Published in final edited form as:

Org Lett. 2018 January 05; 20(1): 68–71. doi:10.1021/acs.orglett.7b03367.

Iron – Catalyzed Synthesis of Tetrahydronaphthalenes via 3,4-Dihydro-2H-pyran Intermediates.

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Abstract

The development of an iron(III)-catalyzed synthetic strategy towards functionalized tetrahydronaphthalenes is described. This approach is characterized by its operational simplicity and is distinct from currently available procedures that rely on [4+2]-cycloadditions. Our strategy takes advantage of the divergent reactivity observed for simple aryl ketone precursors to gain exclusive access to tetrahydronaphthalene products (23 examples). Detailed mechanistic investigations identified pyrans as reactive intermediates that afford the desired tetrahydronaphthalenes in high yields upon iron(III)-catalyzed Friedel-Crafts alkylation.

Table of Contents Graphic.

Tetrahydronaphthalenes are key structural motifs in molecules of interest such as biologically active natural products¹ and pharmaceuticals,² as well as precursors to functional materials, including optoelectronics³ and organic semiconductors.⁴ Consequently, diverse areas of research rely on efficient and economical strategies to synthesize these important building blocks. Existing reports to access this structural motif often utilize Brønsted or Lewis acid-catalyzed [4+2]-cycloaddition reactions of *o*-alkynyl(oxo)-benzenes **5** with alkenes **6**,⁵ or isochromene acetals **8** with vinyl boronates **9** (Fig. 1B).⁶ We herein present a mild and efficient strategy for the synthesis of tetrahydronaphthalenes **4** which was

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The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental details and spectroscopic data for all intermediates, reactants and products (PDF)

inspired by mechanistic insights obtained during our previous studies towards the synthesis of 3,4-dihydro-2*H*-pyrans **2** from aryl ketones **1** bearing α -carbonyl substituents.⁷ The corresponding α -arylated analogs of **1** exhibit divergent reactivity upon Brønsted or Lewis acid-catalysis resulting in either the preferential formation of pyrans **3** or the exclusive formation of tetrahydronaphthalenes **4** depending on the choice of activation (Fig. 1A). Divergent reactivity of the same substrate upon Lewis acid or Brønsted acid catalysis has recently been recognized as an attractive strategy to rapidly access molecular diversity.⁸ Subsequent mechanistic investigations aimed at the optimization of this transformation identified pyrans **3** as reactive intermediates which undergo FeCl₃-catalyzed⁹ Friedel-Crafts alkylation resulting in the exclusive formation of tetrahydronaphthalenes **4** in high yields. This strategy described herein provides a mild reaction protocol to access functionalized tetrahydronaphthalenes relying on iron as an environmentally benign metal catalyst and complements current synthetic approaches.

Following the discovery of divergent reactivity utilizing FeCl₃, we then investigated the suitability of other Lewis acids. When aryl ketone **11** was converted using catalytic amounts of Fe(OTf)₃, the corresponding tetrahydronaphthalene **12** was obtained in 23% yield with full conversion of the substrate (entry 1, Table 1). The use of Bi(OTf)₃¹⁰ resulted in increased yields of 48% while catalytic quantities of GaCl₃ further improved the yield of **12** to 58% (entries 2 and 3, Table 1). Both, SnCl₄ and BF₃·Et₂O resulted in the formation of tetrahydronaphthalene **12** in comparable yields of 87% while AlCl₃, a more potent Lewis acid, formed **12** in diminished yields of 73% (entries 4–6, Table 1). Catalytic amounts of FeCl₃ proved superior and gave rise to the desired tetrahydronaphthalene in 96% yield in an overall shorter reaction time of 8 hours (entry 7). Conducting the reaction with decreased catalyst loadings of 5 mol % FeCl₃ led to the formation of tetrahydronaphthalene **12** in 82% yield, albeit requiring longer reaction times of 24 hours (entry 8). In comparison, higher catalyst loadings of 20 mol % FeCl₃ resulted in decreased yields of **12** in 61% after 4 hours (entry 9). Furthermore, the evaluation of various solvents with FeCl₃ provided diminished reactivity, as dichloromethane, toluene and nitromethane resulted in 68%, 83% and 86% yield, respectively (entries 10–12, Table 1). Overall, 10 mol % of FeCl₃ in dichloroethane provided optimal reaction conditions. Importantly, orthogonal reactivity of aryl ketone **11** was observed upon treatment with 10 mol %, 100 mol %, and 500 mol % HCl, which resulted in the exclusive formation of the corresponding pyran product (**3**, Fig. 1A) (entries 13–15). The optimized reaction conditions for the synthesis of tetrahydronaphthalenes proved applicable to a variety of electronically differentiated aryl ketone substrates (Scheme 1). Electron-deficient aryl ketones incorporating nitro, halogen and nitrile functionalities were converted to the corresponding products **17–18**, **21–22** in yields up to 96% (Scheme 1). In comparison, electron-neutral substrates bearing phenyl (**12**)- and biphenyl (**15**)- groups performed equally well and formed the desired products in yields up to 96% (Scheme 1). Additionally, electron-rich aryl ketones bearing methoxy, hydroxyl and acetate substitution were tolerated under the optimized reaction conditions and gave rise to the corresponding tetrahydronaphthalenes **25–26**, **33** in up to 66% yield (Scheme 1). Thiophene and furan containing substrates proved viable and resulted in the formation of the desired products **19** and **23** in 64% and 56% yield, respectively. Cinnamyl-derived aryl ketones were also identified as suitable substrates for this transformation, tolerating a wide range of electron-

rich and electron-deficient substituents in up to 99% yield (**16**, **20**, **28–29**, **24**, Scheme 1). Importantly, aryl ketones bearing bromine or triflate substituents, which would enable subsequent functionalization *via* cross-coupling reactions, led to the desired tetrahydronaphthalene products in excellent yields of up to 98% (**13** and **14**, Scheme 1). Furthermore, the corresponding tetrahydronaphthalene products such as **16** undergo facile oxidation to the polyaromatic scaffold **35** in 82% yield upon treatment with DDQ (Fig. 2). Notably, this sequence provides an alternative synthetic strategy to current approaches towards functionalized naphthalenes **35** which often rely on gold-catalyzed benzannulation reactions of *o*-alkynyl(oxo)-benzenes **5**.¹¹

Subsequent studies focused on the elucidation of the reaction mechanism. During our evaluation of various Lewis acids, we observed the formation of a new compound after short reaction times. However, prolonged reaction times led to the isolation of the corresponding tetrahydronaphthalenes as the sole products suggesting the intermediacy of this compound in the reaction. Subsequent efforts focused on the isolation of this reactive intermediate, which was later identified as the corresponding pyran **36**. To validate this result, pyran **36** was prepared independently and subjected to the optimized reaction conditions (Fig. 3). After one hour, a mixture of aryl ketone **11** and tetrahydronaphthalene **12** was observed in a 2:1 ratio, respectively, suggesting that the formation of pyran **36** is reversible under Lewis acid catalysis. This hypothesis was further validated when the reaction was quenched after five hours, resulting in the formation of tetrahydronaphthalene **12** in 83% yield as the exclusive reaction product. Subsequent NMR experiments provided additional support for the formation of pyran **36** as a reactive intermediate (Fig. 4). The distribution of starting material **11**, pyran **36**, and tetrahydronaphthalene product **12** was monitored at different time points when ketone **11** was subjected to the optimized reaction conditions (Fig. 4A and 4B). Within the first two hours of the transformation, the majority of starting material **11** was consumed, and a high concentration of pyran **36** was observed. As the reaction progressed, the concentration of pyran **36** decreased as the concentration of tetrahydronaphthalene **12** increased. Figure 4C shows the changing composition of substrate **11**, pyran **36** and product **12** in the reaction mixture after 0 minutes, 30 minutes, 6 hours, and 7 hours. Based on these mechanistic insights, we propose the following mechanism for the synthesis of tetrahydronaphthalenes (Fig. 5). Activation of aryl ketone **37** upon coordination of the Lewis acid leads to initial enolization of the carbonyl to provide **38**, which can subsequently protonate the alkene subunit to form carbocation **39**. The resulting carbocation **39** can either be trapped with the oxygen functionality of the iron-enolate **39** to result in pyran **40** or undergo Friedel-Crafts alkylation with the pendant aromatic moiety to form carbocation **41**. Our experimental observations suggest that under Lewis acidic conditions pyran **40** forms initially. However, the reversibility of this step ultimately leads to the formation of tetrahydronaphthalene **42** following Friedel-Crafts alkylation and rearomatization. In comparison Brønsted acid catalysis does not mediate the desired reaction pathway and provides pyrans **40** as products.

In summary, we have developed a mild and catalytic method for the synthesis of tetrahydronaphthalenes bearing a variety of electronically distinct substituents. Mechanistic investigations suggest the role of intermediate 3,4-dihydro-2*H*-pyrans in the FeCl₃-catalyzed

synthesis of tetrahydronaphthalenes. This transformation illustrates the ability of aryl ketones to be selectively converted into 3,4-dihydro-2*H*-pyran or tetrahydronaphthalene products by the use of either a Brønsted or Lewis acid catalyst.

Supplementary Material

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ACKNOWLEDGMENT

We thank the NIH/National Institute of General Medical Sciences (R01-GM118644) and the Packard Foundation for financial support. R.B.W. thanks the National Science Foundation for a predoctoral fellowship (Grant No. 1256260). We thank Dr. Jeff W. Kampf from the University of Michigan for X-ray crystallographic studies.

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Figure 1.

A Divergent reactivity between Brønsted or Lewis acids. **B** Literature procedures for the formation of tetrahydronaphthalenes based on [4+2]-cycloadditions.

Figure 2.
Oxidation of tetrahydronaphthalene **16** to give rise to functionalized naphthalene **35**.

Pyrans are reactive intermediates and formed reversibly:

Conditions: ^aPercent yield and percent conversion determined by ¹H-NMR using dimethyl terephthalate as an internal standard. ^b**36** does not form **11** or **12** under 1.0 equiv of HCl in 0.1 M DCE after 24 hours.

Figure 3.
Evidence for intermediacy of **36**.

Figure 4.

A Monitoring conversion of aryl ketone **11** to product **12**, via intermediate **36**. **B** Distribution of **11**, **12** and **36** as determined by percent yield using ^1H -NMR with dimethyl terephthalate as an internal standard. **C** Relevant sections of the ^1H -NMR spectra after 0 minutes, 30 minutes, 6 hours, and 7 hours.

Figure 5.
Mechanistic hypothesis for the FeCl_3 -catalyzed formation of tetrahydronaphthalenes.

Scheme 1.

Substrate scope of aryl and alkyl ketones.

Table 1.

Reaction optimization for the Lewis acid-catalyzed formation of tetrahydronaphthalene **12**.

entry	Lewis acid	solvent	time (h)	yield(%) ^a	conversion (%) ^a
1	Fe(OTf) ₃	DCE	24	23	99
2	Bi(OTf) ₃	DCE	24	48	99
3	GaCl ₃	DCE	24	58	99
4	SnCl ₄	DCE	24	87	99
5	BF ₃ ·OEt ₂	DCE	24	87	99
6	AlCl ₃	DCE	24	73	99
7	FeCl ₃	DCE	8	96 ^b	99
8	FeCl ₃ (5 mol %)	DCE	24	82	99
9	FeCl ₃ (20 mol %)	DCE	4	61	99
10	FeCl ₃	DCM	4	68	99
11	FeCl ₃	PhMe	4	83	99
12	FeCl ₃	NO ₂ Me	4	86	99
13 ^c	HCl	DCE	24	0	17
14 ^d	HCl (100 mol %)	DCE	24	0	20
15 ^e	HCl (500 mol%)	DCE	24	0	68

^aPercent yield and percent conversion determined by ¹H-NMR using dimethyl terephthalate as an internal standard.^bIsolated yield.^c4% (24% brsm) pyran **3** observed.^d20% (100% brsm) pyran **3** observed.^e35% (52% brsm) pyran **3** observed.^fAll reactions were performed using 0.113 – 0.189 mmol of aryl ketone.