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Iron(III)-Catalyzed Intramolecular Friedel–Crafts Alkylation of Electron-Deficient Arenes with π-Activated Alcohols

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Abstract: "*Deficient*" *but* "*efficient*", the first example of a catalytic Friedel–Crafts alkylation of arenes, carrying electron-withdrawing groups, with alcohols is reported. The optimized iron(III) chloride (97%) catalyzed allylation, benzylation and propargylation procedures open an access to a range of tetrahydronaphthalenes, tetrahydroisoquinolines and tetrahydrobenzo[*d*]azepines featuring tertiary benzylic stereocenters in excellent yields (up to 92%) and short reaction times.

Keywords: alcohols; aromatic compounds; electron-deficient compounds; Friedel–Crafts alkylation; iron

Friedel–Crafts (FC) alkylations are probably the most ubiquitous protocols for the functionalization of aromatic compounds.[1] Owing to the great structural diversity of naturally occurring benzenes, it is not surprising that for well over 130 years FC alkylations continued to impact synthetic method development with noticeable recent advances in catalytic regio- and stereoselective variants.[2] However, in the realm of FC reactions, the development of mild and efficient catalytic alkylations of aromatics, carrying electron-withdrawing substituents, is an ongoing challenge still to be solved.[3] This lack is still more pronounced if we consider π-activated alcohols as environmentally benign alkylating sources (Figure 1).

The use of alcohols in FC alkylation reactions has been long known.[1] Deactivation of the catalytic species *via* irreversible coordination to the hydroxy group or to the molecules of water released during the process, led to stoichiometric amounts of Lewis acids (LAs) to be required. As a result, the suitability of alcohols in catalytic FC chemistry, has been successfully discovered only recently.[4]

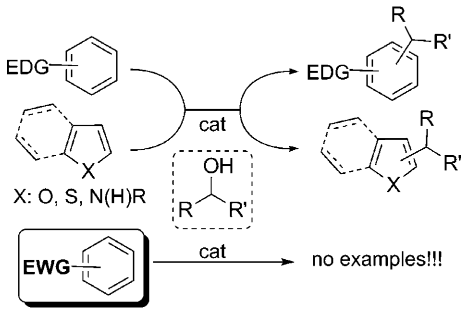


Figure 1. Catalytic Friedel–Crafts alkylations of electron-deficient arenes: a still unsolved synthetic task.

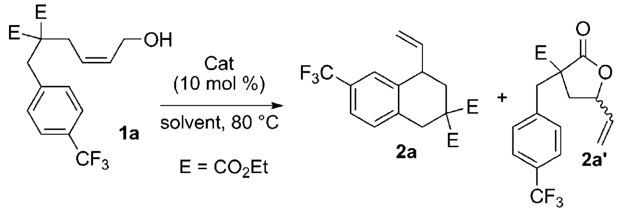
The aim of the present update is to describe the first example of the catalytic FC alkylation of electron-"deficient" arenes with alcohols.

Intramolecular allylic alkylation[5] of **1** type arenes is a practical synthetic route to 1-vinyltetrahydronaphthalenes **2**, that are valuable building blocks for the synthesis of cadinene-type sesquiterpenoids.[6] The process has been previously employed by us[7a] and others,[7b] as a benchmark of new FC catalytic systems. In order to address the lack of deactivated arenes in catalytic FC alkylations, we considered the readily prepared allylic alcohol **1a**, as the model substrate. A survey of organic/inorganic Brønsted acids, and metal σ-/π-acids was undertaken and a collection of results is reported in Table 1.

As expected, most of the catalytic species, that recently emerged in FC alkylations with alcohols and halides[8] [i.e., $InCl_3$, $Zn(OTf)_2$, $Sc(OTf)_3$, $Bi(OTf)_3$, AgOTf, and Au(I) complexes] gave mean yields of **2a**, with the occasional or predominant formation of lactone **2a′**. On the contrary, the cheap and environmentally acceptable $FeCl_3$ (10 mol%)[9] catalyzed the FC ring closure at acceptable rate and promising yield (37%, entry 11).[10]

With the aim to optimize the chemical outcome of the process, several reaction parameters were screened. Interestingly, the combination of $FeCl_3$·

Table 1. Optimization of the reaction conditions for the intramolecular Friedel–Crafts allylic alkylation of **1a**.[a]



Entry	Cat	Solvent/ *t* [h]	Yield **2a** [%][b]	Yield **2a**′ [%][b]
1[c]	(RO)$_2$P(O)OH[d]	DCE/16	–	–
2[c]	HCl (1 M, Et$_2$O)	DCE/16	–	–
3[c]	InCl$_3$	DCE/16	–	–
4[c]	Zn(OTf)$_2$	DCE/16	–	–
5	Cu(OTf)$_2$	DCE/16	traces	38
6	Sc(OTf)$_3$	DCE/16	traces	35
7	Al(OTf)$_3$	DCE/16	traces	70
8	Bi(OTf)$_3$	DCE/16	traces	84
9	AgOTf	DCE/16	traces	64
10	(PPh$_3$)AuOTf	DCE/16	traces	76
11	FeCl$_3$·(97%)	DCE/16	37	10
12[c]	FeCl$_3$·(97%)	CH$_3$CN/16	–	–
13[e]	FeCl$_3$·(97%)	MeNO$_2$/0.2	81	<5
14	FeCl$_3$ (99.99%)	MeNO$_2$/0.5	65	traces
15	FeCl$_2$	MeNO$_2$/32	50	traces
16	Fe(OTf)$_2$(ACN)$_4$	CH$_3$CN/24	65	–

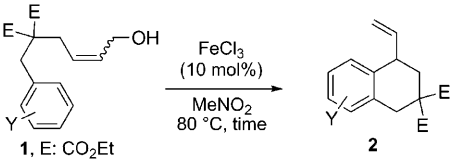
[a] The reactions were carried out under nitrogen atmosphere with anhydrous solvents, unless otherwise specified.
[b] After flash chromatography.
[c] Unreacted **1a** (>90%) was recovered.
[d] (*S*)-1,1′-Binaphthyl-2,2′-diyl hydrogen phosphate.
[e] Reagent grade MeNO$_2$ was used with no moisture restriction.

(97%) and reagent grade MeNO$_2$ (80 °C) worked as the best reaction conditions, leading to **2a** in 81% yield, within *15 min* reaction time (entry 13, Table 1).

Interestingly, both metal purity (entry 14) and oxidation state (entries 15 and 16) of the iron source proved to be crucial for optimal chemical outcomes. In particular, when highly pure FeCl$_3$ (99.99% metal purity, Aldrich) was employed in anhydrous nitromethane, **2a** was formed to a lower extent (65% yield, 30 min). Such a finding could be rationalized in terms of a synergic Lewis-Brønsted[11] acid co-catalysis during the reaction course. On the contrary, the metal contamination co-catalysis (generally copper), frequently encountered in iron(III)-promoted cross-couplings[12] did not seem to be present in our FC-type allylic alkylation.

Next, to prove the generality of the methods, best reaction conditions were applied to a variety of allyl alcohols **1b–j** bearing electron-deactivating groups on the aromatic ring. Typical results are shown in Table 2.

Table 2. Scope of the reaction.[a]



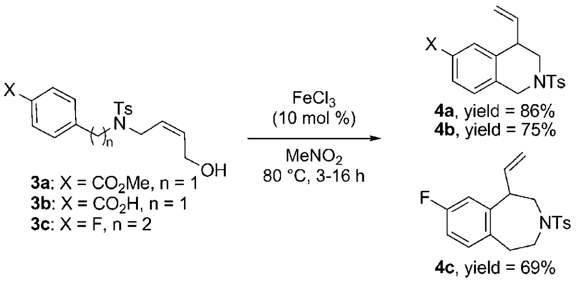
Entry	Alcohols	Y	Time [min]	Yield of **2** [%][b]
1	(*Z*)-**1b**	4-F	30	88
2	(*E*)-**1b**	4-F	15	85
3	(*Z*)-**1c**	4-Cl	30	71
4	(*Z*)-**1d**	4-Br	30	89
5	(*Z*)-**1e**	3-F	15	78 (66:33)[c]
6	(*Z*)-**1f**	4-CN	15	71
7	(*Z*)-**1g**	4-CO$_2$Me	15	75
8	(*Z*)-**1h**	4-CO$_2$Et	60	75
9	(*Z*)-**1i**	4-NO$_2$	60	45
10	(*Z*)-**1j**	2-NO$_2$	60	43

[a] All the reactions were carried out in reagent grade MeNO$_2$ under no moisture restriction.
[b] After flash chromatography.
[c] The ratio was determined by GC-MS and ^{1}H NMR on the reaction crude (see Supporting Information for details).

Halogen atom-containing arenes (**1b–e**) cyclized smoothly leading to the corresponding tetrahydronaphthalenes in excellent yields (71–89%, entries 1–5) and moderate selectivity in the case of 3-fluoro-substituted compound **1e**. Here, a mixture of 8-fluoro-1-vinyl- and 6-fluoro-1-vinyltetrahydronaphthalene in a 33:66 ratio was obtained (see Supporting Information for details).

Tolerance toward numerous electron-withdrawing substituents was highlighted by performing the cycloalkylation of compounds **1f–j**. Here, both cyano and ester moieties provided the corresponding bicyclic compounds in good yields. Also nitroarenes (**1i** and **1j**), that are commonly targeted as *electrophilic* reagents,[13] underwent nucleophilic allylic cyclization in decent yields (entries 9 and 10). Finally, the configuration of the carbon-carbon double bond did not significantly influence the chemical output of the process (compare entries 1 and 2), calling for the presence of positively charged intermediates during the reaction course.

The method proved to be also a suitable synthetic shortcut for 4-vinyltetrahydro-isoquinolines **4**.[14] In particular, the readily accessible primary alcohols **3a** and **b** (see supporting information for details), carrying CO$_2$Me, and CO$_2$H groups, underwent cycloalkylation in satisfactory yields (75–86%) when treated with catalytic amounts of FeCl$_3$ (10 mol%) in MeNO$_2$ (Scheme 1).[15] Interestingly, the methodology has been efficiently applied also to the construction of 7-membered rings, leading to pharmacologically rele-

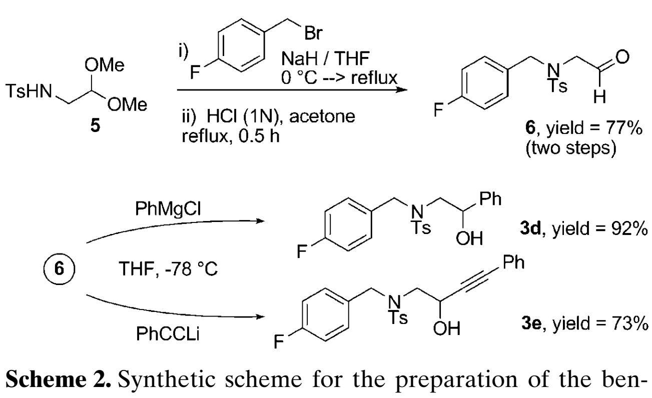


Scheme 1. Synthesis of tetrahydroisoquinolines and substituted tetrahydro-3-benzoazepines through iron-catalyzed intramolecular Friedel–Crafts alkylation with alcohols.

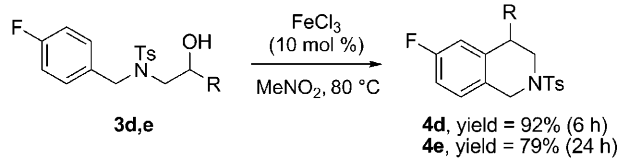
vant 1-vinyltetrahydro-3-benzoazepines.[16] In this case, the model allylic alcohol **3c**, deriving from 2-(4-fluorophenyl)ethylamine, smoothly underwent ring-closure to **4c** in 69% yield after 16 h reaction time (Scheme 1).

The synthetic versatility of the protocol was underlined further by considering benzylation and propargylation FC-type reactions. To this aim, benzylic and propargylic alcohols **3d** and **e** were synthesized from readily available *N*-Tos-(2,2-dimethoxyethylamine) **5**.[17] Here, initial alkylation with 4-fluorobenzyl bromide followed by hydrolysis under acid conditions led the desired aldehyde **6** in 77% overall yield (Scheme 2). Finally, the corresponding secondary benzylic and propargylic alcohols **3d** and **e** were obtained in good yields (73–92%) through the condensation of **6** with PhMgCl or PhC≡CLi, respectively.

4-Phenyl-substituted tetrahydroisoquinolines are important medicinal leads that found unprecedented applications in the treatment of ADHD through inhibition of the neuronal uptake of cathecolamines.[18] Satisfyingly, the present methodology provided a rapid access to such a molecular architecture, in fact, secondary benzylic alcohol **3d** underwent smoothly the Fe(III)-catalyzed ring-closing reaction leading to **4d** in excellent yields (92%, Scheme 3). 4-(2-Phenylethynyl)-tetrahydroisoquinoline **4e** was also accessible in good yield (79%) under Fe-catalyzed FC-propargylation of **3e**.



Scheme 2. Synthetic scheme for the preparation of the benzylic and propargylic alcohols **3d** and **e**.



Scheme 3. Intramolecular iron-catalyzed FC benzylation and propargylation of alcohols **3d** and **e**.

In conclusion, an environmentally benign iron-catalyzed Friedel-Crafts alkylation of electron-deficient arenes with alcohols is described. Intramolecular, allylation, benzylation and propargylation reactions were efficiently investigated leading to a variety of synthetically useful functionalized tetrahydronaphthalenes, -isoquinolines and -benzo[*d*]azepines. Studies toward the application of such a methodology for the synthesis of complex naturally occurring aromatic compounds are ongoing in our laboratories.

Experimental Section

Typical Procedure for the $FeCl_3$-Catalyzed Intramolecular Friedel-Crafts Alkylation

A Shlenk tube was charged with alcohol **1**/**3** (60 μmol) dissolved in 1 mL of reagent $MeNO_2$, and 1 mg of hydrated $FeCl_3$ (10 mol%) dissolved in 1 mL of $MeNO_2$. The yellow-orange mixture was heated up to 80 °C for the indicated time, then cooled to room temperature and the volatiles evaporated under reduced pressure. The crude was directly purified by flash chromatography (eluent: *c*-Hex:AcOEt, see Supporting Information for details).

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