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Catalytic Hydroamination of Unactivated Olefins Using a Co Catalyst for Complex Molecule Synthesis

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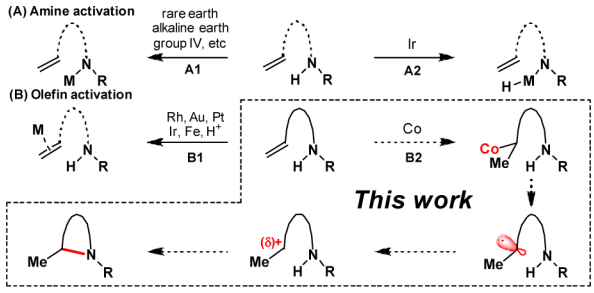
Supporting Information

ABSTRACT: Functional group tolerance is one of the important requirements for chemical reactions, especially for the synthesis of complex molecules. Herein, we report a mild, general, and functional group tolerant intramolecular hydroamination of unactivated olefins using a Co(salen) complex, an *N*-fluoropyridinium salt, and a disiloxane reagent. This method, which was carried out at room temperature (or 0 °C), afforded three-, five-, six-, and seven-membered ring nitrogen-containing heterocyclic compounds and was compatible with diverse functional groups.

The Markovnikov hydroamination of olefins—the direct coupling of olefins with amines or their derivatives including amides, sulfonamides, and carbamates—is a simple and efficient route to compounds with pivotal C−N bonds. In particular, the intramolecular version of this reaction can afford nitrogen-containing heterocycles that are present in biologically and pharmacologically important molecules and natural products.[1] Several studies on the metal-catalyzed hydroamination of olefins were reported over the past decade.[2]

In terms of the activation mode, the intra- and intermolecular hydroamination of olefins can be classified into mainly two groups: the activation of the amine or olefin (Scheme 1A,B).

Scheme 1. Representative Activation Mode of the Substrates in the Hydroamination of Olefins and Our Approach



The former can be further divided into two subgroups. The first subgroup includes the reactions catalyzed by rare-earth,[3] alkaline earth,[4] or group IV[5] metals and involves the deprotonation of N−H bonds to form the corresponding reactive metal amido species (Scheme 1A1); however, this route suffers from low functional group tolerance (e.g., acidic proton, carbonyl group) as well as air and water sensitivity of the catalysts. The second subgroup includes the reactions catalyzed by late-transition-metal catalysts. Ir-catalyzed intermolecular hydroamination reactions that involve the oxidative addition of N−H bonds were reported (Scheme 1A2).[6] The most popular activation mode of hydroamination reactions catalyzed by late-transition metals involves the activation of olefins using Lewis acidic metals as reported by Hartwig,[7] Widenhoefer,[8] Buchwald,[9] Stradiotto,[10] Michael,[11] and others[12] (Scheme 1B1). The strong acid-catalyzed hydroamination of olefins was also reported.[13] The Cu-catalyzed hydroamination of olefins has also been extensively investigated, and various mechanisms were proposed depending on the reaction conditions.[14] Despite the numerous studies on hydroamination,[15] functional group tolerance still remains to be established, as highlighted in recent reviews.[2] Although some metal-catalyzed hydroamination reactions were compatible with a limited range of highly polar functional groups[7c,8e] (e.g., unprotected alcohol, ketone, and ester) or heterocycles,[5b,16] there is an obvious need for a comprehensive and robust method for the utility of metal-catalyzed hydroamination reactions in the synthesis of complex molecules.

Previously, we reported on the incorporation of alcohols into olefins, that is, the hydroalkoxylation of olefins using a Co(salen) complex, *N*-fluoro-2,4,6-trimethylpyridinium salt, and 1,1,3,3-tetramethyldisiloxane ($(Me_2SiH)_2O$) (or phenylsilane) with excellent Markovnikov selectivity and functional group tolerance.[17] Remarkably, the experimental results indicate that the catalysis involves both a putative carbon radical and carbocation (or partial positive charge) species, and the formation of C−O bonds may occur between the cationic species and alcoholic solvent; therefore, we envisioned that the intramolecular hydroamination of olefins can be achieved using aminoalkenes under identical or modified reaction conditions (Scheme 1B2). Furthermore, on the basis of the performance of the related catalysis,[18] including our previous finding,[17] we also expected a high functional group tolerance for this hydroamination reaction. Herein, we report a new concept of an intramolecular hydroamination reaction that involves unactivated olefins using a Co(salen) complex, an *N*-fluoropyridinium salt, and a disiloxane reagent. Importantly, the catalyst system described in this study shows exceptional functional group tolerance and high reactivity at temperatures from 0 °C to room temperature, with a remarkably wide substrate scope. Finally, the limitations of this method, but noteworthy findings on the selectivity of C−N or C−O bond formation using *N*-protected aminoalkenes that contain an

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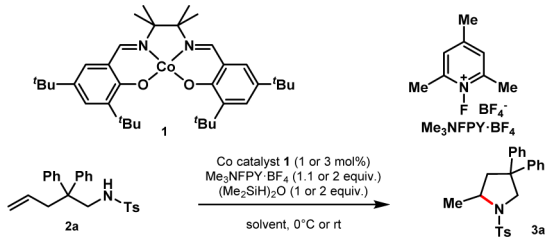
additional oxygen nucleophile attached at a spatially accessible position, are also described.

First, we studied the hydroamination of **2a** under the reaction conditions of the hydroalkoxylation of olefins that we reported previously. The reaction of **2a** catalyzed by the Co complex **1** (3.0 mol %) in methanol and in the presence of *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate ($Me_3NFPY{\cdot}BF_4$, 2.0 equiv) and $((Me_2SiH)_2O$, 2.0 equiv) afforded the desired pyrrolidine, **3a**, in 97% yield (Table 1, entry 1).

Table 1. Optimization of Reaction Conditions[a]



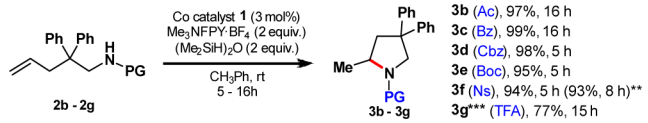
entry	solvent	temp (°C)[b]	time (h)	yield (%)[c]
1	MeOH	0	18	97
2	MeCN	0	18	75
3	CF_3CH_2OH	0	18	79
4	CF_3Ph	0	18	99
5	CH_3Ph	0	18	96
6	CF_3Ph	rt	0.5	97
7	CH_3Ph	rt	5	99
8[d]	CF_3Ph	rt	18	83
9[d]	CH_3Ph	rt	18	99
10[e]	CH_3Ph	rt	18	99

[a]Conditions: **2a**, 0.25 mmol; **1**, 3 mol %; $Me_3NFPY{\cdot}BF_4$, 2 equiv; $(Me_2SiH)_2O$, 2 equiv; and solvent, 0.10 M under Ar. Ts = *p*-toluenesulfonyl. [b]rt = room temperature. [c]Isolated yield. [d]**1**, 1 mol %; $Me_3NFPY{\cdot}BF_4$, 1.1 equiv; $(Me_2SiH)_2O$, 1 equiv; and solvent, 0.17 M in Ar atmosphere. [e]**2a**, 5.00 mmol; **1**, 1 mol %; $Me_3NFPY{\cdot}BF_4$, 1.1 equiv; $(Me_2SiH)_2O$, 1 equiv; and solvent, 0.17 M in Ar atmosphere.

However, we found that these reaction conditions were not always ideal for other substrates; therefore, we evaluated a series of solvents and identified trifluorotoluene and toluene as equally suitable solvents for this reaction (Table 1, entries 2–5). A simple increase in the reaction temperature from 0 °C to room temperature reduced the reaction time from 18 h to 30 min and 5 h for trifluorotoluene and toluene, respectively (Table 1, entries 6 and 7). The desired product **3a** was obtained without the delay of reaction time (5 h) in the presence of 2,6-lutidine (3 equiv), which indicates that HBF_4 is not the active species in the reaction. Furthermore, we could decrease the loading of complex **1** from 3.0 mol % to 1.0 mol %, decrease $Me_3NFPY{\cdot}BF_4$ from 2 equiv to 1.1 equiv, and decrease $(Me_2SiH)_2O$ from 2 equiv to 1.0 equiv; best of all, the reaction was carried out using toluene as the solvent without any loss in yield (Table 1, entry 9). Further investigation was conducted at room temperature because of the shorter reaction time. According to the results obtained using other substrates, toluene was found to be a better solvent than was trifluorotoluene in terms of yields. Notably, this method offers the advantage of scalability; by using 5.00 mmol (1.96 g) of **2a** as the substrate, we could obtain the hydroamination of the product **3a** in excellent yield (Table 1, entry 10).

Encouraged by this result, we evaluated a series of different protecting groups on the nitrogen atom of aminoalkenes, including the acetyl (Ac), benzoyl (Bz), benzyloxycarbonyl (Cbz), *tert*-butoxycarbonyl (Boc), *o*-nitrobenzenesulfonyl (Ns), and trifluoroacetyl (TFA) groups (Scheme 2). This hydroamination reaction of olefins was amenable to all of the protecting groups examined. Notably, **2g**, which contained a highly electron-withdrawing TFA group was cyclized to afford **3g** in 77% yield. Furthermore, the scalability was reexamined using **2f** (5.00 mmol, 2.12 g); this attempt also produced **3f** in excellent yield. The scope of the protecting groups for this method is broad compared to that of previously reported intramolecular hydroamination reactions of olefins. Although the substrate with a free amino group ($-NH_2$, $-NHBn$; see the Supporting Information) was found to be unsuitable for the cyclization, the protection of the nitrogen atom is advantageous owing to the easier handling of a protected amine compared to the highly polar nature of an unprotected amine.

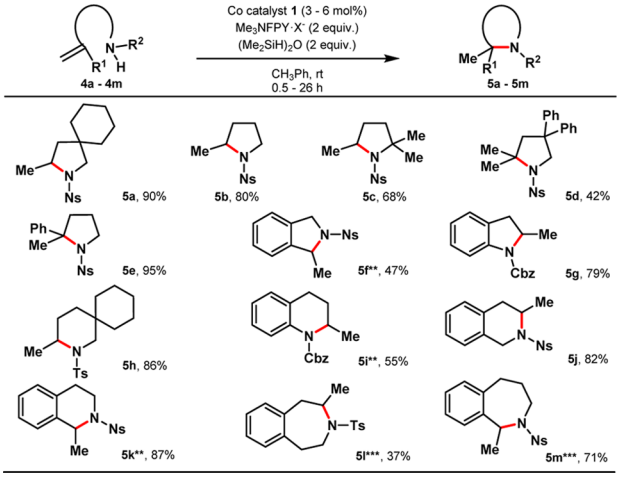
Scheme 2. Scope of Amino Protecting Groups[a]



[a]Conditions: **2b**–**2f**, 0.25 mmol; **1**, 3 mol %; $Me_3NFPY{\cdot}BF_4$, 2 equiv; $(Me_2SiH)_2O$, 2 equiv; and toluene, 0.10 M at room temperature in an Ar atmosphere. **, 5.00 mmol of **2f** was used. ***, 6 mol % of **1** was used. Yield (%) = isolation yield.

Next, the scope of *N*-protected aminoalkenes was investigated (Table 2). Because of the simplicity of the NMR spectra of Ns-protected amino compounds (amide or carbamate protecting groups produce a rotamer, which results in a complicated NMR spectra) and their mild deprotection procedure, the Ns group was used as the protecting group.[19] Irrespective of the electron-withdrawing nature of the Ns group, various nitrogen-containing heterocycles were obtained in good-to-excellent yields. Similar to **3f**, gem-disubstituted **4a** (biased toward cyclization) was cyclized to afford pyrrolidine **5a** in 90% yield (Table 2, entry 1). Substrates **4b** (unbiased toward cyclization) and **4c** (contains a bulky amine moiety) and the

Table 2. Substrate Scope of Aminoalkenes[a]



[a]Yield % = isolation yield. **, $Me_3NFPY{\cdot}OTf$ (2 equiv) was used. ***, 6 mol % of **1** and $Me_3NFPY{\cdot}OTf$ (2 equiv) were used. The reaction times are shown in the Supporting Information.

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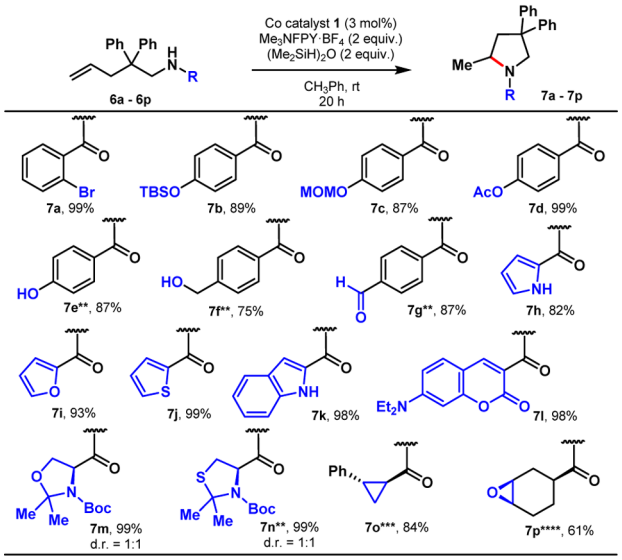
1,1-disubstituted olefins **4d** and **4e** also underwent cyclization reactions to afford the corresponding products in acceptable yields. Isoindoline **5f** could also be obtained by this method together with a complex mixture of byproducts. In the case of the *N*-aryl substrate **4g**, Cbz was found to be a suitable protecting group, and indoline **5g** was obtained in a 79% yield (58% for Ns). In the case of the piperidine formation, Ts protection resulted in a better yield (**5h**, 86%) than did Ns protection (less than 20%) because of the minimized olefin isomerization. Notably, *N*-fluoro-2,4,6-trimethylpyridinium trifluoromethanesulfonate (Me_3NFPY·OTf) performed better than did its corresponding tetrafluoroborate (BF_4) counterpart; it resulted in the formation of tetrahydroquinoline **5i** from **4i** in a 55% yield together with a complex mixture of byproducts. Similarly, in some other cases, the anion exchange of *N*-fluoropyridinium salt improved the isolated yield because of the dramatic inhibition of the side reaction, hydrofluorination.[20] Tetrahydroisoquinolines **5j** and **5k** were also synthesized in two ways. Not only the five- and six-membered ring products, but also the medicinally relevant benzazepine compounds **5l**[21] and **5m** were obtained using this method. At this stage, this method is unsuitable for 1,1,2-trialkylsubstituted olefins (see the Supporting Information).

The results of the investigations on the functional group tolerance of this method are summarized in Table 3. As

Table 3. Scope of Functional Groups[a]

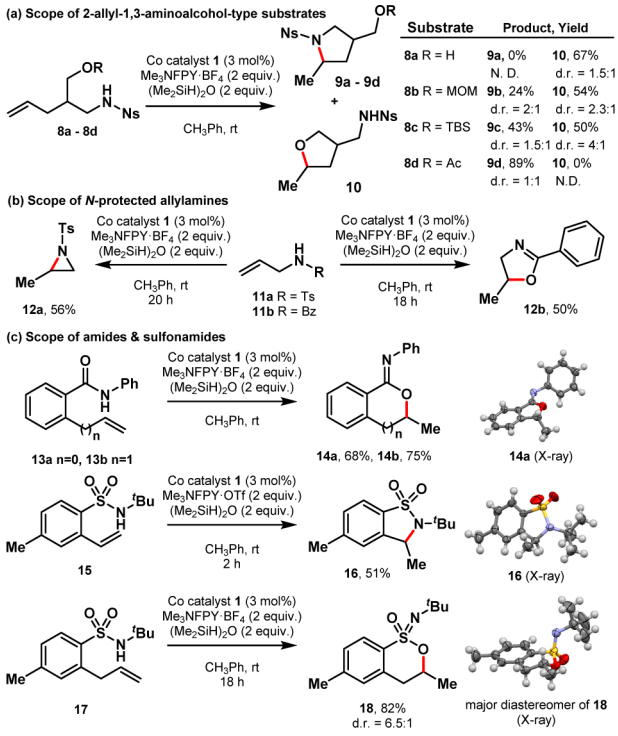


[a]Yield % = isolation yield. **, 6 mol % of **1** was used. ***, 1.5 h reaction time. ****, 2 h reaction time.

expected, various pyrrolidines were obtained in good-to-excellent yields from aminoalkenes that bore a bromo group (**7a**), a fluoroanion-sensitive silyl ether group (**7b**), a polar functional group such as an acetal (**7c**), ester (**7d**), alcohol (**7e** and **7f**), or formyl (**7g**). The heterocycles such as pyrrole (**7h**), furan (**7i**), thiophene (**7j**), indole (**7k**), and fluorescent coumarin (**7l**) were also obtained without any problems. Moreover, the acid-sensitive oxazolidine (**7m**) and sulfide-containing thiazolidine (**7n**) were also produced in excellent yields. The unstable cyclopropane- (**7o**) and epoxide- (**7p**) containing products were successfully isolated in acceptable yields.

Further investigation on the substrate scope indicated that C−O bond formation occurred when the protected amino-alkenes contained an additional oxygen nucleophile at a spatially accessible position (Scheme 3). Substrate **8a** was

Scheme 3. Scope of Substrates Containing an Additional Oxygen Nucleophile Fixed at a Spatially Accessible Position[a]



[a]The reaction times (**8a**−**8d**, **14a**, and **14b**) are shown in the Supporting Information. Yield % = isolation yield.

selectively transformed into hydroalkoxylated product **10** without the formation of hydroaminated product **9a** (Scheme 3a). For the successful hydroamination of the substrates, three types of protecting group were screened. The Ac group was found to be optimal to obtain hydroaminated product **9d** predominantly, whereas the MOM and TBS groups resulted in 24% and 50% yields of **9b** and **9c**, respectively, together with **10** via a deprotective C−O bond formation. This method afforded aziridine **12a** and isoxazoline **12b** from the corresponding *N*-protected allyl amine substrates **11a** and **11b**, respectively (Scheme 3b). Neither a five-membered ring product from **11a** nor a three-membered ring product from **11b** was isolated. Because of the nature of the sulfonamide (Ts) group and the facile 5-exo cyclization (Bz), the results obtained were expected. On the other hand, more attention should be paid to the substrates that afford the same five- or six-membered products by C−N or C−O bond formation (Scheme 3c). The C−O bond formation produced cyclic imidates **14a** and **14b** from the alkenylamides **13a** and **13b**, respectively. Although the corresponding lactams could not be isolated until now, the mild reaction conditions enabled the isolation of acid-sensitive cyclic imidates by avoiding hydrolysis. Notably, an alkenylsulfonamide gave more complex results; sultam **16** was the sole product from **15** via a C−N bond formation. In contrast, the cyclic sulfonimidate **18** was produced from the alkenylsulfonamide **17** with good diastereoselectivity via a C−O bond formation. The structures of the products **14a**, **16**, and **18** were

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fully elucidated by X-ray crystallographic analyses. The structure of **14b** was indirectly determined by further transformation followed by hydrolysis under acidic conditions to afford the corresponding lactone (see the Supporting Information). On the basis of our working hypothesis, we believe that C−N or C−O bond formation should be driven by the generation of a carbocation (or partial positive charge) species; however, the origin of this selectivity is still unclear. For the purpose of the sultam synthesis, this method is complementary to the Au-catalyzed hydroamination reported by Che,[12b] which afforded only six-membered ring sultams via a selective C−N bond formation.

In summary, we developed the Co-catalyzed intramolecular hydroamination of olefins using *N*-fluoro-2,4,6-trimethylpyridinium salt and $(Me_2SiH)_2O$. This mild, general, and functional group tolerant reaction is a powerful tool for the synthesis of diverse substrates via simple and efficient C−N bond formation. Mechanistically, we showed that this Co catalyst system can strongly and selectively activate an olefin moiety in order to react with not only hydroxyl groups, but also with nitrogen atoms, even though they are weakly nucleophilic. Further investigations on this Co catalyst system may aid in the discovery of more bond-forming reactions between olefins and other moieties. Further studies to apply this method to an intermolecular reaction are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data (^1H and ^{13}C NMR) for all new compounds. 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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(21) **5l** was obtained together with recovered **4l** (<32%) and *N*-1-Et-tetrahydroisoquinoline (6%, through isomerization−cylization). A higher temperature (50 °C) did not improve the yield (22%).