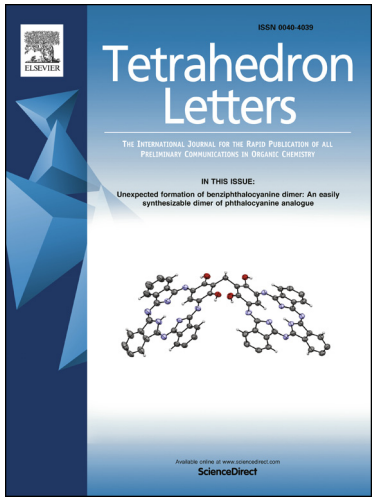

High efficient iron-catalyzed transfer hydrogenation of quinolines with Hantzsch ester as hydrogen source under mild conditions

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High efficient iron-catalyzed transfer hydrogenation of quinolines with Hantzsch ester as hydrogen source under mild conditions

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ABSTRACT

A highly efficient transfer hydrogenation of quinolines with Hantzsch ester as hydrogen source in the presence of 1 mol% $Fe(OTf)_2$ under mild conditions has been developed. A series of substituted 1,2,3,4-tetrahydroquinoline derivatives were afforded in excellent yields with good functional group tolerance.

Introduction

1,2,3,4-Tetrahydroquinoline-based frameworks are widely existed in fine chemicals, pharmaceuticals, agrochemicals, dyes, fragrances, as well as hydrogen-storage materials.[1] Traditionally, the quinoline derivatives were reduced by stoichiometric metal hydrides or reactive metals as reductants.[2] The catalytic hydrogenation and transfer hydrogenation under homogenous or heterogeneous conditions have been developed in the past decades.[3-5] Among which, Reuping et al. reported a pioneering biomimetic transfer hydrogenation of quinolines using diphenyl phosphate as the catalyst and Hantzsch ester as the hydrogen source.[5a] After that, various Brønsted acid-catalyzed transfer hydrogenations of azaarenes including quinolines,[6] quinoxalines,[7] indoles,[8] and pyridines[9] with Hantzsch ester as the hydrogen source have been achieved. By contrast, the combination of metal catalyst and Hantzsch ester promoted transfer hydrogenation was very limited.[10]

With the merits of environment benign, readily accessibility and cost-benefit, iron seems to be promising catalyst in organic synthesis. A number of iron-catalyzed organic transformations have been realized in recent years.[11] To continue our research interest in iron-catalyzed reactions.[12] Herein, we report an iron-catalyzed efficient chemoselective hydrogenation of quinolines employing Hantzsch ester as hydrogen source under mild conditions.

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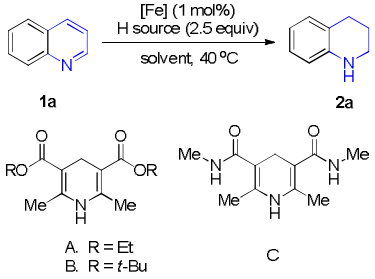
Results and discussion

We initiated our investigation with the reduction of quinoline **1a** in chloroform at 40 °C for 4 h using Hantzsch ester A as hydrogen source. As shown in Table 1, some iron salts including $FeCl_2$, $FeCl_3$, FeS, Cp_2Fe, $Fe(OAc)_2$, $Fe(acac)_3$, $Fe(ClO_4)_2$, and $Fe(OTf)_2$ were screened first. The results revealed that $Fe(OTf)_2$ and $Fe(ClO_4)_2$ performed better than the others, and $Fe(OTf)_2$ afforded 1,2,3,4-terahydroquinoline **2a** with 96% yield (Table 1, entries 1-8). Considering the high catalytic activity of $Fe(OTf)_2$, the reaction was attempted within shorter time. It was found that the yield remained unchanged for 2 h, but reduced by half for 1 h (entries 8-10). A survey of solvents showed that chloroform is the best option comparing to acetonitrile (CH_3CN), tetrahydrofuran (THF), 1,4-dioxane, methanol, toluene, and *N*,*N*-dimethylformamide (DMF) (entries 9, 11-16). And then, other hydrogen sources like NADH analogues B and C, as well as popularly used *i*-PrOH, HCOOH, and HCOOH/Et_3N (5:2) were also evaluated. Among which, the Hantzsch ester A afforded the highest yield (entries 9, 17-21). Furthermore, the amount of Hantzsch ester A was reduced to 1.0 equiv, but the product **2a** was obtained in only 58% yield even if prolonging the reaction time to 4 h (entry 22). To verify the necessity of iron catalyst, control experiments were also performed. No reaction occurred in the absence of iron catalyst (entry 23). When 10 mol% of TfOH was used instead of $Fe(OTf)_2$, the desired product **2a** was detected with 43% yield (entry 24). It means that the strong acid

TfOH generated in situ could promote the reaction with lower catalytic activity. Finally, 1 mol% $Fe(OTf)_2$, 2.5 equiv of Hantzsch ester A, 1 mL of $CHCl_3$, 40 °C, and 2 h were set as the optimal reaction conditions.

Table 1. Screening of reaction conditions for the transfer hydrogenation of quinoline **1a** [a]

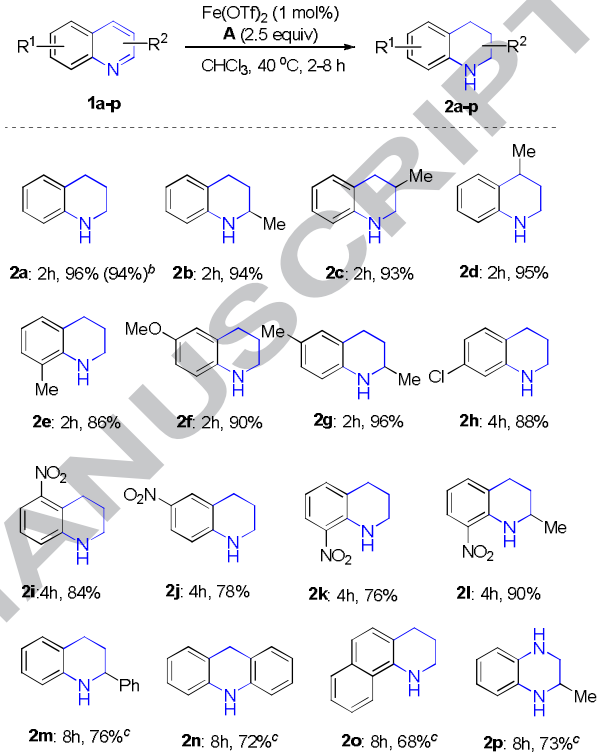


Entry	[Fe]	H source	solvent	Time (h)	Yield (%)[b]
1	$FeCl_2$	A	$CHCl_3$	4	58
2	$FeCl_3$	A	$CHCl_3$	4	64
3	FeS	A	$CHCl_3$	4	30
4	Cp_2Fe	A	$CHCl_3$	4	15
5	$Fe(OAc)_2$	A	$CHCl_3$	4	21
6	$Fe(acac)_3$	A	$CHCl_3$	4	8
7	$Fe(ClO_4)_2$	A	$CHCl_3$	4	89
8	$Fe(OTf)_2$	A	$CHCl_3$	4	96
9	$Fe(OTf)_2$	A	$CHCl_3$	2	96
10	$Fe(OTf)_2$	A	$CHCl_3$	1	46
11	$Fe(OTf)_2$	A	CH_3CN	2	14
12	$Fe(OTf)_2$	A	THF	2	32
13	$Fe(OTf)_2$	A	1,4-dioxane	2	30
14	$Fe(OTf)_2$	A	MeOH	2	15
15	$Fe(OTf)_2$	A	toluene	2	35
16	$Fe(OTf)_2$	A	DMF	2	12
17	$Fe(OTf)_2$	B	$CHCl_3$	2	49
18	$Fe(OTf)_2$	C	$CHCl_3$	2	26
19	$Fe(OTf)_2$	*i*-PrOH	$CHCl_3$	2	11
20	$Fe(OTf)_2$	HCOOH	$CHCl_3$	2	19
21[c]	$Fe(OTf)_2$	HCOOH/TEA	$CHCl_3$	2	24
22[d]	$Fe(OTf)_2$	A	$CHCl_3$	4	58
23[e]	--	A	$CHCl_3$	2	nd
24[f]	TfOH	A	$CHCl_3$	2	43

[a] Reaction conditions: quinoline (**1a**; 0.5 mmol), 1 mol% catalyst, hydrogen source (2.5 equiv), 1 mL solvent.
[b] Determined by GC analysis with an internal standard (mesitylene).
[c] HCOOH/TEA = 5:2 (mol ratio).
[d] 1.0 equiv of Hantzsch ester A was used.
[e] nd = not detected.
[f] 10 mol% TfOH was used.

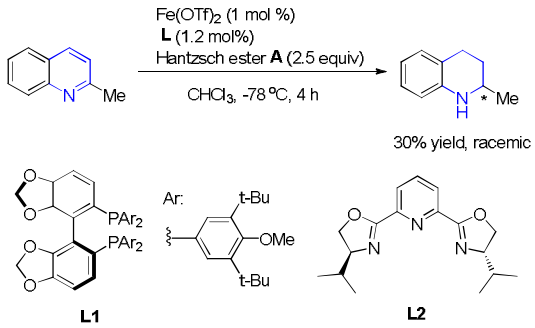
Under the optimal reaction conditions, the scope of the iron-catalyzed transfer hydrogenation of quinoline derivatives was investigated. As shown in Scheme 1, the hydrogenation of electron-rich quinolines **1b-1e** bearing methyl group at different positions and 6-methoxyquinoline **1f** proceeded smoothly affording the corresponding reductive products **2b-2f** with 86-95% yields. Similarly, the 2,6-dimethylquinoline **1g** was hydrogenated to give **2g** in 96% yield. Next, the electron-deficient 7-chloroquinoline **1h** was also subjected to this reaction and the reductive product **2h** was isolated in 88% yield without dechlorination. Interestingly, the chemoselective reduction of electron-withdrawing nitro group substituted quinolines **1i-1l** was observed, and the corresponding products **2i-2l** were obtained in 76-90% yields with nitro group intact. This transfer hydrogenation was also applicable to 2-phenylquinoline **1m**, benzoquinolines **1n** and **1o**, the desired products **2m-2o** were obtained in 68-72% yields by prolonging the reaction time to 8 h. The iron-catalyzed transfer hydrogenation was further applied to 2-methylquinoxaline, affording the reduced product **2p** in 73% yield. To demonstrate the practicality, the gram scale (10 mmol) synthesis of **2a** was also conducted with 94% yield.

Scheme 1. Scope of the transfer hydrogenation of quinolines[a]



[a] Reaction conditions: quinoline (**1**; 0.5 mmol), Hantzsch ester **A** (2.5 equiv), $CHCl_3$ (1.0 mL), 40 °C, 2-8 h, isolated yield.
[b] Gram scale reaction (**1a**; 10 mmol).
[c] 2 mol% $Fe(OTf)_2$ was used.

Scheme 2 Attempt to asymmetric transfer hydrogenation of 2-methylquinoline with iron complexes



After identifying $Fe(OTf)_2$ as a valuable alternative to the established BrØnsted acids[6] and Lewis acids[10a,b] for transfer hydrogenation of quinolines, a preliminary attempt to the asymmetric variant utilizing the complexes of $Fe(OTf)_2$ with chiral phosphine ligand **L1** or bis-oxazoline ligand **L2** was carried out. Unfortunately, only racemic 2-methyl-1,2,3,4-tetrahydroquinoline was observed (Scheme 2).

Conclusion

In summary, we have developed an iron-catalyzed transfer hydrogenation of quinolines with low catalyst loading. The high catalytic activity of iron makes it to be an environment benign alternative to Brønsted acids and other Lewis acids for the reduction of quinolines. Further studies focused on iron-catalyzed asymmetric variant are ongoing in our laboratory.

Acknowledgments

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Highlights

- Environment benign iron-catalyzed transfer hydrogenation.
- Highly catalytic activity of iron with 1 mol% catalyst loading.
- Excellent functional group tolerance
- Mild reaction condition (40 ^{o}C).

Graphical Abstract

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