

Silver catalyzed substitution of allylic and benzylic alcohols having unactivated hydroxy groups

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ABSTRACT

The catalytic Friedel-Crafts substitution of allylic and benzylic alcohols having free hydroxy groups was regioselectively catalyzed by cationic Ag(I) salts. No precautions to exclude moisture or atmosphere were necessary, making the reaction highly robust and facile. Substitution of allylic alcohols with electron rich aromatic nucleophiles favored products with alkenes conjugated to aromatic substituents. Benzylic substitution was impacted by the electronics of the alcohol aryl group, whereas allylic substitution was not. The use of a bromoindole nucleophile allowed for a formal total synthesis of echinosulfonic acid D, where the penultimate synthetic intermediate was synthesized in half the steps previously needed.

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Introduction and background

Reactions that facilitate C—C bond formation from readily available sources such as alkenes, carbonyl derivatives, and alcohols are needed to increase efficiency and sustainability in synthetic organic chemistry. Activated alcohols are easily derived from those sources, and the location of their hydroxy groups adjacent to alkene, aromatic, or alkynyl functionality allows access to various transformations. One of the most efficient uses of these substrates is the catalytic substitution of the hydroxy group to form a new C—C bond without prior modification and without competing hydroxy group elimination to form alkenes at aliphatic substituents. Our goal has been to find a simple, practical, and convenient catalyst for this transformation that is highly tolerant of a variety of functional groups to maximize synthetic utility.

Many transition metal cross-couplings of allylic and benzylic alcohols have been reported [1–8], with several being stereospecific [9–12] or enantioselective (Fig. 1A) [13–17]. However, the use of expensive metals like Rh [18,19,17] or Ir [15,16], of expensive ligands, or of atmospheric intolerant [20] or functional group incompatible precursors motivates identification of a cheaper, less complex solution. Brønsted acids could be an alternative (Fig. 1B), but outside of the use of specially designed substrates [21,22,23,24,25,26] we have found significant issues with hydroxy group elimination being favored over substitution with C—C bond formation. Some early successes have been seen using Bi [27] and Ca [28,29] Lewis acids with specific activated nucleophiles such as allyl silane or acetoacetate, which prompted us to investigate the

possibility of an electrophilic deboronation [30] approach to substitution. Such an approach with soft Lewis acids was highly successful for the direct substitution of propargylic hydroxy groups for the formation of tertiary and quaternary centers with minimal elimination or rearrangement (Fig. 1C) [26c].

Approach

We initially pursued the electrophilic deboronation reaction strategy using knowledge derived during the investigation of propargylic alcohol substitution. In fact, simple Ag⁺ salts effectively catalyzed product formation from unactivated allylic and benzylic alcohols (Table 1, entries 1–2). Control experiments quickly showed that the catalysis functioned even without the nucleophilic activation of boronates (Table 1, entries 3–4), allowing a cheaper and simpler transformation using readily available aromatic nucleophiles in a mild Friedel-Crafts reaction. Notably, elimination was not seen for aliphatic substituents when using cationic Ag(I), which was a problem observed when using hard Lewis acids, and other soft Lewis acids showed no conversion of the alcohol to arylated products (Table 1, entries 5–6). Interestingly, a few trials showed how electrophilic deboronation can be superior to regular Friedel-Crafts reactivity, as **4** was produced in 75% yield from the organoboronic acid but only 12% from anisole (entry 2), and product **2** could only be observed when using non-Ag⁺ Lewis acids when the boronic acid was used (entry 5). Polar solvents shut down the reaction (Table 1, entries 7–8). Surprisingly, one to two equivalents of water proved highly beneficial to the reaction, and the presence of oxygen had no effect, though excess water was deleterious (Table 1, entries [9–13]). Consequently, reactions could be run on the benchtop using Ag⁺ salts weighed in the open air, un-

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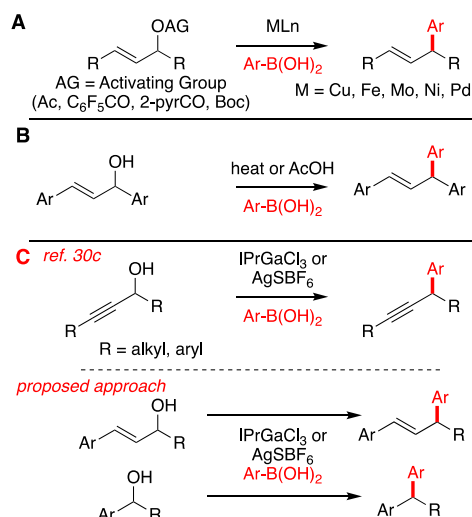


Fig. 1. (A) Transition metal cross-coupling reactions. (B) Electrophilic deboronation. (C) Friedel-Crafts with a soft Lewis acid.

purified or dried commercial solvent, and no precautions to exclude atmosphere from the reaction, making this one of the most tolerant alcohol substitution reactions. Given that Ag^+ salts could form Brønsted acid in the presence of water, we performed control experiments with two substrates to assess the ability of anhydrous HCl to promote the reaction with or without silver (see [Supporting Information](#) for details). Unsurprisingly, the presence of only HCl effected primarily the elimination of the hydroxy group, but in the presence of AgSbF_6 the addition of HCl allylation of the anisole was still the major process. In one case HCl addition resulted in lower conversion, but in the other it accelerated the reaction to be complete in only 2 h. This shows that Brønsted acid is beneficial but not sufficient for reactivity. Conversely, the addition of $\text{K}_2\text{CO}_3(\text{s})$ to the AgSbF_6 -catalyzed reaction eliminated catalysis. We believe this to indicate the intermediate **3-Ag⁺** is important

for catalysis,^[31] and deprotonation of this intermediate by base thus eliminates reactivity. In another control experiment, enantioenriched benzylic alcohol was subjected to the conditions found in [Table 1](#), entry 4, and only racemic product was obtained. This result showed the absence of stereospecificity in the transformation.

Discussion

With generally effective reaction conditions in hand, substrate variations were examined to explore the reaction's scope. Allylic alcohols were initially investigated, as preliminary trials showed they more readily underwent controlled substitution. Regardless of aryl substituent electronics and substitution pattern, regioselective substitution that preserved the conjugation between the alkene and aromatic substituent remained consistent (see **2**, **5–8**, [Fig. 2](#)). Electron deficient aryl rings such as those on **5–8** reacted smoothly. We then wanted to probe whether stabilization from a conjugated aromatic was significant for reactivity. In another approach, aryl-alkene conjugation was disrupted via torsion caused by the allylic strain from ortho substituents as seen in products **7** and **11**, but reactivity was unaffected, and the regioselectivity remained consistent. We then moved to explore increased conjugative stabilization by adding an additional aromatic group adjacent to the hydroxy group. This also seemed to have minimal impact on reactivity and selectivity (see **8** and **9**). Likewise, removal of the allylic substituent entirely allowed for secondary carbon formation with no change in regioselectivity, but with slightly lower yield (see **10**). The synthesis of **10** and **13** showed that the isomeric allylic alcohol both functioned as a viable starting material and exhibited the same regioselectivity. As expected, electron rich aromatic nucleophiles were needed for reactivity, and even *ortho*-substituted arylated products were formed well (see **12**), but unfortunately heteroaryl nucleophiles displayed inconsistent and unpredictable reactivity in combination with allylic alcohols, and were not tolerated as well as they are in electrophilic deboronations ^[32]. Aliphatic alcohols functioned less well in the re-

Table 1
Key optimization and control experiments.

Entry	ROH	Lewis acid	Solvent	Time	Yield 2 or 4 ^a
1 ^b	allylic 1	AgOTf	CH_2Cl_2	24 h	25% 2
2 ^b	benzylic 3	AgOTf	CH_2Cl_2	24 h	75% (12 %) 4
3	allylic 1	AgSbF_6	CH_2Cl_2	15 h	86% 2
4	benzylic 3	AgSbF_6	$\text{ClCH}_2\text{CH}_2\text{Cl}_2$	24 h	80% 4
5	allylic 1	$\text{La}(\text{OTf})_3$, $\text{Cu}(\text{OTf})_2$, InCl_3 , $\text{Yb}(\text{OTf})_2$, $\text{Sc}(\text{OTf})_3$, or AgBr	CH_2Cl_2	24 h	0% 2 10–20% 2 ^b
6	benzylic 3	LiOTf , $\text{Cu}(\text{OTf})_2$, InCl_3 , $\text{Yb}(\text{OTf})_2$, or $\text{Sc}(\text{OTf})_3$	CH_2Cl_2	24 h	0% 4
7	benzylic 3	AgSbF_6	MeCN , THF , or Et_2O	24 h	0% 4
8	allylic 1	AgSbF_6	MeCN , THF , or Et_2O	24 h	0% 2
9 ^d	allylic 1	AgSbF_6	$\text{ClCH}_2\text{CH}_2\text{Cl}_2$	12 h	84% 2
10 ^{e,f}	allylic 1	AgSbF_6	$\text{ClCH}_2\text{CH}_2\text{Cl}_2$	12 h	2–9% 2
11 ^d	benzylic 3	AgSbF_6	$\text{ClCH}_2\text{CH}_2\text{Cl}_2$	12 h	68% 4
12 ^e	benzylic 3	AgSbF_6	$\text{ClCH}_2\text{CH}_2\text{Cl}_2$	12 h	86% 4
13 ^f	benzylic 3	AgSbF_6	$\text{ClCH}_2\text{CH}_2\text{Cl}_2$	12 h	0% 4

^a Yield based on ^1H NMR peak integration.

^b *p*-anisolyboronic acid used in lieu of anisole.

^c When anisole was used.

^d 1 equiv H_2O added and/or open to air.

^e 2 equiv H_2O added.

^f 4–8 equiv H_2O added.

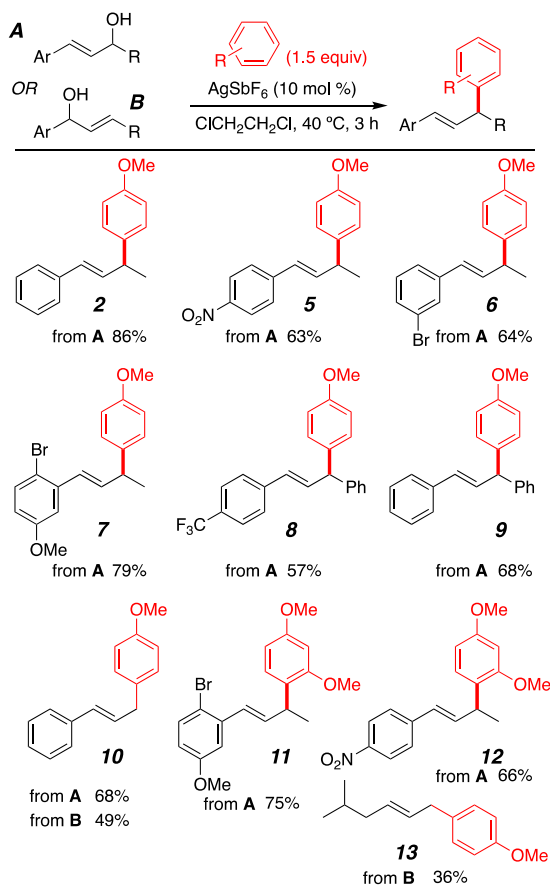


Fig. 2. Scope of Allylic Substitution.

action, perhaps because of some competing elimination to volatile alkenes that were not reactive.

For benzylic alcohols that were only activated by an adjacent phenyl ring, undesired reactivity (e.g., elimination) often competed with direct substitution, and many reactions took longer than the corresponding allylic substrates, likely due to decreased stabilization of cationic intermediates. While alkyl substituted aryl rings proved more reactive than the original benzylic substrate (compare **4** to **14** and **19**, Fig. 3), the ether substitution in example **15** had a negative impact on product yield. Interestingly, naphthalenyl substrates reacted more cleanly, which produced products in good yields from a variety of nucleophiles (see **17**, **20**, and **21**). As is typical with Friedel-Crafts type reactions, double addition, such as that seen in product **21** can be favored when the equivalents of the nucleophile are limited. When comparing these results with the allylic substitution in Fig. 2, cation stability seems to have a more significant effect on reactivity for the benzylic substitution, which appears more reliant on aryl electronics. Therefore, we wanted to probe whether substitution could occur alpha to other functional groups such as carbonyls. While phenyl-substituted α -hydroxy esters failed to produce $\alpha\alpha$ -diarylesters, we hypothesized that pairing increased electron density for benzylic stabilization and using stronger nucleophiles might be fruitful. Gratifyingly, $\alpha\alpha$ -bisindole ester **22**, which is the penultimate intermediate to the recently synthesized natural product echinosulfonic acid [33], can be produced in useful yields using 6-bromoindole under very mild conditions in three total steps, where previously it had taken 7. This reduction to less than half the required steps shows the utility of this direct substitution approach. In general, indole proved to be reactive for benzylic substitution (see **22** and **23**), though when

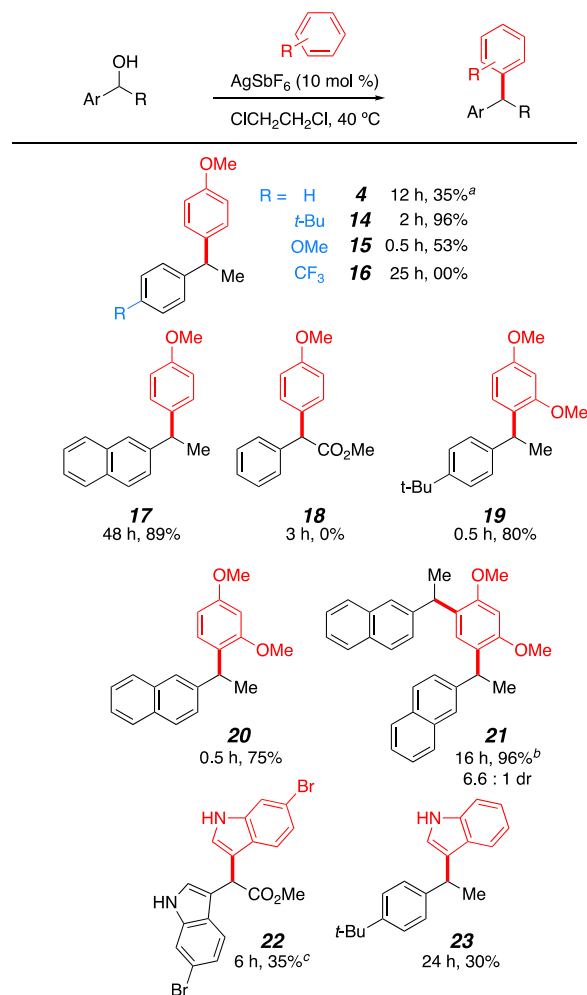


Fig. 3. Scope of Benzylic Substitution. ^aAn 8% yield of the *ortho*-product was also produced. ^bRatio of benzylic alcohol **3** to dimethyl resorcinol was 2:1. ^cReaction conducted at $20\text{ }^\circ\text{C}$. Yield for 2 steps: reduction of the ketoester and then hydroxy group substitution.

it had been used for allylic substitution numerous side reactions had been seen.

Conclusion

The catalytic substitution of activated alcohols having free hydroxy groups proved effective when catalyzed by cationic $Ag(I)$ salts. Surprisingly, no precautions to exclude moisture or atmosphere from the reaction were necessary, and small amounts (1–2 equiv) of water even improved the reaction yields. Substitution of allylic alcohols was regioselective and favored conjugated products. Benzylic substitution was impacted by aryl electronics, whereas allylic substitution was not. Several electron-rich aromatic rings were competent nucleophiles, and benzylic alcohols with adjacent esters also underwent substitution and were compatible with indoles. The latter reactivity allowed for a formal total synthesis of echinosulfonic acid D, where the penultimate intermediate was synthesized in half the steps previously needed.

Data availability

All data found in [supporting material](#)

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.tetlet.2023.154572>.

References

- [1] M.I. Calaza, X. Yang, D. Soorukram, P. Knochel, *Org. Lett.* 6 (2004) 529–531.
- [2] C. Feng, Y. Kobayashi, *J. Org. Chem.* 78 (2013) 3755–3766.
- [3] Y. Kobayashi, Y. Tokoro, K. Watatani, *Eur. J. Org. Chem.* (2000) 3825–3834.
- [4] Y. Kayaki, T. Koda, T. Ikariya, *Eur. J. Org. Chem.* (2004) 4989–4993.
- [5] K. Manabe, K. Nakada, N. Aoyama, S. Kobayashi, *Adv. Synth. Catal.* 347 (2005) 1499–1503.
- [6] H. Tsukamoto, M. Sato, Y. Kondo, *Chem. Commun.* 4 (2004) 1200–1201.
- [7] A.V. Malkov, P. Spoor, V. Vinader, P. Kocovsky, *J. Org. Chem.* 64 (1999) 5308–5311.
- [8] S. Teranishi, T. Kurahashi, S. Matsubara, *Synlett* 24 (2013) 2148–2152.
- [9] H.D. Srinivas, Q. Zhou, M.P. Watson, *Org. Lett.* 16 (2014) 3596–3599.
- [10] J. Ye, J. Zhao, J. Xu, Y. Mao, Y.J. Zhang, *Chem. Commun.* 49 (2013) 9761–9763.
- [11] C. Li, J. Xing, J. Zhao, P. Huynh, W. Zhang, P. Jiang, Y.J. Zhang, *Org. Lett.* 14 (2012) 390–393.
- [12] H.B. Wu, X.T. Ma, S.K. Tian, *Chem. Commun.* 50 (2014) 219–221.
- [13] P.M. Lundin, G.C. Fu, *J. Am. Chem. Soc.* 132 (2010) 11027–11029.
- [14] F. Paquin, J. Rivnay, A. Salleo, N. Stingelin, C.J. Silva, *Mater. Chem. C.* 3 (2015) 10715–10722.
- [15] F.A. Moghadam, E.F. Hicks, Z.P. Sercel, A.Q. Cusumano, M.D. Bartberger, B.M. Stoltz, *J. Am. Chem. Soc.* (2022) 7983–7987.
- [16] J.Y. Hamilton, D. Sarlah, E.M. Carreira, *J. Am. Chem. Soc.* 135 (2013) 994–997.
- [17] S.B. Tang, X. Zhang, H.F. Tu, S.L. You, *J. Am. Chem. Soc.* 140 (2018) 7737–7742.
- [18] T. Gendrineau, J.P. Genet, S. Darses, *Org. Lett.* 12 (2010) 308–310.
- [19] G.W. Kabalka, G. Dong, B. Venkataiah, *Org. Lett.* 5 (2003) 893–895.
- [20] Y.B. Wang, B.Y. Liu, Q. Bu, B. Dai, N. Liu, *Adv. Synth. Catal.* 362 (2020) 2930–2940.
- [21] J.A. Malone, A.H. Cleveland, F.R. Fronczek, R. Kartika, *Org. Lett.* 18 (2016) 4408–4411.
- [22] X.-D. Li, L.-J. Xie, D.-L. Kong, L. Liu, L. Cheng, *Tetrahedron* 72 (2016) 1873–1880.
- [23] M. Ueda, D.L. Nakakoji, T. Morisaki, I. Ryu, *Eur. J. Org. Chem.* (2017) 7040–7045.
- [24] Y. Karuo, S. Dousei, M. Sakamoto, A. Tarui, K. Sato, K. Kawai, M. Omote, *Heterocycles* 101 (1) (2020) 363–372.
- [25] J. Le Bras, J. Muzart, *Tetrahedron* 63 (2007) 7942–7948.
- [26] P. Trillo, A. Baeza, C. Nájera, *J. Org. Chem.* 77 (2012) 7344–7354.
- [27] S. Dhiman, S.S.V. Ramasastry, *Org. Biomol. Chem.* 11 (2013) 4299–4303.
- [28] V.J. Meyer, M. Niggemann, *Eur. J. Org. Chem.* (2011) 3671–3674.
- [29] D. Lebœuf, M. Pesset, B. Michelet, C. Bour, S. Bezzene-Lafollée, V. Gandon, *Chem. Eur. J.* 21 (2015) 11001–11005.
- [30] (a) Nguyen, T. N.; Nguyen, T. S.; May, J. A. *Org. Lett.* 2016, 18, 3786–3789; (b) Nguyen, T. N.; May, J. A. *Org. Lett.* 2018, 20, 112–115; (c) Donald, C. P.; Boylan, A.; Nguyen, T. N.; Chen, P. A.; May, J. A. *Org. Lett.* 2022, 24, 6767–6771; (d) Nguyen, T. N.; May, J. A. *Org. Lett.* 2018, 20, 3618–3621; (e) Roscales, S.; Ortega, V.; Csáky, A. G. *J. Org. Chem.* 2013, 78, 12825–12830; (f) Sánchez-Sancho, F.; Csáky, A. G. *C-H Synth.* 2016, 48, 2165–2177; (g) Roscales, S.; Csáky, A. G. *Chem. Commun.* 2014, 50, 454–456; (h) Roscales, S.; Csáky, A. G. *Chem. Soc. Rev.* 2014, 43, 8215–8225; (i) Roscales, S.; Ortega, V.; Csáky, A. G. *J. Org. Chem.* 2018, 83, 11425–11436; (j) Roscales, S.; Csáky, A. G. *Chem. Commun.* 2016, 52, 3018–3021; (k) Ortega, V.; Del Castillo, E.; Csáky, A. G. *Org. Lett.* 2017, 19, 6236–6239.
- [31] M. Vayer, S. Rodrigues, S. Miaskiewicz, D. Gatineau, Y. Gimbert, V. Gandon, C. Bour, *ACS Catal.* 12 (1) (2022) 305–315.
- [32] P.Q. Le, T.S. Nguyen, J.A. May, *Org. Lett.* 14 (2012) 6104–6107.
- [33] T. Abe, R. Nakajima, T. Yamashiro, D. Sawada, *J. Nat. Prod.* 85 (2022) 2122–2125.