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Ag(I)-Catalyzed Sequential C−C and C−O Bond Formations between Phenols and Dienes with Atom Economy

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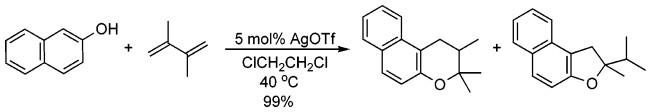

Mild, efficient, and economical Ag(I)-catalyzed sequential C−C/C−O bond formations between phenols and dienes were developed to afford in good yields a variety of dihydrobenzopyran and dihydrobenzofuran ring systems, which are important motifs in both naturally occurring and biologically active compounds.

Heterocyclic synthesis catalyzed by transition metal complexes has attracted the most attention among a variety of synthetic transformations because a transition-metal-catalyzed reaction can directly construct complicated molecules from readily accessible starting materials under mild conditions.[1] In comparison with other transition metals, silver(I) complexes have long been believed to have low catalytic efficiency, and most commonly, they served as either cocatalysts or Lewis acids. Only recently Ag-catalyzed reactions have emerged as important synthetic methods for a variety of organic transformations.[2] Ag(I) is known to interact with multiple bonds, such as alkenes,[2b,e] alkynes,[2d,f−h] and allenes.[3] Recently, an interesting Ag(I)-catalyzed intramolecular addition of alcohols to olefins has been reported.[2b] The intramolecular hydroalkoxylation is an attractive approach to the synthesis of cyclic ethers.[2b,4] Therefore, we envisioned the addition of the OH groups of phenols across dienes to afford dihydrobenzopyran or dihydrobenzofuran ring systems, which are pervasive motifs in biologically active natural products and pharmaceutical drug targets.[5] The dihydrobenzofurans are generally prepared in two steps from allyl aryl ethers by the Claisen rearrangement followed by cyclization of the resulting 2-allylphenols with strong acid.[6,7] The dihydrobenzopyrans are constructed typically by intramolecular hydroarylation from arene-ene substrates[8] or by cycloaddition of *o*-quinonemethides generated from salicylaldehydes and alcohols with alkenes using a protic acid or Lewis acid.[9] Pd-catalyzed telomerizations of dienes in the presence of alcohols are well-known reactions;[10] however, there are few examples of the 1:1 addition of an alcohol across a diene.[11−13] Moreover, previously reported synthetic methods for the 1:1 addition of a phenol across a diene usually give a complicated mixture of several products, such as 2- or 4-alkenylphenol, allylic ether, dihydrobenzopyran, etc.[12] Efficient and clean process for this reaction is very rare. Despite the recent success to produce allylic ethers from phenols and dienes by a Pd catalyst,[11a] reactions to afford annulated arene heterocycles (cyclic ethers) are very limited.[12,13] In parallel with our efforts to develop a catalytic system for heterocyclic synthesis,[8,14] we were interested in developing a one-pot synthesis of dihydrobenzopyrans and dihydrobenzofurans from phenols and dienes, whereby a single catalytic system would invoke sequential C−C and C−O bond formations with high efficiency and complete atom economy.[15] Herein we report the discovery of AgOTf for the sequential addition/cyclization of phenols with dienes in an atom economic manner.

We focused our initial efforts in this area on the reaction between *p*-methoxyphenol and isoprene, which were selected as the first substrates for screening of several metal salts and complexes. Transition metal complexes that were previously

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(11) For synthesis of allylic ethers, see: (a) Utsunomiya, M.; Kawatsura, M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 5865−5868. (b) Jolly, P. W.; Kokel, N. *Synthesis* **1990**, 771−773.

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(13) For Au(I)-catalyzed hydroamination of 1,3-dienes, see: (a) Bronwer, C.; He, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 1744−1747. The author reported that $Ph_3PAuOTf$ catalyzed the addition of alcohols to 1,3-dienes with low efficiency (∼30−40% conversion) based on preliminary studies. During the preparation of this manuscript, a similar study was published; see: (b) Nguyen, R.-V.; Yao, X.; Li, C.-J. *Org. Lett.* **2006**, *8*, 2397−2399. They reported that only cyclic dienes were used for the annulation of phenols or naphthols in the presence of $AuCl_3$/AgOTf, and the use of acyclic dienes led to a complicated mixture.

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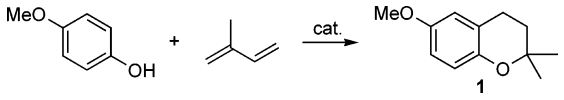
TABLE 1. Optimization Studies for the Reaction of *p*-Methoxyphenol and Isoprene[a]



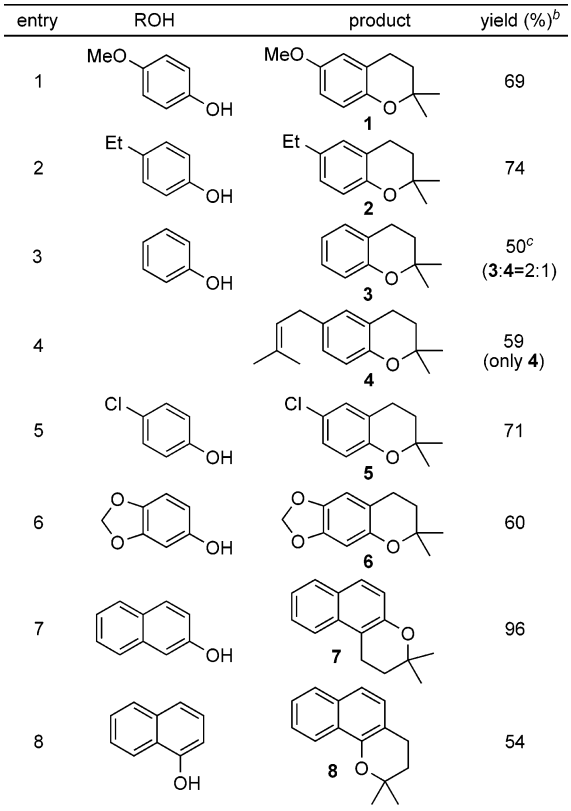
entry	catalyst	solvent	yield (%)[b]
1	AgOTf	$ClCH_2CH_2Cl$	60
2	AgOTf	1,4-dioxane	–
3	AgOTf	toluene	40
4	AgOTf	CH_3CN	–
5	$AgSbF_6$	$ClCH_2CH_2Cl$	20
6	$AgBF_4$	$ClCH_2CH_2Cl$	30
7	$AgClO_4$	$ClCH_2CH_2Cl$	40
8	$Ag(O_2CCF_3)$	$ClCH_2CH_2Cl$	–
9	$AgNO_3$	$ClCH_2CH_2Cl$	–
10	AgOTs	$ClCH_2CH_2Cl$	–
11	$Cu(OTf)_2$	$ClCH_2CH_2Cl$	–
12	$Sc(OTf)_3$	$ClCH_2CH_2Cl$	20
13	$RuCl_3$/AgOTf[c]	$ClCH_2CH_2Cl$	45
14	$AuCl_3$/AgOTf[c]	$ClCH_2CH_2Cl$	40
15	AuCl/AgOTf[d]	$ClCH_2CH_2Cl$	50
16	AuCl/AgOTf/PPh_3[e]	$ClCH_2CH_2Cl$	55
17	AgOTf/PPh_3[f]	$ClCH_2CH_2Cl$	60

[a] Reaction conditions: *p*-$MeOC_6H_4OH$ (1 equiv), isoprene (1.5 equiv), catalyst (5 mol %), solvent (0.1 M), room temperature, 24 h. [b] Determined by ^1H NMR using trichloroethylene as internal standard. [c] Performed with 5 mol % of $RuCl_3$ or $AuCl_3$ and 10 mol % of AgOTf. [d] Performed with 5 mol % of AuCl and 5 mol % of AgOTf. [e] Performed with 5 mol % of AuCl, 5 mol % of AgOTf, and 5 mol % of PPh_3. [f] Performed with 5 mol % of AgOTf and 5 mol % of PPh_3.

reported to either promote hydroarylation[8] and hydroalkoxylation[2b,7,16] or activate the alkenes[2b,e] were included in the screen (Table 1). We were delighted to identify an exciting lead, which unambiguously stood out in the array of experiments. We discovered that 5 mol % of AgOTf was optimal in this reaction system to produce dihydrobenzopyran **1** in 60% yield (Table 1, entry 1). Various solvents were examined, and $ClCH_2CH_2Cl$ appeared preferable. With the exception of $AgSbF_6$, $AgBF_4$, and $AgClO_4$, other silver salts were not effective (Table 1, entries 5−10). $Cu(OTf)_2$ did not promote the reaction at all, whereas scandium, ruthenium(III), gold(I), and gold(III) triflate salts produced low to moderate conversions (Table 1, entries 11−16). The reaction also occurred in the presence of phosphine ligand; however, there was no increase in the yield of **1** (Table 1, entry 17).[2b,c] We suspected that trace amounts of TfOH, which could be formed in situ via metathesis of Ag(I) with the OH bond of *p*-methoxyphenol, might catalyze the coupling reaction. However, $Cu(OTf)_2$ was inactive and other triflate salts gave lower conversions than AgOTf. In addition, a catalytic amount of TfOH (5 mol %) did result in the production of **1**, albeit only in 18% yield. These results suggest that silver plays an important role in this coupling process.

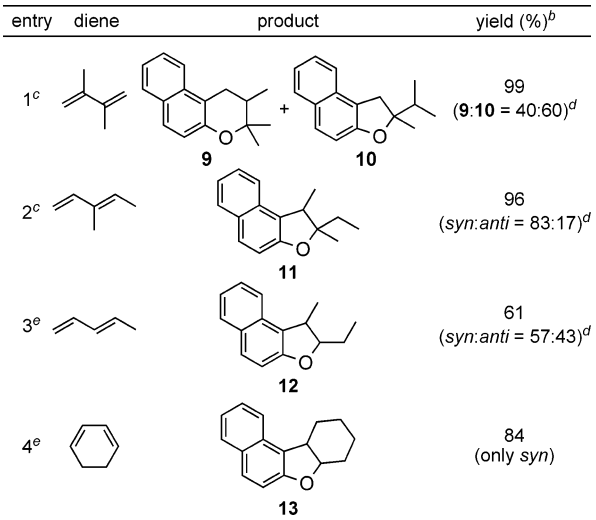
With the establishment of a viable one-pot reaction system, we set out to explore the scope of this coupling process. As shown in Table 2, a variety of phenols underwent tandem addition/cyclization in the presence of AgOTf to form the corresponding dihydrobenzopyrans. Both electron-rich and electron-deficient phenols were all successful in this reaction (Table 2). In the case of phenol, the reaction using 1 equiv of isoprene gave a mixture of **3** and **4**, with **3** as a major product, whereas **4** was the only product for the reaction with 1.5 equiv of isoprene (Table 2, entries 3 and 4).[12b,e]

TABLE 2. Ag(I)-Catalyzed Reaction of ROH with Isoprene[a]



[a] Reaction conditions: ROH (1 equiv), isoprene (1.5 equiv), AgOTf (5 mol %), $ClCH_2CH_2Cl$ (0.1 M), room temperature, 1−3 days, unless otherwise noted. [b] Isolated yields. [c] Performed with 1 equiv of isoprene for 48 h.

TABLE 3. Ag(I)-Catalyzed Reaction of 2-Naphthol with Dienes[a]



[a] Reaction conditions: 2-naphthol (1 equiv), diene (1.5 equiv), AgOTf (5 mol %), $ClCH_2CH_2Cl$ (0.1 M), 1−3 days. [b] Isolated yields. [c] Performed at 40 °C. [d] The ratio of two isomers was determined by NMR. [e] Performed at 80 °C.

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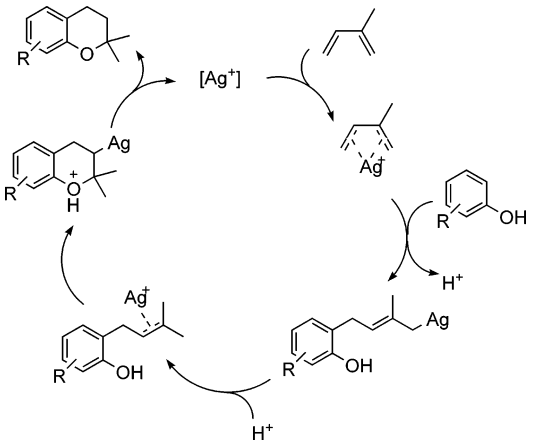
SCHEME 1. Possible Mechanism for the Ag(I)-Catalyzed Reactions



Subsequently, the reaction was examined on a range of dienes (Table 3). Good yields were obtained for all cases. With the exception of 2,3-dimethyl-1,3-butadiene, all dienes gave the corresponding dihydrobenzofurans as the sole products.[13]

Regioselectivity of the Ag(I)-catalyzed reaction presented herein parallels the regioselectivities observed for Al-,[12a,b] Pd-,[11,12c] Pt-,[12c] and Au-catalyzed[13] reactions of alcohols (or amines) with dienes, which suggests that C−C/C−O bond formation occurs by a similar mechanism in those reactions. By analogy with the mechanisms established for the related Al-,[12b] Au-,[13] and Ag-catalyzed[2b] reactions of alcohols with C═C bonds, we propose a plausible mechanism for Ag(I)-catalyzed sequential addition/cyclization (Scheme 1). Activation of the diene by coordination to Ag(I) is followed by intermolecular nucleophilic attack by the arene. The reactions of 2-naphthol with 1-substituted-1,3-diene substrates occur by either 1,2- or 1,4-addition, whereas the reactions of phenols with isoprene and 2,3-dimethyl-1,3-butadiene seem to take place by a 1,4-addition. The resulting Ag−C bond is protonated to give the 2-allylphenol intermediate. Then recoordination of C−C π-bond by Ag(I) activates the olefin toward intramolecular nucleophilic attack by the phenolic oxygen. Subsequent proton transfer produces the final product and regenerates the Ag(I) catalyst.[17]

In summary, we have developed mild and efficient Ag(I)-catalyzed sequential C−C/C−O bond formations between phenols and dienes. Both electron-rich and electron-deficient phenols successfully underwent this reaction, and both cyclic and acyclic dienes could be applied. The use of silver(I) is economic relative to other expensive transition metals employed previously to promote the reactions of phenols with dienes. This one-pot reaction represents an attractive means for the facile and atom economical construction of dihydrobenzopyran and dihydrobenzofuran ring systems, which are important motifs in both naturally occurring and biologically active compounds.

Experimental Section

General Procedure for the Ag(I)-Catalyzed Reaction of Phenols and Dienes. To a solution of phenol and diene (1.5 equiv) in $ClCH_2CH_2Cl$ (0.1 M) was added AgOTf (5 mol %). The resulting mixture was stirred at the reported temperature for 1−3 days. The solvent was evaporated, and the residue was purified by column chromatography on silica gel (EtOAc:*n*-hexanes = 1:50−1:100) to give the corresponding product.

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Supporting Information Available: Experimental procedures and spectral characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Another possible mechanism might involve the intermolecular attack by the OH group first. Then either direct hydroarylation or Claisen rearrangement followed by intramolecular cyclization could proceed. However, it has been reported that AgOTf did not promote both the direct hydroarylation (ref 8) and Claisen rearrangement/cyclization (ref 7a). Moreover, the direct hydroarylation cannot give **10**.