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Ytterbium(III) Triflate Catalyzed Tandem Friedel−Crafts Alkylation/Hydroarylation of Propargylic Alcohols with Phenols as an Expedient Route to Indenols

Xiaoxiang Zhang, Wan Teng Teo, and Philip Wai Hong Chan*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637616, Singapore

waihong@ntu.edu.sg

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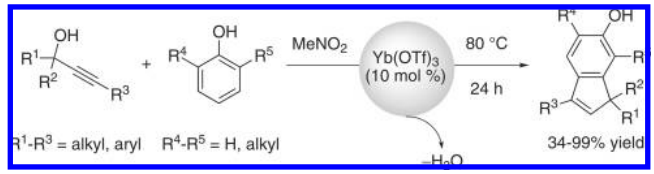
ABSTRACT



A method to prepare indenols efficiently by ytterbium(III) triflate catalyzed tandem Friedel−Crafts alkylation/hydroarylation of propargylic alcohols with phenols is described. The reaction was accomplished in moderate to excellent yields and regioselectivity under mild conditions and offers a straightforward and convenient one step synthetic route to bioactive indenols and its derivatives.

Indenes are important core structures in organic chemistry as a result of their presence in many natural products and role as privileged scaffolds in bioactive pharmaceutical compounds.[1] They are also versatile building blocks for functional materials[2] and are utilized as ligands in metallocene-based olefin polymerization catalysts.[3] While this has led to many synthetic methods,[4] those that describe the construction of 6-hydroxyindenes have remained sparse. The only member in the indene family of compounds to also exhibit potential estrogenic bioactivity, their synthesis has been reported to need several steps and often harsh conditions.[5] Hence, mild and efficient approaches to this class of carbocycles from commercially available substrates or ones that can be accessed in one step are desirable.

Recent reports have demonstrated the use of propargylic compounds as efficient substrates in several Lewis and Brønsted acid catalyzed carbon−carbon and carbon−

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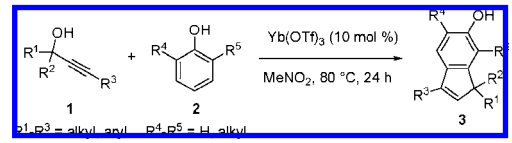
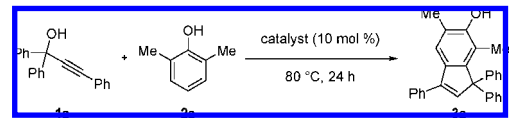
heteroatom bond formation strategies.[6−14] For instance, we recently reported $Yb(OTf)_3$ to be an efficient catalyst for the regioselective formation of conjugated enynes based on nucleophilic ring opening of unactivated 1-cyclopropyl-2-propyn-1-ols with aryl sulfonamides.[7] On the basis of these earlier studies we reasoned that a strategy that made use of propargylic alcohols[8] and phenols in the presence of a rare earth metal Lewis acid catalyst[9] would hold promise as a new method for indenol synthesis. To our knowledge, approaches to indenes that explore combining ecologically benign Lewis acid catalysts[10] with propargylic alcohols have thus far been limited to three recent reports describing the synthesis of 3-phenyl-1*H*-indenes,[11] spiroindenes,[12] and indenyl sulfonamides.[13] In addition, those that involve the use of phenols have been previously reported to typically give the propargylation, benzofuran, and benzopyran products.[6i,14] As part of an ongoing program examining the utility of alcohols in organic synthesis,[7,15] we report herein the use of $Yb(OTf)_3$ for tandem Friedel−Crafts alkylation/hydroarylation of propargylic alcohols with phenols (Scheme 1). The reactions were found to proceed to give 6-indenols in good to excellent yields up to 99% and with complete regioselectivity for a wide variety of substrates under mild conditions.

Scheme 1. $Yb(OTf)_3$-Catalyzed Formation of 6-Indenols from Propargylic Alcohols and Phenols



Initially, we chose to focus our attention on the reaction of 1,1,3-triphenylprop-2-yn-1-ol **1a** and 2,6-dimethylphenol **2a** by a variety of Lewis acid catalysts to establish the reaction conditions (Table 1). This revealed treating a solution of reaction containing **1a** (1 equiv) and **2a** (2 equiv) with 10 mol % $Yb(OTf)_3$ at 80 °C for 24 h gave the best result (entry 1). Under these conditions, 5,7-dimethyl-1,1,3-triphenyl-1*H*-inden-6-ol **3a** was afforded in 90% yield. The indenol product was confirmed by ^1H NMR analysis and an X-ray crystal structure determination of a closely related product (see below). On the other hand, a slightly lower product yield was observed when the reaction was performed

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	solvent	yield (%)[b]
1	$Yb(OTf)_3$	$MeNO_2$	90
2	$Yb(OTf)_3$	MeCN	77
3	$Yb(OTf)_3$	$(CH_2Cl)_2$	86
4	$Cu(OTf)_2$	$MeNO_2$	46
5	$InCl_3$	$MeNO_2$	47
6	$FeCl_3{\cdot}6H_2O$	$MeNO_2$	*c*
7	$AlCl_3$	$MeNO_2$	26
8	$AuBr_3$	$MeNO_2$	85
9	$PtCl_2$	$MeNO_2$	82
10	TfOH	$MeNO_2$	64
11	TfOH	$MeNO_2$	72[d]

[a] All reactions were performed at 80 °C for 24 h with catalyst/**1a**/**2a** ratio = 1:10:20. [b] Isolated yield. [c] Mixture of unknown side products afforded based on ^1H NMR analysis of the crude mixture. [d] Reaction conducted with TfOH catalyst loading of 20 mol %.

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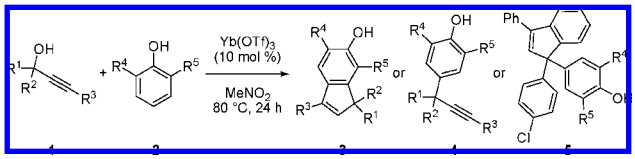
in MeCN and 1,2-dichloroethane in place of $MeNO_2$ as solvent (entries 2 and 3). Similar product yields were also obtained when the reaction was repeated with $AuBr_3$ and $PtCl_2$ as catalyst (entries 8 and 9). In contrast, while the use of $Cu(OTf)_2$, $InCl_3$ and $AlCl_3$ as the catalyst provided **3a** in markedly lower yields of 26−47%, the expected indenol product was not obtained employing $FeCl_3{\cdot}6H_2O$ (entries 4−7). In this latter case, the reaction was found to result in the formation of a mixture of side products that could not be identified by ^1H NMR analysis (entry 6). Additional control experiments with TfOH at catalyst loadings of 10 and 20 mol % led to lower catalytic activities, providing evidence that the cationic Yb(III) complex is the active species (entries 10 and 11).[16]

To define the scope of the present procedure, we next turned our attention to the reactions of a variety of propargylic alcohols with **2a** (Table 2). Reactions of propargylic alcohols with a pendant electron-withdrawing or electron-donating group on the carbinol or alkyne carbon with **2a** gave the desired indenols in good to excellent yields (entries 1−13). We also tested the effect of an aliphatic substitutent and found that, for substrates where R^1 or R^3 = alkyl, lower yields were obtained for **3o** (56% and requiring reflux conditions and a longer reaction time of 48 h; entry 14), **3p** (44%; entry 15), **3q** (34%; entry 17), respectively. In contrast, in the case of starting alcohols where R^1 and R^2 = alkyl or R^2 = H, the corresponding propargylation adducts **4a** and **4b** were preferentially furnished in yields of 61% and 83%, respectively (entries 16 and 18). A propargylic alcohol containing a terminal alkyne moiety was also examined under the standard conditions but was found to give a mixture of decomposition products that could not be identified by ^1H NMR analysis of the crude mixture (entry 19). On the other hand, reactions of starting alcohols with **2b** were found to proceed well and provide the corresponding indenols in excellent yields (entries 20−23). Under the standard conditions, reactions of **1l** with the less electron-rich or extremely sterically bulky phenols **2c** and **2d** were the only instances where the corresponding 4-(1*H*-inden-1-yl)phenols were preferentially obtained in moderate yields (entries 24 and 25).

We tentatively propose the present $Yb(OTf)_3$-catalyzed indenol-forming reaction to proceed by the mechanism outlined in Scheme 2, although it is highly speculative. This could involve activation of the alcohol substrate through coordination of the metal catalyst with the hydroxyl functional group. This delivers the Yb(III)-coordinated intermediate **A**, which undergoes elimination to give the alkynyl cation species **B** and its allenic resonance form **C**. Friedel−Crafts reaction at the acetylenic carbon center in **B** or allenic carbocation center in **C** with **2** followed by subsequent Yb(III)-mediated intramolecular hydroarylation and re-aromatization would provide the indenyl−ytterbium complex

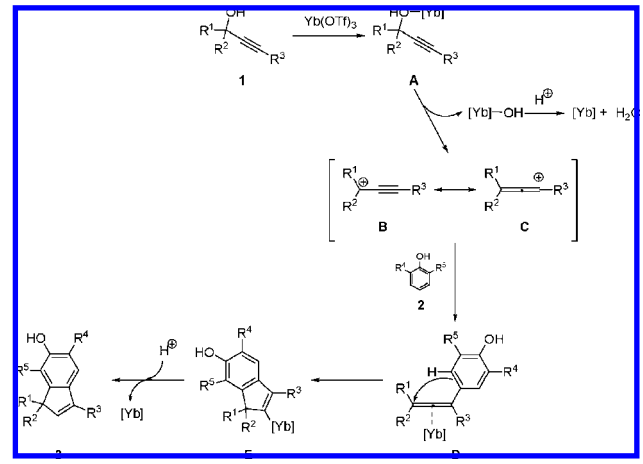
Table 2. $Yb(OTf)_3$-Catalyzed Synthesis of 6-Indenols **3b**−**u**[a]



entry	**1**, $R^1/R^2/R^3$	**2**, R^4/R^5	**3/4/5**	yield (%)[b]
1	**1b**, 4-$FC_6H_4/C_6H_5/C_6H_5$	**2a**	**3b**	92
2	**1c**, 4-$ClC_6H_4/C_6H_5/C_6H_5$	**2a**	**3c**	87
3	**1d**, 4-$BrC_6H_4/C_6H_5/C_6H_5$	**2a**	**3d**	82
4	**1e**, 4-$CNC_6H_4/C_6H_5/C_6H_5$	**2a**	**3e**	99
5	**1f**, 4-$MeC_6H_4/C_6H_5/C_6H_5$	**2a**	**3f**	84
6	**1g**, 4-FC_6H_4/4-FC_6H_4/C_6H_5	**2a**	**3g**	94
7	**1h**, 4-ClC_6H_4/4-ClC_6H_4/C_6H_5	**2a**	**3h**	91
8	**1i**, 4-BrC_6H_4/4-BrC_6H_4/C_6H_5	**2a**	**3i**	98
9	**1j**, 4-MeC_6H_4/4-MeC_6H_4/C_6H_5	**2a**	**3j**	72
10	**1k**, C_6H_5/C_6H_5/4-FC_6H_4	**2a**	**3k**	89
11	**1l**, C_6H_5/C_6H_5/4-ClC_6H_4	**2a**	**3l**	76
12	**1m**, C_6H_5/C_6H_5/4-MeC_6H_4	**2a**	**3m**	80
13	**1n**, C_6H_5/C_6H_5/4-$MeOC_6H_4$	**2a**	**3n**	50
14	**1o**, iPr/C_6H_5/C_6H_5	**2a**	**3o**	56[c]
15	**1p**, Me/C_6H_5/C_6H_5	**2a**	**3p**	44
16	**1q**, Me/Me/C_6H_5	**2a**	**4a**	61
17	**1r**, C_6H_5/C_6H_5/*n*-Bu	**2a**	**3q**	34
18	**1s**, H/C_6H_5/C_6H_5	**2a**	**4b**	83
19	**1t**, C_6H_5/C_6H_5/H	**2a**	*d*	
20	**1a**	**2b**, Me/H	**3r**	83
21	**1c**	**2b**	**3s**	80
22	**1e**	**2b**	**3t**	89
23	**1h**	**2b**	**3u**	77
24	**1l**	**2c**, H/H	**5a**	53
25	**1l**	**2d**, *i*Pr/*i*Pr	**5b**	40

[a] All reactions were performed at 80 °C for 24 h with $Yb(OTf)_3$/**1**/**2** ratio = 1:10:20. [b] Isolated yield. [c] Reaction conducted at reflux for 48 h. [d] Mixture of unknown side-products afforded based on ^1H NMR analysis of the crude mixture.

Scheme 2. Tentative Mechanism for $Yb(OTf)_3$-Catalyzed Tandem Friedel−Crafts Alkylation/Hydroarylation of **1** with **2**



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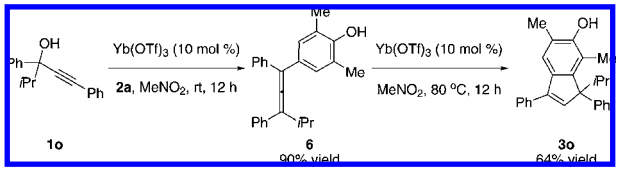
E. A final protodemetalation step would then deliver the indenol product **3**. The product regioselectivities obtained could be due to trapping at the sterically less hindered carbon center of the presumed ionized species **B** or **C** when R^1 and R^2 = aryl.[17] In this manner, any unfavorable steric interactions between these substitutents of the cationic intermediate and the incoming nucleophile would be limited. The possibility of such steric interactions on the regioselectivities obtained would account for our earlier findings showing the exclusive formation of the propargylation product in cases where less sterically demanding secondary and 1,1-dimethyl-substituted alcohols were examined (entries 16 and 18 in Table 2).[17] Indeed, this is further supported by the fact that when a $MeNO_2$ solution containing **1a** and **2a** was treated with 10 mol % of $Yb(OTf)_3$ at room temperature under the conditions shown in Scheme 3, the allene adduct **6** was

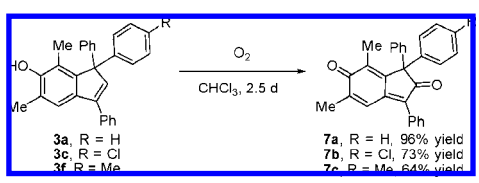
Scheme 3. Synthesis of **6** and Its Conversion to **3o**



obtained as the sole product in 90% yield. On retreating compound **6** to the standard conditions of 10 mol % of $Yb(OTf)_3$ in $MeNO_2$ at 80 °C for 12 h, the expected indenol **3o** was obtained in 64% yield, which is comparable to that furnished from **1o** shown in entry 14 in Table 2. The origin of the indene products **5a** and **5b** could be due to competitive cyclization between one of the Ph groups and the phenolic moiety on the respective allene intermediates **D** presumably formed in these reactions. In the former case, it is possible that the proximity of a geminal electron-withdrawing group (R^3 = *p*-ClC_6H_4) to that of the phenol moiety (R^4 and R^5 = H) makes hydroarylation via the slightly more electron-rich Ph group in **D** more favorable. In the latter case with steric factors coming to the fore, cyclization of phenol unit (R^4 and R^5 = *i*Pr) onto the allene functional group in **D** is now sterically unfavorable.

In this work, the conversion of indenols to their indendione derivatives was also examined (Scheme 4). Subjecting a

Scheme 4. Oxidation of **3a**, **3c**, and **3f** to **7a**−**c**



$CHCl_3$ solution containing **3a** to an atmosphere of oxygen for 2.5 days was found to give **7a** in 96% yield.[18] The structure of **7a** was established by X-ray crystallographic analysis (please refer to Figure S50 in Supporting Information). Under similar conditions, the oxidation of **3c** and **3f** gave the corresponding indendiones **7b** and **7c** in 73% and 64% yield, respectively. In view of the reported potential antifungal, antibiotic, antimalarial, and antitumor activities exhibited by a myriad of compounds with an indendione moiety,[19] the present method also provides a new route to this important class of carbocycles.

In summary, an efficient ytterbium-catalyzed synthetic route to 6-indenols based on the tandem reaction of propargylic alcohols with phenols has been reported. These results show that the reaction tolerates a structurally diverse set of alcohol substrates that can be accessed in one step from commercially available and low-cost starting materials. Our studies show that while TfOH can also mediate the tandem Friedel−Crafts alkylation/hydroarylation process, the lower yields obtained with TfOH and the milder conditions of ytterbium catalysis provides an attractive alternative synthetic route to 6-indenols. The utility of the present method to this class of carbocycles was also shown by the conversion of three adducts obtained to their indendione derivatives, which are also bioactive compounds of current interest. Efforts are currently underway to apply the method to natural product synthesis and will be reported in due course.

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Supporting Information Available: Detailed experiment procedures, characterization data and ^1H and ^{13}C NMR spectra for all starting materials and products, and CIF files of **7a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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