese trees *Taiwania cryptomerioides* (Taxodiaceae)[14] and *Justicia ciliata*,[15] respectively. Very limited approaches appeared in the literature for synthesis of these natural products (**4**–**6**)[16] using multiple steps and several linear functional group transformations. Our retrosynthetic analysis indicated that lignan natural products **4** and **5** can be synthesized in two steps and **6** in three steps by applying our protocol (see the Supporting Information).

To test our hypothesis, diphyllin synthesis was initiated by carrying out a reaction with ethyl 3-(3,4-dimethoxyphenyl)-3-

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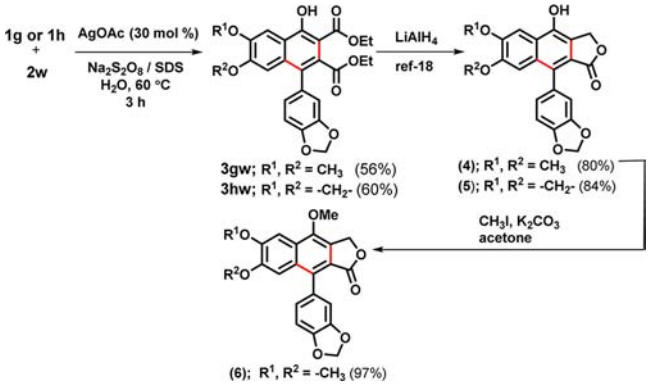
oxopropanoate (**1g**) and ethyl 3-(benzo[*d*][1,3]dioxol-5-yl) propiolate (**2w**)[17] to furnish the functionalized synthon, i.e., 1-naphthol **3gw**, in moderate yield (56%). Further, reductive cyclization of **3gw** in the presence of $LiAlH_4$ occurred to produce the desired natural product diphyllin (**4**) in excellent yield (80%).[18] The same protocol was applied to the synthesis of taiwanin E (**5**, 84%) by simply replacing one of the coupling partners **1g** with **1h**. Finally, alkylation of the phenolic hydroxy of diphyllin (**4**) with methyl iodide in the presence of K_2CO_3 in acetone smoothly furnished the anticancer natural product justicidin A (**6**) in almost quantitative yield (97%, Scheme 6).[19]

Scheme 6. Synthesis of Lignan Natural Products Diphyllin, Taiwanin E, and Justicidin A



In conclusion, we have developed an innovative approach for the construction of polysubstituted aryl-α-naphthols, arylanthracenol, and 1,1′-binaphthols through a Ag(I)-catalyzed C(sp^3)−H/C(sp)−H and C(sp^2)−H/C(sp)−H functionalization of β-ketoesters and alkynes with high regioselectivity in water. The present protocol provides the highly functionalized and distinctly substituted 1-naphthols in good yields under mild and environmentally benign conditions. This approach was also successfully applied to the synthesis of bioactive lignan natural products.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedure and spectroscopic data for all of the compounds and X-ray analysis data of compounds **3ac** and **3av**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01477.

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Notes

The authors declare no competing financial interest.

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