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Iron-Catalyzed Arene Alkylation Reactions with Unactivated Secondary Alcohols

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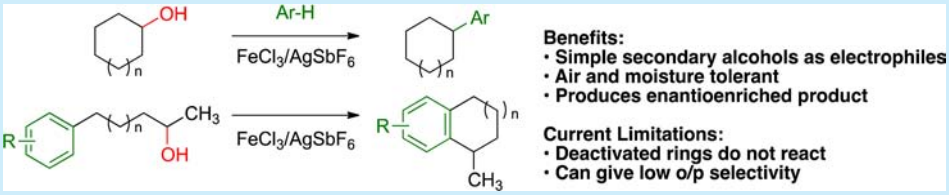
Supporting Information



ABSTRACT: A simple, iron-based catalytic system allows for the inter- and intramolecular arylation of unactivated secondary alcohols. This transformation expands the substrate scope beyond the previously required activated alcohols and proceeds under mild reaction conditions, tolerating air and moisture. Furthermore, the use of an enantioenriched secondary alcohol provides an enantioenriched product for the intramolecular reaction, thereby offering a convenient approach to nonracemic products.

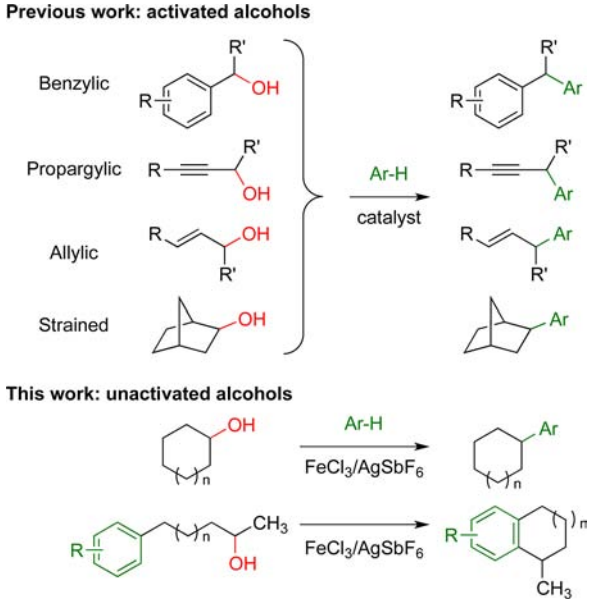
The Friedel–Crafts acylation and alkylation reactions have occupied a central role in synthesis for nearly a century and a half.[1] The basic Friedel–Crafts alkylation utilizes nucleophilic arenes, secondary or tertiary halides, and a strong Lewis or Brønsted acid catalyst to create a new carbon–carbon bond. Traditionally, Lewis acids (e.g., $AlCl_3$,[1] BF_3,[2] $ZnCl_2$,[3] $SbCl_5$,[4] $Sc(OTf)_3$,[5] and Fe salts[6a,b]) or strong Brønsted acids (e.g., HF, H_3PO_4, and H_2SO_4[7]) have been employed to accelerate these reactions. Since these reactions typically proceed through a carbocation intermediate, stereochemical control remains a critical unmet challenge.[8]

Unfortunately, this venerable carbon–carbon bond-forming reaction comes with significant drawbacks. The use of potent, and usually toxic, alkylating agents, such as alkyl halides, combined with the frequent need for superstoichiometric amounts of the acid catalyst creates a significant waste stream with excess salt byproducts. Therefore, strong demand exists for alternative alkylating agents and catalysts that can be used in substoichiometric quantities.

The direct catalytic functionalization of alcohols remains a long-standing challenge in synthesis. More recently, the desire for "greener" methods in pharmaceutical synthesis has led to renewed interest in the direct displacement of alcohols over more wasteful "activation" methods.[9] Since hydroxide is such a poor nucleofuge, however, derivatization of the alcohol remains the preferred route in modern Friedel–Crafts-type alkylation methods.[5e,f,6b,10] If the direct displacement of an alcohol can be achieved stereoselectively, it would represent an attractive approach to nonracemic arylation products.

Recent progress has employed alcohols "activated" by strain[11] or adjacent π systems, such as benzylic,[6b,12] allylic,[5e,6a,13] or propargylic alcohols[14] (Scheme 1). With this limited substrate scope, the transition from π-activated alcohols to less reactive alkyl alcohols remains a major aim.[6a,8b,15] Despite this critical goal, there exists only a single report, to the best of our knowledge, describing two isolated examples of a Friedel–Crafts-type alkylation using unactivated secondary alcohols with expensive Yb salts.[16] More recently, arene alkylation reactions based on unactivated alcohols have been reported with a Ru-catalyzed C–H activation[17] and redox chain reaction.[18] Here we report a method for the inter- and intramolecular arylation of unactivated secondary alcohols

Scheme 1. Advances in Friedel–Crafts Reactions with Secondary Alcohols



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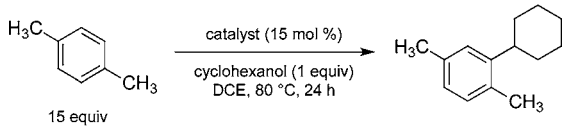
using a simple iron-based catalytic system that tolerates air and moisture.

Cognizant of reports on the difficulty of alcohol-based electrophiles in the Friedel–Crafts-type alkylation,[6a] we were surprised to find that $FeCl_3$ catalyzes the intermolecular Friedel–Crafts-type alkylation of *p*-xylene (**1**) with cyclohexanol in low, but isolable, 4% yield (Table 1, entry 1). During an extensive evaluation of Lewis acidic metal salts (Cu and Zn shown in Table 1, entries 6–8), iron(III) chloride was found to be uniquely effective in catalyzing the desired reaction. We reasoned that the addition of silver salts to the iron catalyst might provide a more active, cationic iron complex for the dehydration. We were pleased to find both $AgSbF_6$ and $AgAsF_6$ led to substantially higher yields of desired product **2** (Table 1, entries 9–10). Furthermore, $AgSbF_6$ proved critical in the successful, albeit low yielding, alkylation with other Lewis acids (see Supporting Information (SI)). Because of the greater cost of $AgAsF_6$, we decided to proceed with the $FeCl_3/AgSbF_6$ combination for subsequent studies. Interestingly, both a lower catalyst loading (<15 mol %) and temperature (<50 °C) resulted in a significantly lower yield (see SI). The alkylation of *p*-xylene proved difficult under the influence of a variety of Brønsted acids (Table 1, entry 15 and SI), thereby demonstrating that strong acids traditionally used in Friedel–Crafts alkylations are ineffective in substoichiometric quantities.

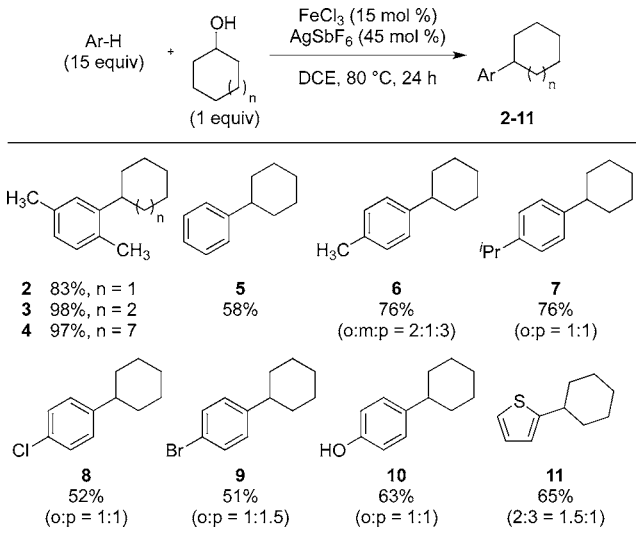
Table 1. Select Catalytic Conditions Evaluated for the Intermolecular Friedel-Crafts-Type Reaction of Unactivated Secondary Alcohols



entry	catalyst	% yield
1	$FeCl_3$	<5
2	$FeCl_2$	0
3	$FeCl_3{\cdot}6H_2O$	0
4	$Fe(BF_4)_2{\cdot}3H_2O$	0
5	$FeF_3{\cdot}3H_2O$	0
6	CuOTf	0
7	$CuCl_2$	0
8	$ZnCl_2$	0
9	**$FeCl_3$ w/ 3$AgSbF_6$**	**83**
10	$FeCl_3$ w/ 3$AgAsF_6$	83
11	$FeCl_3$ w/ 3$AgPF_6$	<5
12	$FeCl_3$ w/ 3AgOTf	<5
13	$FeCl_3$ w/ 3$AgNO_3$	<5
14	$FeCl_3$ w/ 3AgOAc	<5
15	H_2SO_4	<5

With the identification of suitable reaction conditions for the intermolecular alkylation of *p*-xylene (**1**) with cyclohexanol, the substrate scope was evaluated (Scheme 2). It was determined that the reaction followed traditional electrophilic aromatic substitution trends where electron-rich arenes reacted faster, and in higher yield, than electron-neutral or -deficient arenes. For example, benzene, chlorobenzene, and bromobenzene only produced modest 50+% yields (**5**, **8**, and **9**, Scheme 2) while *p*-xylene, toluene, cumene, and phenol provided the desired products in significantly higher yields (**2**–**4**, **6**, **7**, and **10**, Scheme 2). Electron-deficient arenes such as perfluorobenzene,

Scheme 2. Intermolecular Friedel-Crafts-Type Alkylation of Secondary Alcohols[a]



[a]Yields are isolated yields. Regioselectivity provided in parentheses.

2-acetylfuran, ethyl-2-furoate, ethyl-3-furoate, 2-acetylthiophene, and 2-naphthaldehyde failed to react under these conditions, in contrast to the numerous side reactions observed with strong Brønsted acid promoted Friedel–Crafts alkylations.[15] While thiophene proved to be a competent nucleophile for this reaction (**11**, Scheme 2), furan produced an intractable mixture. Nitrogen-containing arenes such as pyrrole, *N*,*N*-dimethylaniline, and pyridine all returned the starting arene, consistent with previous reports devoid of nitrogen-containing substrates.[6b] Attemps to attenuate the lone-pair basicity of aniline substrates through the use of *N*-phenyl methanesulfonamide or *N*-phenyl acetamide also resulted in the recovered arene, suggesting the electron-withdrawing group on nitrogen is sufficient to deactivate the aromatic ring.

Interestingly, modest regioselectivity (*o*/*p* ratios) was observed in many cases with substituted benzene derivatives **6**–**11**, which is consistent with other Friedel–Crafts-type reactions.[5f,11] Even increasing the steric hindrance of the alcohol from cyclohexanol to cyclododecanol did not affect the regioselectivity of **6** and **7**. This low regioselectivity denotes insensitivity to steric encumbrance and suggests a particularly facile alkylation event from the iron-activated intermediate. While the reaction proceeded well with a range of cyclic, secondary alcohols (**2**–**11**), low weight linear alcohols, such as isopropanol and 2-butanol, provided low yields, likely due to competitive olefin formation while higher weight linear alcohols, such as 2-hexanol and 2-octanol, led to a mixture of product isomers.

This methodology is useful for the synthesis of the recently reported antiproliferative compound **12** (Scheme 3).[19] Previous syntheses of **2** utilize mesylated cyclohexanol in combination with expensive $Sc(OTf)_3$[5f] or cyclohexene and air sensitive $CpMoCl(CO)_3$[11] to produce a low yield (34%) of cyclohexylated *p*-xylene **2**. In contrast, our mild, iron-catalyzed reaction provides gram quantities of **2** in 74% yield. Treating **2** under traditional Friedel–Crafts alkylation conditions (superstoichiometric $AlCl_3$) provides **12** in 90% yield.

To further explore the synthetic versatility of this iron-catalyzed alkylation, different intramolecular variants were explored to access interesting polycyclic ring systems (Scheme

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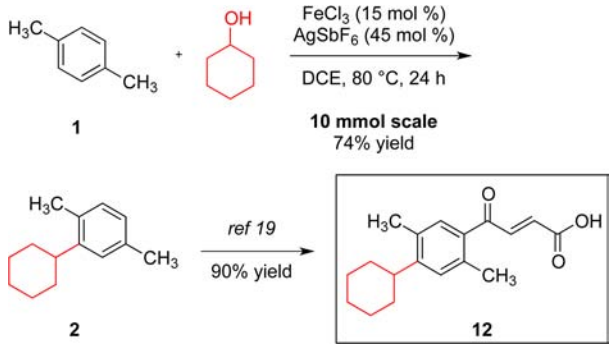
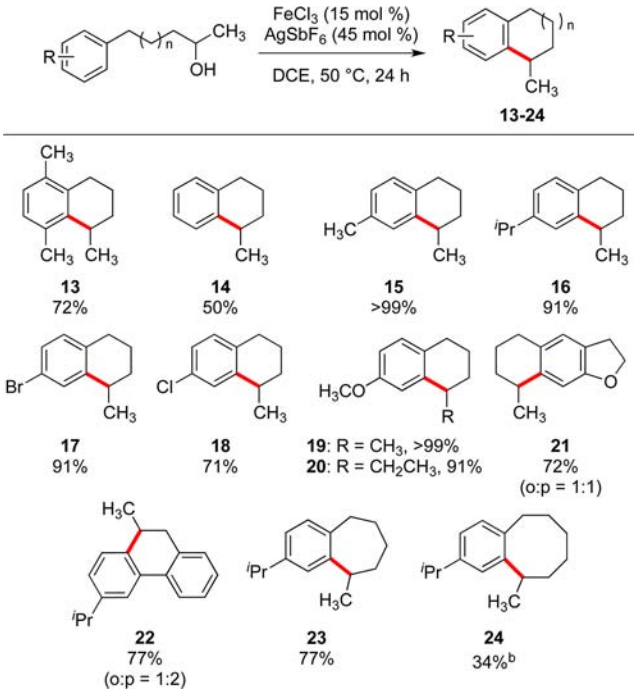
Scheme 3. Synthesis of Antiproliferative Compound 12



4). The intramolecular variant proceeded best with the same $FeCl_3/AgSbF_6$ system, but at a lower temperature (see SI).

Scheme 4. Intramolecular Friedel-Crafts-Type Alkylation of Secondary Alcohols[a]

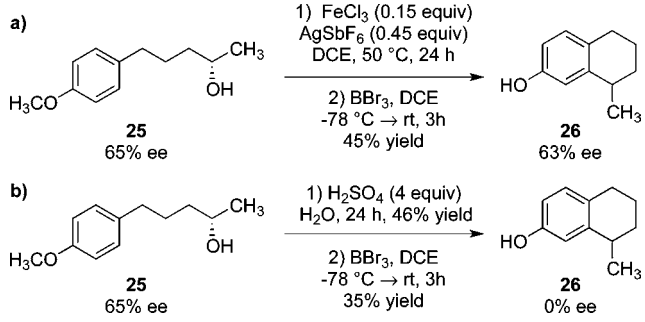


[a]Yields are isolated yields. Regioselectivity provided in parentheses. [b]This isolated yield is after an osmylation reaction to remove the contaminating olefin.

Similar to the intermolecular case, the reaction followed traditional electrophilic aromatic substitution trends where arenes possessing pendant electron-donating substituents reacted faster, and in higher yield, than electron-neutral or -deficient arenes. For example, while the slightly activated phenyl product **14** was produced in moderate, 50% yield, a >90% yield was achieved for *p*-methyl **15**, *p*-isopropyl **16**, and *p*-methoxy **19**. When the aromatic ring carried the ortho/para directing, deactivating halogens, *p*-bromo and *p*-chloro, good yields were obtained, 91% for **17** and 72% for **18**. When unsymmetrical arene substrates **21**–**22** were employed, good yields were obtained, but only modest regioselectivity was observed, again mirroring the results of the intermolecular reactions. Although the substrates were subjected to reaction conditions for 24 h for convenience, it is noteworthy that some of the more electron-rich substrates are finished within just a few hours. Interestingly, attempts to close a five-membered ring led to low conversion and substantial olefin formation (data not shown), while the larger, and traditionally more difficult to close, seven-membered ring **23** proceeded in 77% yield. The closure of eight-membered ring **24** also led to significant elimination products, but was isolated in 34% yield.

In the field of drug discovery, the evaluation of enantiopure compounds is of critical importance.[20] With this in mind, nonracemic secondary alcohol **25** was evaluated for a stereospecific alkylation reaction. Using the CBS reduction of the parent ketone,[21] we prepared and isolated optically active **25** in 65% ee. When **25** was subjected to the optimized reaction conditions, only slight erosion of the enantiomeric excess was observed (Scheme 5a). This is in stark contrast to the

Scheme 5. (a) Transfer of Stereochemistry in the Reaction of Enantioenriched 25; (b) Racemization of Enantioenriched 25 under Standard Friedel–Crafts Conditions



formation of racemic **26** under standard Friedel–Crafts conditions (Scheme 5b).[22]This result represents the first example of a stereoselective arylation of unactivated alcohols.[23]

In summary, we have developed a general method for the arylation of unactivated secondary alcohols using a simple-to-prepare catalytic system that tolerates air and stoichiometric water generation. The synthesis of a variety of alkylated arenes is possible under mild reaction conditions (50–80 °C) without strong acids or bases. A variety of substituted ring systems can be accessed with six-, seven-, and eight-membered carbocycles. The use of iron and secondary alcohols renders this approach a particularly advantageous variant of Friedel–Crafts chemistry, as the only stoichiometric byproduct of the reaction is water. Furthermore, the conversion of chiral alcohols to enantioenriched arylation products provides a synthetically appealing approach to nonracemic compounds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data for all new compounds are provided. 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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