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AuCl-Catalyzed Synthesis of Benzyl-Protected Substituted Phenols: A Formal [3+3] Approach

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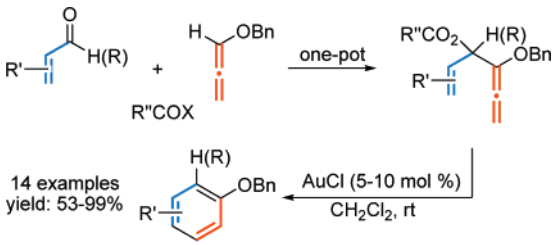
ABSTRACT

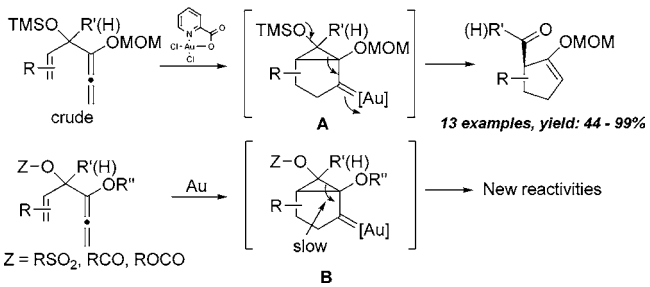


A AuCl-catalyzed synthesis of highly substituted, benzyl-protected phenols is developed. This reaction unites enal/enones and benzyl allenyl ether in a [3+3] fashion in two steps, allowing flexibility in phenol synthesis and excellent control of substitution at the benzene ring.

We have previously developed a two-step, highly stereoselective synthesis of cyclopentanone enol ethers containing an all-carbon quaternary center.[1] In this chemistry, a Au(III)-catalyzed[2] intramolecular [3+2] was proposed to account for the high stereoselectivity, and the overall sequence is a formal [3+2] cycloaddition of allenyl MOM ether and enals/enones. The key transformation in the proposed Au catalysis is the siloxy group-assisted, highly selective fragmentation of the Au carbenoid-containing bicyclo[3.1.0]-hexane intermediate **A** (Scheme 1). We reason that this mode of fragmentation can be substantially slowed down by replacing the TMS group with an electron-withdrawing group, thus allowing other reaction pathways to compete effectively and offering novel reactivities. Herein, we report a study of this concept, offering a modular synthesis of benzyl-protected substituted phenols.

We started with allenyl alkenyl carbinol acetate **1**, where the TMS group was replaced with an acetyl group. Acetate **1** was prepared in one pot from cyclohex-1-enecarbaldehyde and allenyl benzyl ether (Scheme 2), and the use of the benzyl group instead of MOM is to avoid the liability of the latter under acidic conditions. When compound **1** was treated with $Ph_3PAuNTf_2$[3] (5 mol %) in CH_2Cl_2 at room temperature, indeed a different reaction mode was observed and benzyl-protected 5,6,7,8-tetrahydro-2-naphthol (i.e., **2**) was formed as the major isolable product (33% yield, Table 1, entry 1).[4] Noteworthy is that the benzene ring of **2** consisted of three carbons from the allene moiety of allenyl benzyl ether and

Scheme 1. Exploration of the New Reactivity of Au-Catalyzed Reactions of Allenyl Alkenyl Carbinol Derivatives



(1) Huang, X.; Zhang, L. *J. Am. Chem. Soc.* **2007**, *129*, 6398−6399.

(2) For recent reviews on Au/Pt catalysis, see: (a) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271−2296. (b) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333−346. (c) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395−403. (d) Fürstner, A.; Davis, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410−3449. (e) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180−3211.

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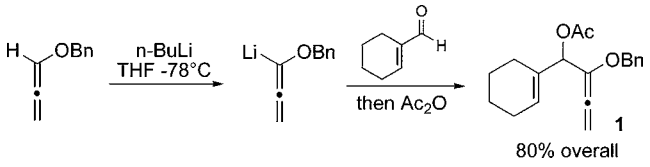
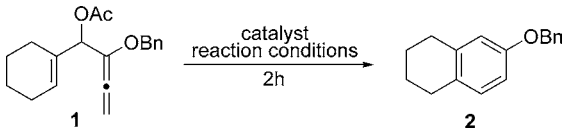
Scheme 2. Preparation of Allenyl Alkenyl Carbinol Acetate **1**



the other three carbons from the enal moiety of cyclohex-1-enecarbaldehyde. Therefore, this reaction constitutes a formal [3+3] approach toward phenol synthesis.[5] Moreover, it is regiospecific owing to the necessity of the initial union of the two components.

Table 1. Screening Reaction Conditions



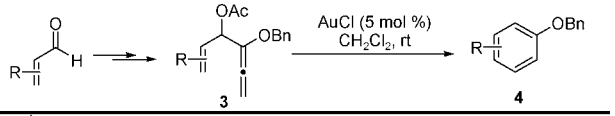
entry[a]	catalyst	reaction conditions	yield [%][b]
1	$Au(PPh_3)NTf_2$ (5 mol %)	CH_2Cl_2, rt	33
2	$AuCl_3$ (5 mol %)	CH_2Cl_2, rt	51
3	Au(III)[c] (5 mol %)	CH_2Cl_2, rt	75
4	$PtCl_2$ (5 mol %)	toluene, 80 °C	50
5	**AuCl (5 mol %)**	**CH_2Cl_2, rt**	**80**[d]
6	AuCl (5 mol %)	CH_3CN	17
7	AuCl (5 mol %)	toluene	53
8	AuCl (5 mol %)	THF	47
9	AuCl (5 mol %)	CH_2Cl_2, 40°C	70
10	TsOH (5 mol %)	CH_2Cl_2, rt	*e*

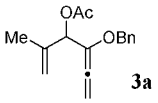
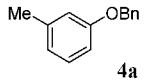
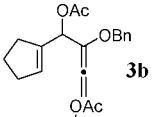
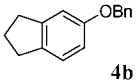
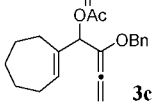
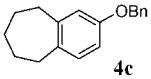
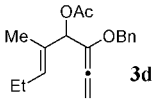
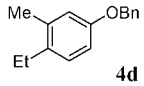
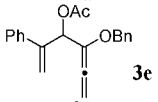
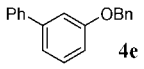
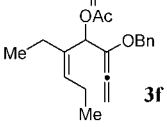
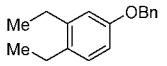
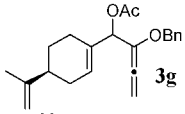
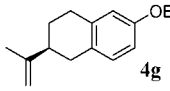
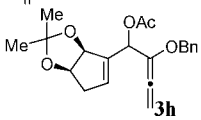
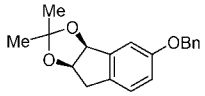
[a] Substrate concentration was 0.05 M. [b] NMR yield with diethyl phthalate as internal reference. [c] Dichloro(pyridine-2-carboxylato)gold(III). [d] Isolated yield. [e] The starting material decomposed completely.

To improve the reaction, various catalysts and reaction conditions were examined. As shown in Table 1, while Au(III) catalysts such as $AuCl_3$ (entry 2) and dichloro(pyridine-2-carboxylato)gold(III) (entry 3)[6] and $PtCl_2$ (entry 4) all led to improved yields of **2**, AuCl in CH_2Cl_2 was found to give the best result (entry 5). The reaction solvent appeared important as CH_3CN, THF, and toluene (entries 6−8) all led to inferior yields of **2**. Noteworthy is that Brønsted acid TsOH did not catalyze this reaction, and acetate **1** suffered complete decomposition (entry 10).

With the optimized conditions in Table 1, entry 5, the initial scope study was focused on substrates prepared from various enals by using the procedure outlined in Scheme 2. As shown in Table 2, a range of substrate **3** with di- or

Table 2. Reaction Scope with Substrates Prepared from Enals



entry[a,b]	substrate **3**	time (h)	product **4**	yield[%][c]
1	 **3a**	3	 **4a**	67
2	 **3b**	0.2	 **4b**	99
3	 **3c**	3	 **4c**	72
4	 **3d**	3	 **4d**	83
5	 **3e**	3	 **4e**	53
6	 **3f**	3	 **4f**	53[d]
7	 **3g**	10	 **4g**	65[d]
8	 **3h**	6	 **4h**	60[d]

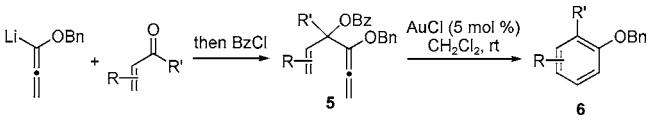
[a] Substrate concentration was 0.05 M. [b] Au precipitate appeared after 0.5 h. [c] Isolated yield. [d] 10 mol % of AuCl was used.

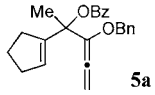
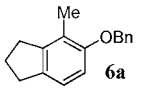
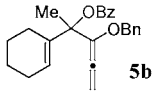
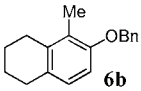
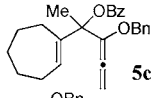
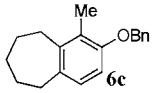
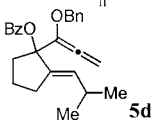
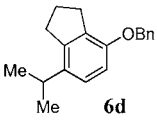
trisubstituted olefins worked well, yielding the phenolic product **4** in fairly good to excellent yields. It appeared that complete substitution at the proximal end of the alkene was required as acetate **3** derived from cinnamaldehyde gave rather messy results. Noteworthy is the excellent efficiency in the case of cyclopentene substrate **3b** as evidenced by the reaction time and the yield of **4b** (entry 2) and the tolerance of a *Z*-double bond (entry 6). One advantage of this formal [3+3] approach is that the readily available functionalities in enals can be carried over to the phenol product. While certainly those functional groups have to tolerate the basic conditions for substrate synthesis, two examples (entries 7 and 8) were successfully implemented, and functionalized phenol products were obtained in fairly good yields.

Expanding the reaction scope to include substrates derived from enones was troubled by the difficulty in converting the corresponding tertiary alcohol into the desired acetates.[7] We attempted to trap the lithium tertiary alkoxides formed in situ with benzoyl chloride and gratifyingly, benzoate **5** (Table 3) was formed efficiently in the crude residue after the usual

(3) Mezailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7*, 4133−4136.
(4) The structure of **2** was confirmed by synthesizing it via benzylation of commercially available 5,6,7,8-tetrahydro-2-naphthol.
(5) For a review on [3+3] approaches for phenol ring formation, see: Feist, H.; Langer, P. *Synthesis* **2007**, 327−347.
(6) Hashmi, A. S. K.; Weyrauch, J. P.; Rudolph, M.; Kurpejovic, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 6545−6547.

Table 3. Reaction Scope with Substrates Prepared from Enones

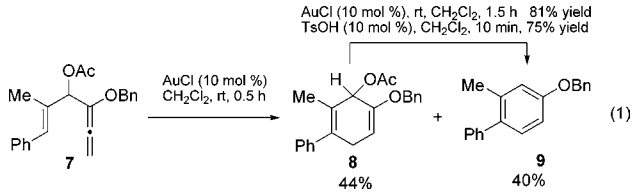


entry[a,b]	substrate	time (h)	product	yield[%][c,d]
1	 **5a**	3	 **6a**	70
2	 **5b**	3	 **6b**	66
3	 **5c**	3	 **6c**	53
4	 **5d**	3	 **6d**	64

[a] Substrate concentration was 0.05 M. [b] Au precipitate appeared after 0.5 h. [c] Due to the presence of inseparable impurity, the crude residue after concentration was treated with KOH (2 equiv) in refluxing MeOH/H_2O (1:1) for 2 h before workup and purification. [d] Overall isolated yield from enone.

workup. While compound **5** decomposed readily on column, we found that the crude residue can be, to our advantage, used directly for the Au catalysis as we did in our previous study.[1] Thus, as shown in Table 3, cycloalken-1-ylethanones with different ring sizes all participated in this two-step, formal [3+3] cycloaddition, leading to 2,3,4-trisubstituted phenol product **6** in fairly good overall yields (entries 1−3). Noteworthy is that the substitution patterns in the benzene ring of compounds **6a**−**c** are complementary to the Au-catalyzed phenol synthesis developed by Hashmi and co-workers, where the positions of the methyl and the oxygen atom are switched.[8,9] Significantly, 2-isobutylidenecyclopentanone was suitable for this chemistry as well, and the crude benzoate **5d** was converted to benzyl-protected bicyclic phenol **6d** in 64% overall yield.

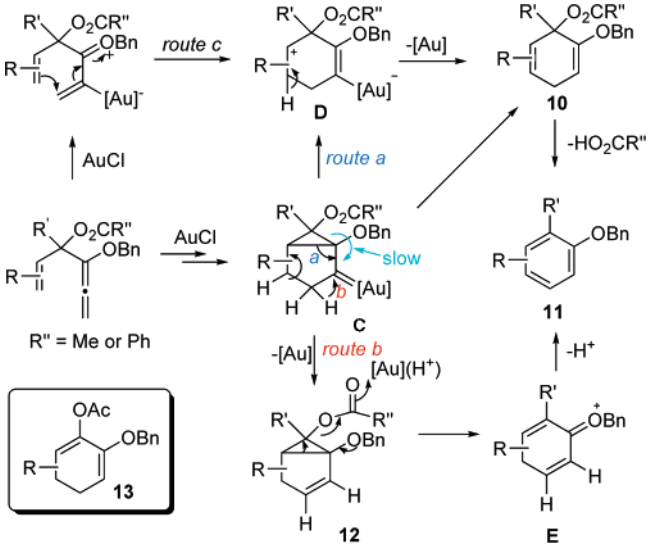
In all the reactions studied except entry 2 in Table 1, the starting material was generally consumed in half an hour, accompanied by catalyst decomposition and initial formation of a substantial amount of the phenolic product as well as other compounds. Upon further stirring, more of the product was formed slowly at the expense of other species. While those intermediate structures were difficult to purify, fortunately a major intermediate, assigned as compound **8**, was isolated pure along with 40% of phenolic product **9** after acetate **7** derived from α-methylcinnamaldehyde was treated with AuCl for 0.5 h (eq 1). As expected, either AuCl[10] or



TsOH promoted the conversion of **8** to **9** efficiently. Of note, the AuCl-catalyzed conversion of **8**[11] was relatively slow compared to the initial formation of **9**, which suggests there are likely competing mechanistic pathways.

Our proposed mechanism for this reaction is shown in Scheme 3. Similar to our previous study,[1] a Au-catalyzed

Scheme 3. Proposed Reaction Mechanism



intramolecular [3+2] cycloaddition between the allene and the alkene forms bicyclic Au carbenoid **C**.[12] While Au carbenoid **A** containing a TMSO group undergoes selective bond fragmentation (Scheme 1),[1] the acyloxy group in **C** must retard such bond breaking, allowing two competing processes to happen: (i) Breaking of the ring fusion bond heterolytically (route a) results in the formation of homoallylic cation **D**, which can undergo E1-type elimination and protiodeauration and thus forms 1,4-cyclohexadiene **10**; alternatively, cation **D** can also be formed via the cyclization of the alkene to the Au-activated allene (route c);[13] and phenolic product **11** is formed from **10** via elimination in the presence of AuCl or H^+.[14] (ii) Alternatively, Au carbenoid

(7) A combination of AcCl and DMAP gave almost no reaction, and reaction of the corresponding lithium alkoxide with acetic anhydride failed to reach full conversion.

(8) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553−11554.

(9) Interestingly, Hashmi and coworkers have recently reported that a phenol with identical substitution pattern to **4b** was formed selectively from γ-alkylfurnas with a ketal auxiliary. For reference, see: Hashmi, A. S. K.; Kurpejovic, E.; Woelfle, M.; Frey, W.; Bats, J. W. *Adv. Synth. Catal.* **2007**, *349*, 1743−1750.

(10) Au precipitates appeared during the reaction. It is possible that HCl thus generated also catalyzed the aromatization.

(11) The addition of HOAc (1 equiv) did not accelerate the reaction to an observable extent. HOAc (1 equiv) alone promoted the aromatization slowly (12% conversion in 5 h).

(12) Buzas, A.; Gagosz, F. *J. Am. Chem. Soc.* **2006**, *128*, 12614−12615.

C can undergo 1,2-hydride shift and elimination of the Au catalyst, forming bicyclo[3.1.0]hexene **12** (route b); coordination of the acetoxy group to either AuCl or H^+ will trigger electrocyclic ring opening of the cyclopropane ring, generating cyclohexadienyl cation **E**; and subsequent proton loss affords **11**. It is possible that the initial rapid formation of product **11** is partly due to the rapid conversion of intermediate **12**. Two issues with this proposed mechanism worth further comments: (a) 1,3-Cyclohexadiene **13** could also form from cation **D** when R′ = H, but in eq 1 we did not observe it at all; it is possible that 1,4-cyclohexadiene **10** forms directly from carbenoid **C** via a E2-type process without the intermediacy of cation **D**. (b) The expected stereoelectronic effect in the cyclopropane ring opening[15] (i.e., from **12** to **E**) suggests that only the diastereomer of **12** with the acyloxy group at the concave face of the bicyclo-[3.1.0]hexene would undergo facile, concerted acyloxy cleavage and ring opening, but it is possible that the BnO group may substantially promote the cyclopropane ring fragmentation regardless of the stereochemistry of the acetoxy group.

In conclusion, we have developed a Au-catalyzed synthesis of highly substituted, benzyl-protected phenols. This reaction unites enal/enones and benzyl allenyl ether in a [3+3] fashion in two steps, allowing synthetic flexibility and excellent control of the substitutions on the benzene ring. This method would offer a rather unique and potentially efficient dissecting of the benzene ring in phenolic compounds such as pisiferol[16] and (+)-4-propyl-9-hydroxynaphthoxazine, a potent dopamine agonist (Figure 1).[17]

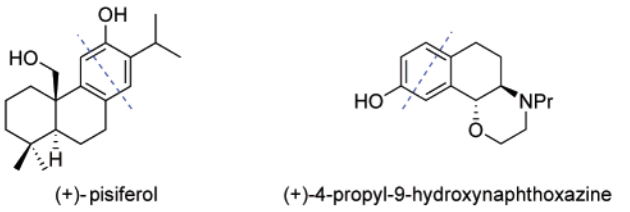


Figure 1. Phenolic compounds.

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Note Added after ASAP Publication. In Table 3, the structures of **6b** and **6c** were mistakenly switched in the version published ASAP October 3, 2007; the corrected version was published ASAP October 4, 2007.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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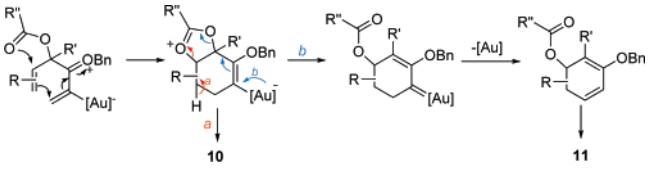
(13) One reviewer suggested that the carboxyl group may assist the cyclization via neighboring group participation as shown below, which is possible. For a related case, see: Lim, C.; Kang, J.-E.; Lee, J.-E.; Shin, S. *Org. Lett.* **2007**, *9*, 3539−3542. Moreover, an additional route toward product **11** via a cyclohexene gold carbenoid cannot be ruled out.



(14) H^+ can be from the decomposition of AuCl or from the combination of AuCl and the carboxylic aicd formed during the reaction.

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