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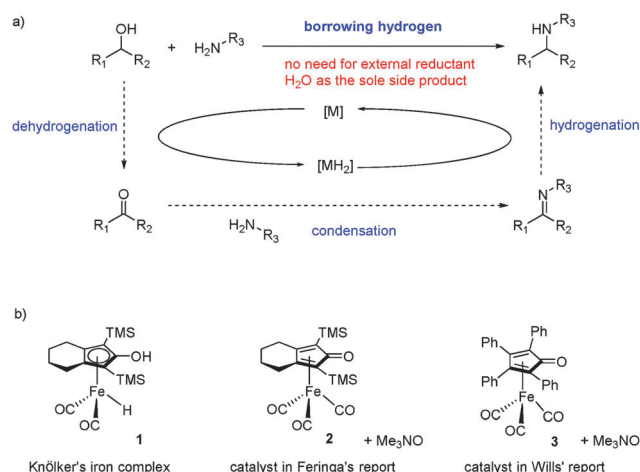
Iron-catalyzed amination of alcohols assisted by Lewis acid†

Hui-Jie Pan, Teng Wei Ng and Yu Zhao*

An efficient Lewis acid-assisted, iron-catalyzed amination of alcohols using borrowing hydrogen methodology was developed. In particular, silver fluoride was identified to be a highly effective additive to overcome the low efficiency in the amination of secondary alcohols catalyzed by Knölker's complex.

Owing to the widespread use of amines in pharmaceuticals, agrochemicals, additive and dyes, the development of efficient and environmentally benign methods to prepare amines has long been an important goal in organic synthesis.¹ Among the various strategies for amine synthesis, the amination of alcohols using a borrowing hydrogen methodology² (or hydrogen auto-transfer process) has been recognized as a highly atom economical choice (Scheme 1a). In this overall redox-neutral process, the alcohol substrate serves another role as the H₂ donor so no external reductant is needed, and water is generated as the only side product. Various catalytic systems have been developed for this transformation, most of which use catalysts based on precious metals such as Ir,³ Ru⁴ and others.⁵ The development of efficient catalytic systems using abundant, inexpensive and environmentally friendly metals (and especially iron) will be highly desired.⁶

Our group has been interested in the application of borrowing hydrogen methodology to chiral amine synthesis⁷ and we recently reported the first example of enantioselective amination of alcohols based on the cooperative catalysis of a chiral iridium complex and a chiral phosphoric acid.^{7a} The extension of this system to dynamic kinetic amination of α -branched alcohols was also achieved.^{7b} In an effort to discover more efficient and economical catalysts for this process, we were particularly attracted to the possibility of using Knölker's complex **1**⁸ (Scheme 1b) for amination of alcohols. The use of **1** for hydrogenation and transfer hydrogenation of carbonyls is well established,⁹ and the Beller group has reported highly



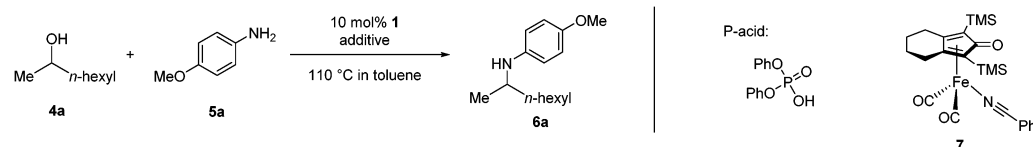
Scheme 1 Fe-complexes used in the amination of alcohols.

efficient and enantioselective hydrogenation of imines catalyzed by **1** and a chiral phosphoric acid.¹⁰ Very recently, the Feringa group and the Wills group reported successful amination of alcohols catalyzed by iron complex **2** (precursor to Knölker's complex) and the analogous complex **3**, respectively (Scheme 1b),¹¹ which prompted us to report our investigation on related studies as soon as possible. It is noteworthy that in their reports as well as other early reports on Fe-catalyzed amination reactions through a borrowing hydrogen process, only primary alcohols (and selected symmetrical secondary alcohols) can be effectively transformed into achiral amine products. Secondary alcohols, on the other hand, are in most cases unreactive (consistent with our own findings). In our studies, we have identified silver fluoride as an effective additive that enabled highly efficient amination of a wide range of secondary alcohols catalyzed by **1**.

The amination of 2-octanol with *p*-anisidine was chosen as the model reaction (Table 1). When the reaction was carried out using 10 mol% **1**, **6a** was formed in only 4% yield after refluxing in toluene for 48 h (entry 1). In the crude reaction mixture, the

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Table 1 Screening of Brønsted and Lewis acid additives for the iron-catalyzed amination of secondary alcohol^a


Entry	Additive	Time (h)	Yield ^b (%)	Entry	Additive	Time (h)	Yield ^b (%)
1	None	48	4	17	20 mol% Ni(OTf) ₂	48	36
2	20 mol% HCOOH	48	29	18	20 mol% Ni(acac) ₂	48	29
3	20 mol% TsOH	48	4	19	20 mol% Co(acac) ₂	48	4
4	20 mol% P-acid	48	<2	20	20 mol% Co(acac) ₃	48	11
5	20 mol% Cu(OTf) ₂	48	22	21	20 mol% Ti(OiPr) ₄	48	55
6	20 mol% CuCl ₂	48	<2	22	20 mol% Ag ₂ O	48	6
7	20 mol% CuCl	48	<2	23	20 mol% AgBF ₄	48	9
8	20 mol% CuBr	48	<2	24	20 mol% AgOTf	48	23
9	20 mol% CuI	48	<2	25	20 mol% AgSbF ₆	48	39
10	20 mol% FeCl ₂	48	<2	26	20 mol% Ag ₂ CO ₃	48	8
11	20 mol% FeBr ₂	48	<2	27	20 mol% AgF	48	67
12	20 mol% FeCl ₃	48	<2	28	5 mol% AgF	24	18
13	20 mol% FeBr ₃	48	<2	29	10 mol% AgF	24	46
14	20 mol% Fe ₂ O ₃	48	30	30	40 mol% AgF	24	97
15	20 mol% Fe(acac) ₃	48	38	31	20 mol% CsF	24	<2
16	20 mol% NiCl ₂	48	<2	32 ^c	40 mol% AgF	24	70

^a Unless noted otherwise, the reaction was carried out with **5a** (0.2 mmol), **4a** (5 equiv.), **1** (10 mol%) and the additive (20 mol%) in refluxing toluene. ^b Yield of **6a** was determined by GC analysis using *n*-dodecane as the internal standard. ^c **7** was used as the catalyst instead of **1**.

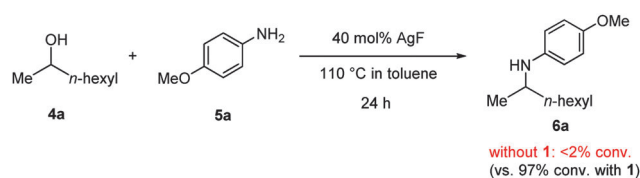
corresponding ketone could be observed in a substantial amount together with a small amount of imine (<5%), providing experimental support for the borrowing hydrogen process. However, the overall efficiency was disappointing by the use of only **1** as the catalyst. In our previous system a chiral Brønsted acid proved essential for facilitating the imine condensation as well as the asymmetric reduction step.^{7a} Inspired by this observation as well as the report from the Beller group,¹⁰ we screened various Brønsted acids for this reaction (entries 2–4). Unfortunately no significant improvement was observed in most cases, with only formic acid leading to an improved but still poor yield of 29% (entry 2). The use of phosphoric acid proved ineffective (entry 4). Chiral phosphoric acids were also examined; no product formation was observed to our disappointment (results not shown).

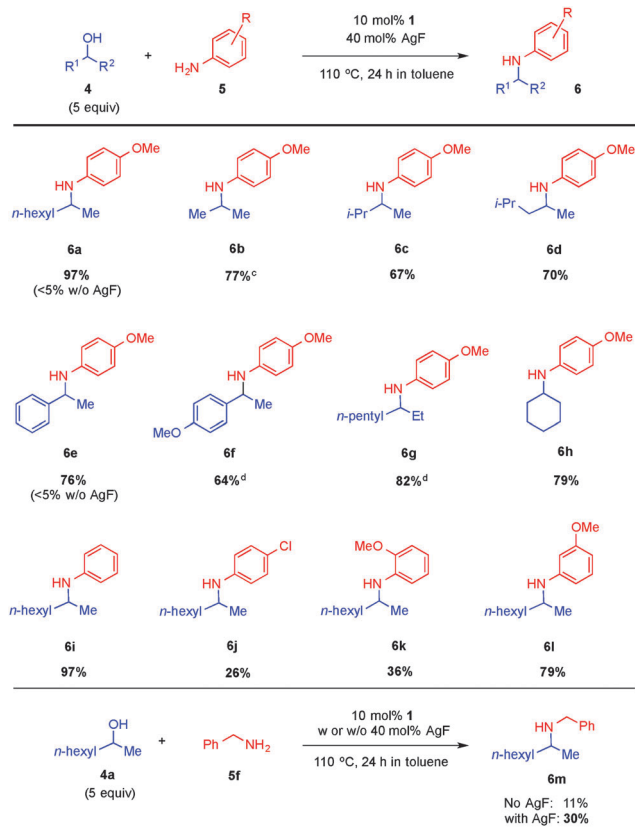
At this stage, it was decided that a wide range of Lewis acids should be examined. Various readily available salts of Cu, Fe, Ni, Co, Ti and Ag were then subjected to the reaction catalyzed by **1**. As summarized in entries 5–27, Table 1, no general trend could be observed, but the strongly Lewis acidic triflate and antimonate salts all resulted in noticeable improvement (entries 5, 17, 24 and 25). Ti(OiPr)₄ and AgF, in particular, proved to be the most effective additives, which yielded **6a** in 55% and 67% yield, respectively (entries 21 and 27). Further optimization with Ti(OiPr)₄ was not successful. To our excitement, the test of loading of AgF proved fruitful (entries 28–30): an excellent 97% yield of **6a** was obtained in 24 h when 40 mol% AgF was used. When other F-source such as CsF was used instead, no reaction was observed (entry 31). Finally, complex **7**,¹² an air-stable precursor of **1**, was tested. Under otherwise identical conditions, a slightly reduced yield of 70% was obtained (entry 32).

As Ag-catalyzed reactions of alcohols and amines *via* direct nucleophilic substitution have been documented in the literature,¹³

we tested the amination of **4a** using 40 mol% AgF in the absence of **1** (Scheme 2). No product formation was observed under these conditions, further supporting a borrowing hydrogen process catalyzed by **1** instead of the Ag-catalyzed nucleophilic substitution mechanism.

With the optimized conditions in hand, we moved on to explore the substrate scope. As shown in Scheme 3, a wide range of secondary alcohols underwent reactions to yield the corresponding amines in good to excellent yields. In the case of aliphatic alcohols, not only the linear ones such as **4a** and **4b**, but also those with α - and β -substituents could also be converted to the desired products **6c** and **6d** in good yields. Benzylic amines **6e** and **6f** could also be accessed in good yields. Again, no conversion to these products was observed in the absence of AgF. In Wills' report using **3** as the catalyst it was also noted that the reactions of aniline and secondary benzylic alcohols resulted in only low conversion to impure products. Besides 2-octanol, 3-octanol bearing an ethyl substituent was also a suitable substrate yielding **6g** in 82% yield, although a longer reaction time of 48 h was needed to achieve high conversion. It is noteworthy that the amination of symmetrical secondary alcohols such as cyclohexanol and isopropanol using aniline were reported by the Feringa group; the yield of the corresponding products **6b** and **6h** was only 12–14%,

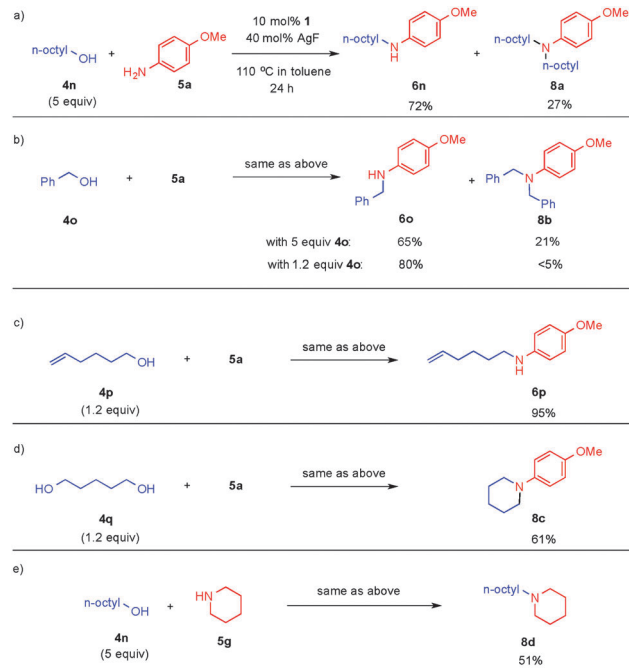
**Scheme 2** Test of AgF-catalyzed amination of alcohol.



Scheme 3 Scope of amination of secondary alcohols. See Table 1 for general conditions. All the yields refer to isolated yields of **6**. Isopropyl alcohol as the solvent. 48 h reaction.

further highlighting the beneficial effect of AgF. Different anilines could also be used for the amination reaction (**6i**–**6l**). While aniline worked well to yield **6i** in excellent yield, the electron deficient *p*-Cl aniline proved to be much less efficient (**6j**). In addition to different anilines, the use of benzylamine such as **5b** for amination reaction was also examined. Unfortunately, in this case the improvement provided by AgF was not significant; amine **6m** was produced in a 30% yield that will require further optimization.

The amination of selected primary alcohols that were used in Feringa's and Wills' reports were also tested (Scheme 4). Under the optimized conditions as before, 1-octanol and benzyl alcohol underwent reaction with *p*-anisidine to yield a mixture of secondary amine and tertiary amine products. In this case, the higher reactivity of this system resulted in a partial double amination reaction to yield the tertiary amine side product. A simple solution was to use close-to-stoichiometric loading of the alcohol. As an example, secondary amine **6o** could be obtained in a high yield of 80% when 1.2 equiv. of **4o** was used (Scheme 4b). Under similar conditions, an alkene-containing substrate underwent amination smoothly to yield **6p** in excellent yield (Scheme 4c). The alcohols containing other functionalities such as an ester or an ether group, however, failed to yield any product, representing some limitations of the current catalytic system. The use of diol as in previous work by Feringa worked

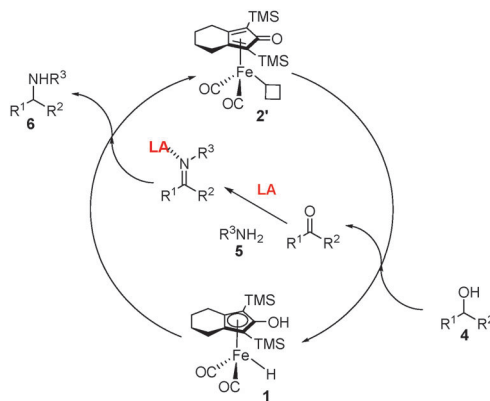


Scheme 4 Amination of primary alcohols.

out well (Scheme 4d). Finally, secondary amines such as piperidine **5g** could undergo reaction with **4n** to yield tertiary amine **8d** in a moderate yield of 51% (Scheme 4e).

This reaction is believed to proceed through a borrowing hydrogen mechanism, consistent with previous reports. A control reaction using enantiopure alcohol yielded the amine product in a racemic form. The exact nature of activation by AgF is not clear at this point. Considering the general improvement of the product yield by various Lewis acids examined in Table 1, we believe that AgF serves as the Lewis acid to facilitate imine condensation and activate the imine intermediate towards reduction by the iron hydride species **1** in the catalytic cycle shown in Scheme 5. Computational studies will be carried out to help elucidate the details of this activation by AgF.

In conclusion, we report herein a highly efficient iron-catalyzed amination of primary as well as secondary alcohols



Scheme 5 Proposed catalytic cycle.

assisted by Lewis acid. The development of an enantioselective variant of this reaction by examining chiral Lewis acids and chiral analogs of Knölker's complex is currently under investigation in our laboratory.

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