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Synthesis of the Privileged 8-Arylmenthol Class by Radical Arylation of Isopulegol

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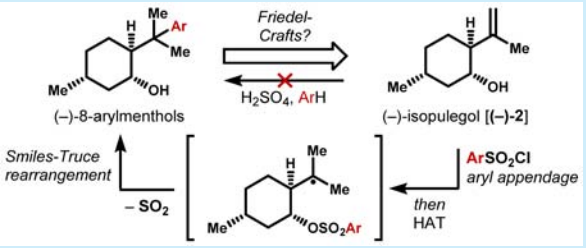
Supporting Information

ABSTRACT: Hydrogen atom transfer (HAT) circumvents a disfavored Friedel–Crafts reaction in the derivatization of the inexpensive monoterpene isopulegol. A variety of readily prepared aryl and heteroaryl sulfonates undergo a formal hydroarylation to form 8-arylmenthols, privileged scaffolds for asymmetric synthesis, as typified by 8-phenylmenthol. High stereoselectivity is observed in related systems. This use of HAT significantly extends the chiral pool from the inexpensive monoterpene isopulegol.



New chemical reactions to modify abundant terpenes find application in polymer science, medicine, and chemistry, as well as the flavor and fragrance industry.[1] Chiral catalysts, reagents, and auxiliaries, for example, can be sourced from cyclic monoterpenes,[2] which are usually inexpensive, abundant, and easily removed from reaction mixtures. During recent studies of the isocyanoterpene (ICT) class,[3] we required access to *aryl derivatives* of the broadly applicable chiral controller, 8-phenylmenthol (**1**).[4] The parent alcohol (−)-**1** or (+)-**1** can be appended to carboxylic acids to effect highly stereoselective reactions, as shown in Figure 1a,b.[5,6] Many reports have also documented substantial variations in diastereocontrol achieved due to variations in the identity of the aryl group,[7,9b,c,e−i] but short routes to these aryl analogs are not available.

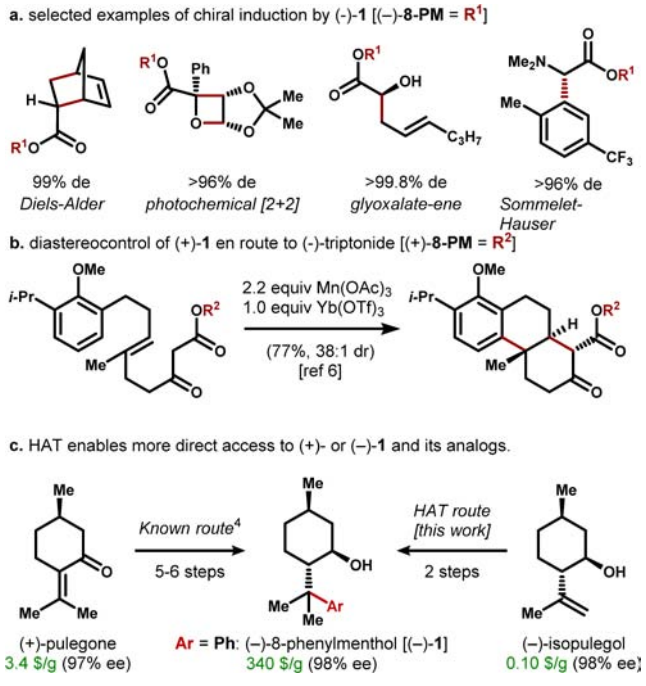


Figure 1. Uses and synthesis of 8-phenylmenthol (**1**).

Although either enantiomer of **1** is commercially available, the high cost [(−)-**1**: 340 $/g; (+)-**1**: 840 $/g] and low supply of these molecules impedes direct functionalization[7] and probably reflects the cost of their five- or six-step syntheses from (+)- or (−)-pulegone (3.4 $/g at 97% purity and 206 $/g, respectively; prices from Sigma; see Figure 1c).[4] Desymmetrization of (±)-*trans*-2-cumyl-cyclohexanol using a lipase can be an effective alternative to **1**,[8] but yields range from 31% to 48% over two resolution cycles and commercial costs are high (214 $/g for (−)-2-cumylcyclohexanol; (+)-isomer discontinued). Analogs of **1** have been synthesized by Corey's route,[9] but are not widely available, and we could find no examples in the literature of heteroaryl analogs.[10]

Here we report a radical method that provides rapid access to (+)- and (−)-8-phenylmenthol and numerous chiral arylated menthol derivatives. Combination of hydrogen atom transfer (HAT) radical generation[11,12] with a radical Smiles–Truce rearrangement[13,14] allows homoallylic alcohols to be formally hydroarylated using arylsulfonyl halides. Electron-deficient, -neutral, and -rich arenes may be engaged, as well as electron-rich sites on heterocycles, orthogonal to the Minisci reaction.

The obvious precursor to (−)-8-phenylmenthol is (−)-isopulegol [(−)-**2**], whose low cost of 0.10 $/g reflects its intermediacy in the multikiloton industrial synthesis of (−)-menthol itself (Figure 2).[15] However, direct Brønsted acid mediated Friedel–Crafts phenylation of isopulegol results in complex mixtures due to selective ionization of the alcohol functionality. Therefore, we turned away from a cationic mechanism to investigate radical arylation.

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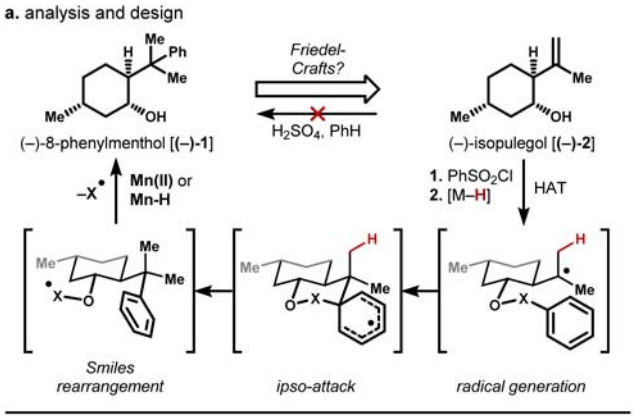
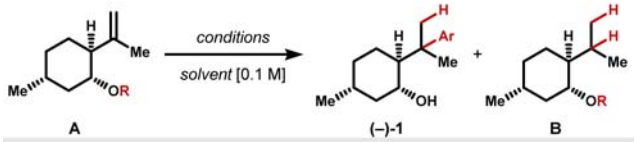


b. execution



entry	substrate	conditions	observed products
1	R = Bz	$Mn(dpm)_3$, $PhSiH_3$	only B
2	R = 3-CF_3-Bz	$Mn(dpm)_3$, $PhSiH_3$	only B
3	R = 2,3,4-F-Bz	$Mn(dpm)_3$, $PhSiH_3$	only B
4	R = 2,4-F,3-CF_3-Bz	$Mn(dpm)_3$, $PhSiH_3$	only B
5	R = $SiMe_2Ph$	$Co(Salen^{tBu,tBu})Cl$, $PhSiH_3$, PhH	only recovered A
6	R = $SiPh_3$	$Co(Salen^{tBu,tBu})Cl$, $PhSiH_3$, PhH	only recovered A
7	R = SO_2Ph (3)	$Mn(dpm)_3$, $PhSiH_3$ ***(see Figure 3)***	(–)-1 and B

Figure 2. Aryl transfer strategy and execution.

We previously reported that carbon-centered radicals generated under Mukaiyama-type conditions[16,17] are sufficiently persistent to engage proximal arenes.[11f,18,19] Frequently, the chemoselectivity of these conditions is orthogonal to Brønsted acid mediation. To effect aryl transfer to the isopulegol alkene, we imagined appending an arene to the proximal alcohol with a single-electron nucleofuge (Figure 2).[14] However, benzoates (entries 1–4) or (phenyl)silyl[20] ethers (entries 5–6) led only to hydrogenation products **B** or recovered starting materials **A**, even if strong electron-withdrawing groups were appended. The sulfonate linker alone (**3**, entry 7) was competent to produce aryl transfer product (−)-**1**, which is the targeted auxiliary. Radical Smiles–Truce rearrangements reported by Motherwell, Studer, Tada, and Stephenson also utilize a sulfonate radical nucleofuge,[13,14] which appears to provide both Thorpe–Ingold acceleration and an inductive electron-withdrawing effect. A range of metal complexes could affect this transformation in the absence of O_2, but stoichiometric metal reagents were required consistently, presumably due to metal sequestration via irreversible binding of sulfite radical ($ROSO_2\cdot$) or liberated sulfur dioxide (SO_2).[21] Despite extensive efforts, attempts to effect metal turnover were unsuccessful, although addition of TBHP accelerated the reaction.[22]

As shown in Figure 3, we found that a diverse set of aryl sulfonates function well in this chemistry. Most of the arylsulfonyl chloride/fluoride precursors are commercially available, and all are accessible in short sequences (see Supporting Information [SI]). Notably, anisole can be appended at its more electron-rich *ortho*- (**4a**) and *para*- (**4b**) positions. As expected, electron-rich tolyl groups (**5a–c**) do not engage the electron-rich *tert*-alkyl radical as efficiently as electron-deficient halogenated aromatics (**6a–c**), but still

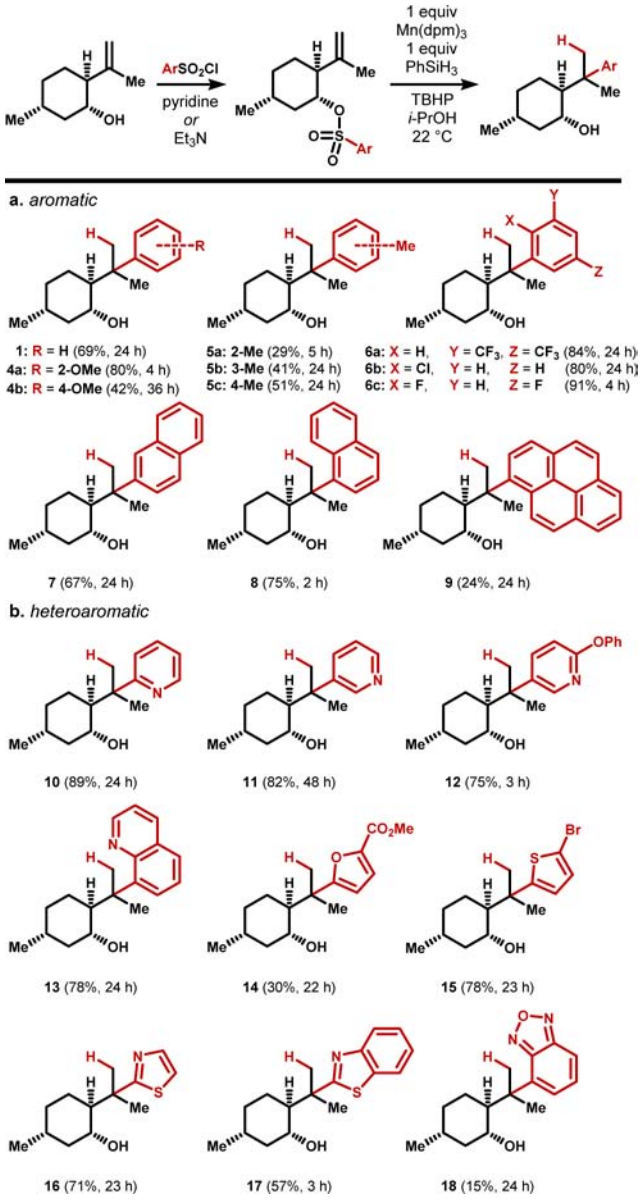


Figure 3. Survey of aryl sulfonate transfer using (−)-isopulegol.

competently generate the arylated products, which are easy to separate from hydrogenation byproducts. Naphthyl groups transfer efficiently (**7–8**), and the 1-naphthyl derivative (**8**) shows restricted bond rotation (see SI), illustrating the steric clash this rearrangement will tolerate. Even a 1-pyrenyl substituent can be transferred: **9** may be of some utility for enantioselective catalysis.[23] Pyridyl groups are very efficient in accepting alkyl radicals, as observed by Minisci in intermolecular settings,[24] and we accordingly observed efficient 2-pyridyl transfer (**10**). However, in this case, electron-poor (**11**) or -rich (**12**) 3-pyridyl groups can be selectively engaged, whereas the 3-position is generally unreactive in intermolecular Minisci coupling. These nitrogen heterocycles appended to the menthyl skeleton may be appealing chiral Lewis bases to investigate for enantioselective catalysis. Other heteroaromatics—quinolines, furans, thiophenes, thiazoles, and benzothiazoles (**13–17**) all transfer efficiently. The benzofurazan will transfer (**18**), albeit in very modest yield. In this case, we attempted to improve the yield by varying the metal complex,

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but found instead that $Fe(acac)_3$ caused double N−O bond cleavage,[25] and only trace aryl transfer product was observed.

Although use of stoichiometric $Mn(dpm)_3$ is not cost-prohibitive, we discovered that its partial replacement with the inexpensive salt $Mn(OAc)_3{\cdot}2H_2O$ could effectively lower its loading to 5 mol %, albeit with longer reaction times. The presence of $Mn(OAc)_3{\cdot}2H_2O$ in solution presumably allows the active $Mn(dpm)_n$ complex to reform *in situ*. Indeed, addition of 20 mol % of ligand (Hdpm) with 1 equiv of $Mn(OAc)_3{\cdot}2H_2O$ behaves identically to 5 mol % $Mn(dpm)_3$. At 1/20 the price ($1.1 vs $24/mmol, Sigma) and a much reduced formula weight, we found this to be convenient and scalable.

These optimized conditions were successfully applied to the scaled synthesis of both isomers of **1** (Figure 4), with (+)-**1** originating from (−)-citronellal; (+)-isopulegol is more expensive than (−)-**2**. Cyclization of **19** occurred in high yield and high diastereoselectivity to deliver (+)-isopulegol, as precedented.[26] Sulfonylation and aryl transfer proceeded smoothly to yield 1.3 g of (+)-**1** (96% ee) in 41% overall yield from commercial materials.

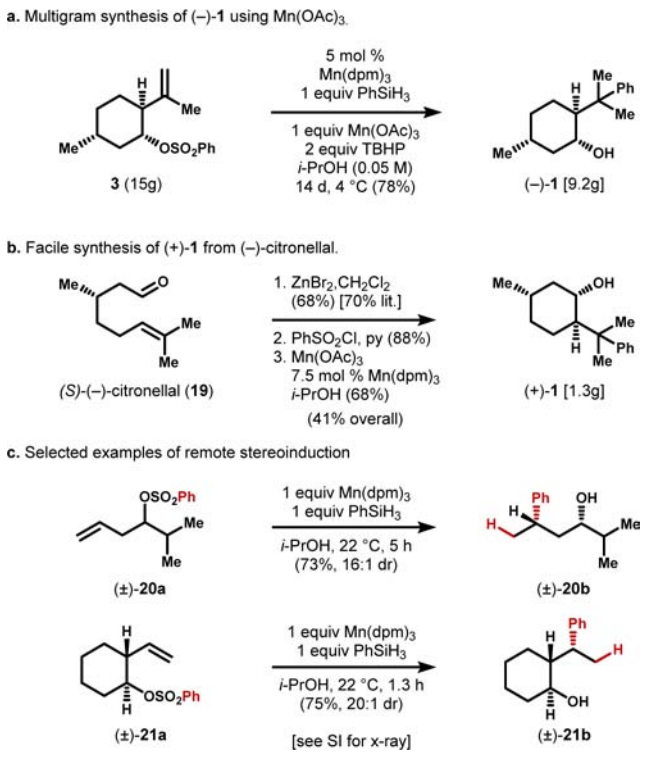

Figure 4. Further applications for HAT-initiated aryl transfer.

We were curious to see whether radicals derived from prochiral alkenes or linear aryl sulfonates were competent to undergo stereoselective aryl transfer. As shown in Figure 4c, simple linear sulfonate **20a** undergoes radical aryl transfer to give γ-phenyl alcohol **19b** in both good yield (73%) and high stereoselectivity (16:1 dr). Identical selectivity is observed in reactions involving classically generated radicals.[14b,e] The terminal alkene is key to obtaining high yields because the initial HAT reaction is not regioselective in sterically and electronically equivalent alkenes, e.g. 1,2-disubstituted alkenes. In a similar manner, the substrate **21a** undergoes clean rearrangement with very high stereoselectivity (>20:1) to give the stereochemically dense alcohol **21b** (assigned by X-ray crystallography; see SI). These results suggest that such a transformation may find utility beyond the intended application of aryl menthol synthesis.

In summary, we demonstrate an inexpensive, two-step route for the synthesis of arylated menthols from the simple building blocks isopulegol and arene sulfonyl halides. This strategy leverages HAT to generate quaternary sp^3−sp^2 carbon−carbon bonds with exclusive Markovnikov selectivity and is sufficiently mild to tolerate a wide array of electronically, sterically, and functionally differentiated arenes and heteroarenes. More importantly, this HAT strategy for terpene functionalization significantly expands the reach of the monoterpene chiral pool, especially to chiral Lewis bases such as pyridine **10**, quinoline **13**, thiazole **16**, and their derivatives. We anticipate this expansion will prove valuable for the development of new chiral catalysts and reagents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01047.

X-ray crystallography data (CIF, CIF)
Detailed experimental procedures, spectral data, and chromatograms (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to E. J. Corey.

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