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Silver-Catalyzed Tandem Hydroamination/Hydroarylation of 1-(2-Allylamino)phenyl-4-hydroxy-but-2-yn-1-ones to 1′-Allylspiro[indene-1,2′-indolin]-3′-ones

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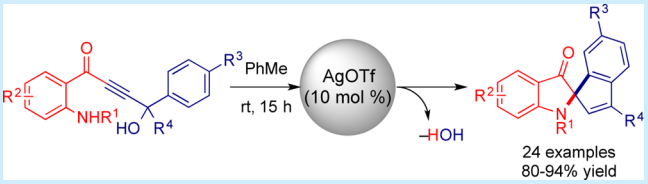
Supporting Information

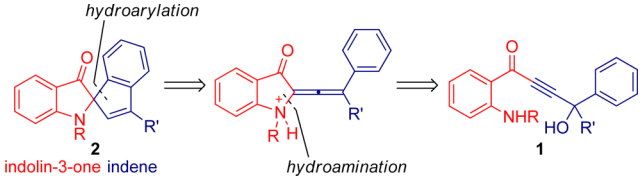
ABSTRACT: An efficient silver triflate-catalyzed tandem hydroamination/hydroarylation cascade generating 1′-allylspiro[indene-1,2′-indolin]-3′-ones from 1-(2-allylamino)-phenyl-4-hydroxy-but-2-yn-1-ones is described. The reaction conditions are mild and general in scope and proceed to highly functionalized spiro-targets in high yield. This novel class of molecule possesses both the privileged indene and indolin-3-one scaffold, which may lead to possible pharmacological applications.



The indene and indolin-3-one motifs are prevalent in biologically active molecules, pharmaceutical compounds, and functional materials.[1−3] With such diverse and important utility, these scaffolds are consequently considered as 'privileged' fragments. As a result, these structures have and continue to receive significant synthetic interest, with new and efficient processes widely pursued.[4−6] Also found in abundance in natural products is the spirocyclic structural motif, which has significance and growing importance in pharmaceutical chemistry.[7]

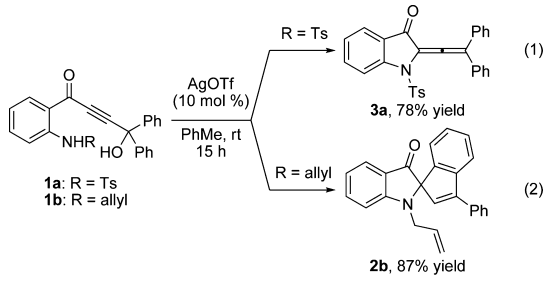
Extensive research in transition-metal-catalyzed cycloisomerizations has led to the establishment of this field as one of the most important and expedient methods in the assembly of both hetero- and carbocycles.[8,9] In particular, hydroamination and hydroarylation processes are of immense interest in accessing the respective indole and indene motifs.[10−13] In the context of our ongoing interests in developing synthetically useful reactions to access these structures, we envisioned a cascade to 1′-allylspiro[indene-1,2′-indolin]-3′-ones **2** by tandem hydroamination/hydroarylation of propargylic alcohol **1** under suitable Lewis acid catalyst activation (Scheme 1).[14,15] Herein, we report the details of this chemistry that rapidly increases the molecular complexity to provide an efficient synthetic route to a new class of spirocycles of pharmacological potential in excellent yields from readily accessible and inexpensive substrates.[3]

Scheme 1. Proposed Route to a Novel Indene and Indolin-3-one Spirocyclic Structure



We commenced our investigations by examining the AgOTf-catalyzed dehydrative cycloisomerization of *N*-tosyl and *N*-allyl-protected alkynes **1a** and **1b** (Scheme 2). This initially revealed

Scheme 2. AgOTf-Catalyzed Cycloisomerization of *N*-Protected 1-(2-Amino)phenyl-4-hydroxy-but-2-yn-1-ones



that treating the *N*-tosyl-protected substrate with 10 mol % of AgOTf in toluene at rt for 15 h afforded the indolin-3-onyl allene **3a** as the only product in 78% yield (Scheme 2, eq 1). However, increasing the reaction temperature to 80 °C for a further 12 h did not trigger the anticipated hydroarylation step. Gratifyingly, when the *N*-allyl-protected alcohol **1b** was submitted to similar conditions, the desired tandem hydroamination/hydroarylation furnished spirocycle **2b** as the only product in 87% yield (Scheme 2, eq 2). With this initial result, we proceeded to optimize the reaction conditions and assessed a panel of Lewis and Brønsted acid catalysts (Table 1). These studies subsequently showed lower product yields of 35−81% were obtained on repeating the reaction of **1b** with $AgSbF_6$ or

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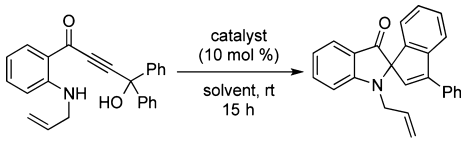
Table 1. Optimization of the Reaction Conditions[a]



1b 2b

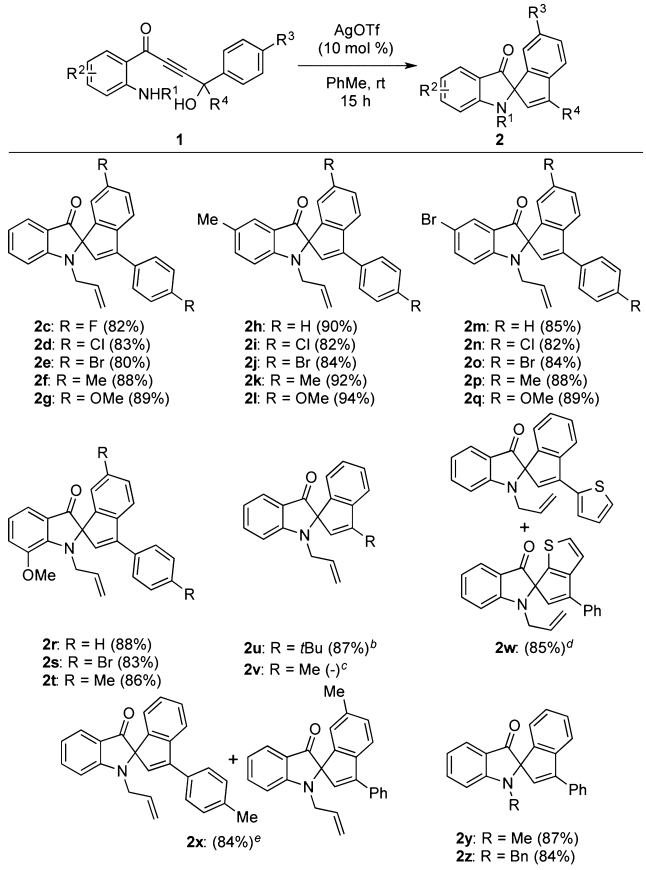
entry	catalyst	solvent	yield (%)[b]
1	$AgSbF_6$	PhMe	35
2	$AgBF_4$	PhMe	–[c]
3	AgOAc	PhMe	–[c]
4	$AgNTf_2$	PhMe	–[c]
5	AuCl/AgOTf	PhMe	80
6	$Cu(OTf)_2$	PhMe	–[d]
7	$Yb(OTf)_3$	PhMe	–[d]
8	TfOH	PhMe	–[e]
9	Tf_2NH	PhMe	–[e]
10	AgOTf	1,4-dioxane	–[c]
11	AgOTf	MeCN	–[c]
12	AgOTf	CH_2Cl_2	72
13	AgOTf	$MeNO_2$	81

[a]All reactions were performed at the 0.14 mmol scale with a catalyst/**1b** ratio of 1:10 at rt for 15 h. [b]Isolated product yield. [c]No reaction based on TLC and ^{1}H NMR analysis of crude reaction mixture. [d]Trace amount of product detected based on TLC and ^{1}H NMR analysis of the crude reaction mixture. [e]Decomposition observed based on TLC and ^{1}H NMR analysis of the crude reaction mixture.

AuCl/AgOTf in place of AgOTf as the catalyst or changing the solvent from toluene to CH_2Cl_2 or $MeNO_2$ (entries 1, 5, 12, and 13). In contrast, control experiments mediated by $AgBF_4$, AgOAc, $AgNTf_2$, $Cu(OTf)_2$, and $Yb(OTf)_3$ or employing polar solvents such as 1,4-dioxane or acetonitrile were found to result in trace product formation or no reaction (entries 2–4, 6, 7, 10, and 11). The analogous reactions catalyzed by the Brønsted acids TfOH and Tf_2NH were observed to lead to substrate decomposition (entries 8 and 9). In view of the above results, the procedure described in Scheme 2, eq 2 was regarded to provide the optimum reaction conditions.

The scope of the present procedure was next assessed with a series of propargylic alcohols, and the results are presented in Scheme 3. Overall, these experiments showed that with AgOTf as the catalyst, the reaction conditions proved to be broad and a variety of substituted 1′-allylspiro[indene-1,2′-indolin]-3′-ones could be afforded in 80–94% yield from the corresponding substrates **1c**–**1z**. Starting alcohols bearing an electron-withdrawing (**1c**–**1e**) or electron-donating (**1f** and **1g**) group on the propargylic phenyl rings were found to proceed well. These transformations gave the corresponding targets **2c**–**2g** in 80–89% yield with the structure of **2d** being confirmed by the X-ray crystallography.[16] Likewise, substrates possessing an electron-donating (**1h**–**1l** and **1r**–**1t**) or electron-withdrawing (**1m**–**1q**) group on the aminophenyl ring led to the spirocycles **2h**–**2t** in 82–94% yield. In instances where the substrate contained a geminal Ph and 2-thiophenyl or $pMeC_6H_4$ group on the carbinol carbon center, as in **1w** and **1x**, a mixture of regioisomers of **2w** and **2x** were obtained in respective ratios of 1:1 and 2:1.1 and yields of 85 and 84%. The effect of alternative amino substituents was also examined with the *N*-methyl (**1y**) and *N*-benzyl (**1z**) derivatives and found to give **2y** and **2z** in 87% and 84% yield, respectively. In our hands, the only exceptions were the cyclization of substrates in which one of the propargylic aryl moieties was replaced by a *t*Bu (**1u**) or Me

Scheme 3. Tandem Hydroamination/Hydroarylation of 1c–z Catalyzed by AgOTf[a]



[a]All reactions were performed at the 0.14 mmol scale with a AgOTf/**1** ratio of 1:10 at rt for 15 h, with values in parentheses denoting isolated product yields. [b] Reaction conducted at 100 °C for 5 h. [c] Decomposition observed based on TLC and ^{1}H NMR analysis of the crude reaction mixture. [d] Obtained as a 1:1 mixture based on ^{1}H NMR analysis of the reaction mixture. [e] Obtained as a 2:1.1 mixture based on ^{1}H NMR analysis of the reaction mixture.

(**1v**) substituent. In these experiments, a reaction temperature of 100 °C for 5 h was required to convert the first substrate to **2u** in 87% yield while the second example led to a mixture of unknown decomposition products being furnished when subjected to the standard conditions.

A tentative mechanism for the present AgOTf-catalyzed tandem 1′-allylspiro[indene-1,2′-indolin]-3′-one forming reaction is presented in Scheme 4. Using **1b** as a representative example, we propose that the cyclization proceeds with initial activation of the alkyne functionality in the substrate by the metal catalyst to produce Ag(I)-coordinated intermediate **Ib**.[17] As a consequence, this may result in 5-*exo*-*dig* hydroamination involving intramolecular nucleophilic attack of the C≡C bond by the amino group in the Lewis acid activated propargylic alcohol to give the vinyl silver species **IIb**.[18−20] Subsequent dehydration and demetalation of the organosilver complex might next provide the allenamide **3b**. Further activation of the allenic moiety in this newly formed *N*-heterocycle by the metal salt might then generate the Ag(I)-coordinated adduct **IIIb**. This is the active species that undergoes the 5-*endo*-*trig* hydroarylation process, which, upon rearomatization and protodemetalation of the ensuing spirocyclic Wheland intermediate **IVb**, would regenerate the Ag(I) catalyst and

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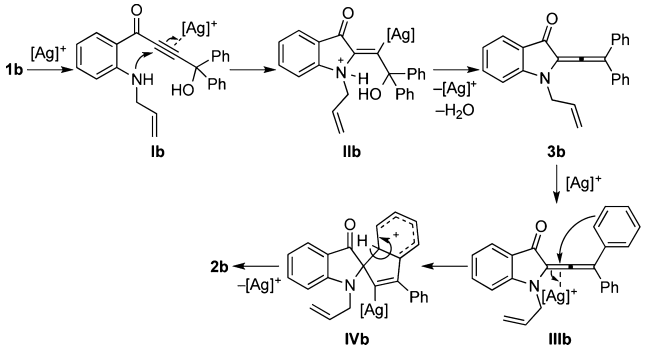
Scheme 4. Proposed Mechanism for Ag(I)-Catalyzed Hydroamination/Hydroarylation of 1-(2-Allylamino)phenyl-4-hydroxy-but-2-yn-1-ones



deliver the spirocyclic product **2b**. The proposed involvement of cationic intermediates would be consistent with the slight correlation between product yields and aromatic substitution in the substrate as well as contrasting reactivities of examples containing an alkyl group. The presence of electron-donating groups on the propargylic phenyl rings in the substrate may stabilize the buildup of positive charge and correspond to the marginally higher yields observed. In contrast, the inverse is true for electron-withdrawing moieties or when the carbinol carbon center of the substrate contained a pendant alkyl group. The observed regioselectivities for reactions with **1w** and **1x** may be due to comparable reactivities between the 2-thiophenyl and Ph moieties in the former and the directing effect of the *p*MeC$_6$H$_4$ group disfavoring hydroarylation occurring from this ring in the latter. In the case of **3a**, the reluctance of the indolin-3-one adduct to undergo hydroarylation may be due to the steric demand of the bulky Ts moiety preventing efficient coordination of the metal catalyst and/or the lower eletrophilicity of the *N*-tosyl-allenamide system precluding this pathway.[21,22]

In summary, we have described an efficient AgOTf-catalyzed synthetic approach for the assembly of 1′-allylspiro[indene-1,2′-indolin]-3′-ones from readily accessible and inexpensive 1-(2-(allylamino)phenyl-4-hydroxy-but-2-yn-1-ones. The developed methodology has been shown to be general in scope, robust, and efficient, accessing the novel spirocyclic products in high yield. The target scaffold contains both the privileged indolin-3-one and indene motifs, which may have future pharmacological potential.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization data and ^{1}H and ^{13}C NMR spectra for all starting materials and products, and CIF file of **2d**. 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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(16) The ORTEP figure of **2d** can be located in the Supporting Information. CCDC 844472 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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