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Calcium(II)-Catalyzed Intra- and Intermolecular Hydroamidation of Unactivated Alkenes in Hexafluoroisopropanol

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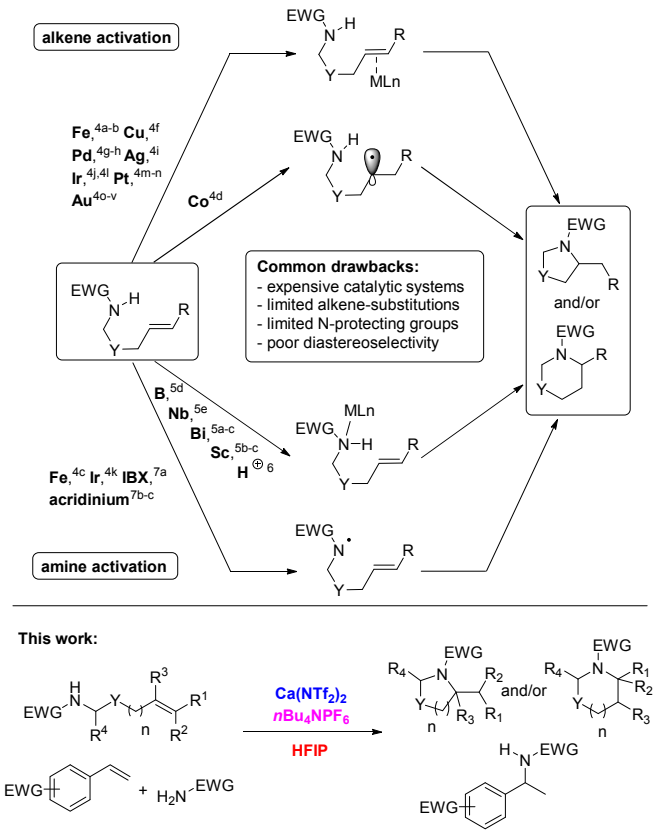
ABSTRACT: A combination of a calcium(II) triflimide salt and hexafluoroisopropanol (HFIP) was found to be a highly efficient promoter system for the intra- and intermolecular hydroamidation of unactivated alkenes. Unlike other methods, a vast array of functional groups is tolerated at the nitrogen and alkene moieties. The reaction produces the corresponding nitrogen-containing compounds in excellent yields and good diastereoselectivities. The use of HFIP as solvent proved crucial for the proper carrying out of this transformation. Its role, as well as that of calcium and its NTf_2 ligand, was rationalized by DFT computations. These calculations show how the $[(NTf_2)Ca(HFIP)_n]^+$ complex can activate the amide via a basic site of the NTf_2 ligand, and the alkene with one acidic HFIP proton. The acidity of HFIP is exacerbated by the coordination to the calcium center, the more so as n increases.

Keywords: hydroamidation, calcium, hexafluoroisopropanol, alkenes, heterocycles, DFT computations.

Introduction

Pyrrolidines and piperidines are ubiquitous nitrogen-containing heterocycles in crop science and medicinal chemistry.[1] Over the last half-century, their construction has been a fascinating topic for chemists, and has triggered the development of new catalytic systems, ever more efficient and selective. Among the numerous methods described towards their synthesis, hydrofunctionalization of alkenes, including hydroamination and hydroamidation, holds a salient position,[2,3] providing an efficient and atom-economical route for the preparation of these highly valuable scaffolds. In this respect, tremendous efforts have been devoted to the development of a large variety of versatile transition-metal-,[4] Lewis[5] and Brønsted[6] acid-, and organic[7]-based catalytic systems in order to enable the hydroamidation of unactivated alkenes via either the activation of the alkene or that of the amine (Scheme 1). However, despite remarkable progress made in this field, several major challenges remain to be addressed. For instance, most of these methods are extremely dependent on the nitrogen protecting group. Those that display a high Lewis basicity can preclude the hydroamidation because of a strong interaction between the catalyst and the nitrogen functionality. Among other drawbacks, we can also cite the difficulty to activate styrene derivatives bearing strong electron-withdrawing groups and, on the other hand, the too high reactivity of styrenes bearing electron-donating groups, which can lead to side-reactions such as self-polymerization.[2,3] All these limitations restrict the access to molecules of potential interest. In this context, devising a robust and simple catalytic system, that could circumvent most of these problems, without having to rely on precious transition-metals, is highly sought-after.



Scheme 1. Hydroamidation of unactivated alkenes.

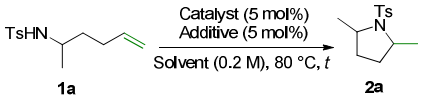
Recently, we have demonstrated that the acidity of hexafluoroisopropanol (HFIP) could be significantly harnessed by calcium(II) salts in order to activate Csp^3-O bonds, outperforming common Lewis and Brønsted acids in terms of activity and efficiency in the aza-Piancatelli cyclization[8] through the coordination of HFIP to calcium

and the formation of H-bond clusters.[9,10] Moreover, due its strong H-bond donor ability, HFIP has the capacity to facilitate the release of Lewis acids trapped by unwanted coordination to the substrate (or the product), allowing the catalytic process to turn over.[8a,10c] We wondered whether these abilities could be exploited in the activation of Csp^2-Csp^2 bonds for the intra- and intermolecular hydroamidation of unactivated alkenes, while unlocking, in the process, the reactivity of "challenging" substrates. Outlined herein is a new approach relying on an acidic Ca(II)/HFIP combination that can grant a straightforward access to a wide range of functionally diverse nitrogen-containing derivatives.

Results and Discussion

We began our investigations with *N*-tosylaminoalkene **1a** as a model substrate in the presence of a combination of $Ca(NTf_2)_2$ and nBu_4NPF_6 (5 mol%) (Table 1, entries 1-6).[11] The presumed role of the ammonium salt is to promote the formation of the $[Ca(NTf_2)]^+[PF_6]^-$ species,[12] which is more Lewis acidic than $Ca(NTf_2)_2$.[12b] Conducting the reaction in HFIP at 80 °C proved to be very effective to give rise to the corresponding pyrrolidine **2a** in 95% yield with a good diastereoselectivity in favour of a *trans* relationship (entry 1). Reactions ran in other solvents proceeded at a slower rate with lower yields and selectivities (entries 2-5). A series of control experiments was also carried out to ascertain the necessity of each component (ligand, catalyst and additive) (entries 7-10). As anticipated, no reaction was observed in the absence of $Ca(NTf_2)_2$ and/or nBu_4NPF_6.[13]

Table 1. Reaction optimization for the formation of pyrrolidine **2a**.

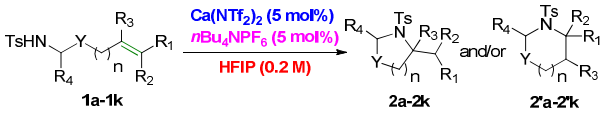


1a **2a**

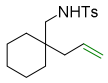
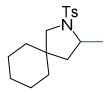
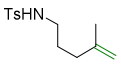
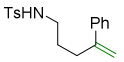
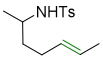
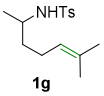
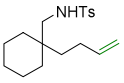
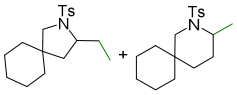
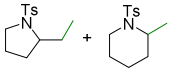
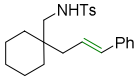
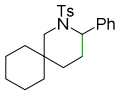
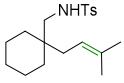
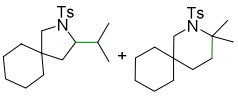
Entry	Catalyst	Additive	Solvent	*t* [h]	Yield **2a** [%] (*trans*/*cis*)
1	$Ca(NTf_2)_2$	nBu_4NPF_6	HFIP	1	95 (4.8:1)
2	$Ca(NTf_2)_2$	nBu_4NPF_6	1,2-DCE	4	87 (2.8:1)
3	$Ca(NTf_2)_2$	nBu_4NPF_6	Toluene	4	60 (3.5:1)
4	$Ca(NTf_2)_2$	nBu_4NPF_6	$MeNO_2$	4	88 (2.5:1)
5	$Ca(NTf_2)_2$	nBu_4NPF_6	TFE	2	81 (4:1)
6	$Ca(NTf_2)_2$	nBu_4NBF_4	HFIP	1.5	90 (4.4:1)
7	$Ca(OTf)_2$	nBu_4NPF_6	HFIP	4	NR
8	$Ca(NTf_2)_2$	-	HFIP	4	NR
9	-	nBu_4NPF_6	HFIP	4	NR
10	-	-	HFIP	4	NR

Having identified the best reaction conditions, we sought to explore the scope of this transformation using a broad array of *N*-tosylaminoalkenes to access pyrrolidine or piperidine derivatives (Table 2). In general, the corresponding products were obtained in good to almost quantitative yields within 2 hours at 80 °C in HFIP. It is noteworthy that the *gem*-disubstituent effect does not seem to play a critical role in terms of reaction rates (**2b** vs **2c**).[14] In the case of 2,2-disubstituted *N*-tosylaminoalkenes (**1d** and **1e**), the reaction can even be performed at room temperature to deliver **2d** and **2e** in 82% and 66% yield, respectively. The reaction is also compatible with the presence of various secondary sulfonamides (**1f** and **1g**) to afford the products **2f** and **2g** in excellent yields and good diastereoselectivities. In an attempt to specifically prepare piperidine derivatives, we studied the reactivity of *N*-tosylaminoalkenes **1h** and **1i**. However, under the reaction conditions, pyrrolidines **2h** and **2i** were obtained as major products, which suggest that the substrates experienced a fast isomerization process before undergoing the hydroamidation step.[5c] This process can be slowed down by using a less acidic solvent such as toluene (**2h**/**2'h**). On the other hand, with a phenyl substituent at the alkene moiety (**1j**), piperidine **2'j** was obtained as a sole product. Another interesting feature revolved around substrate **1k**. While pyrrolidine **2g** was exclusively formed in the absence of a *gem*-disubstituent effect, piperidine **2'k** was generated as a major product in its presence, thus, counterbalancing the isomerization. In this case, using toluene as a solvent even led to the exclusive formation of **2'k**.

Table 2. Scope of intramolecular hydroamidation of *N*-tosylaminoalkenes **1**.

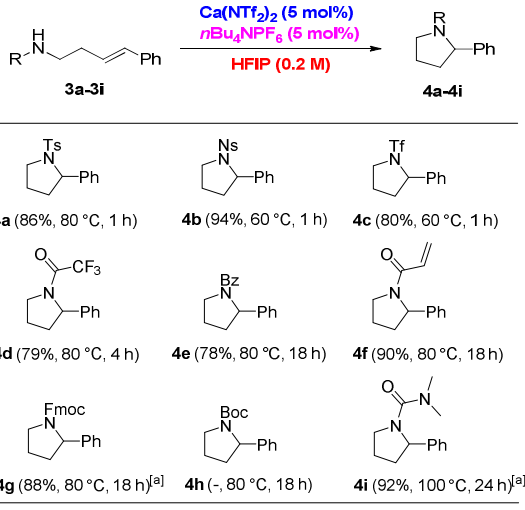


1a-1k **2a-2k** **2'a-2'k**

Entry	Substrate	Product
1	 **1b**	 **2b** (98%, 80 °C, 1 h)
2	 **1c**	 **2c** (98%, 80 °C, 1 h)
3	 **1d**	 **2d** (82%, 25 °C, 1 h)
4	 **1e**	 **2e** (66%, 25 °C, 1 h)
5	 **1f**	 **2f** (94%, 80 °C, 1 h) *trans/cis* 8.1:1
6	 **1g**	 **2g** (67%, 80 °C, 1 h) *trans/cis* 4:1
7	 **1h**	 **2h/2'h** (74%, 5:1, 80 °C, 1 h) in toluene: **2h/2'h** (63%, 2.5:1, 80 °C, 24 h)
8	 **1i**	 **2i/2'i** (88%, 6:1, 80 °C, 2 h)
9	 **1j**	 **2'j** (99%, 80 °C, 0.5 h)
10	 **1k**	 **2k/2'k** (93%, 1:3, 80 °C, 1 h) in toluene: **2k/2'k** (97%, <1:20, 80 °C, 1.5 h)

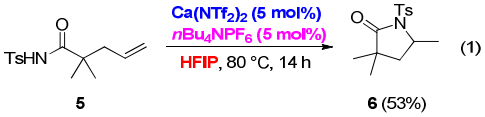
As mentioned in the Introduction, nitrogen-protecting group that display a strong Lewis basicity can prevent the hydroamidation step by trapping the catalyst. This is why sulfonamides have been primarily reported, but removing the sulfonyl protecting group can be sometimes a tedious task. On the other hand, carbamates, carboxamides and ureas, which are easier to remove than sulfonamides, proved to be more problematic in terms of reactivity, especially for intramolecular reactions, and often required the use of transition metals to trigger the hydroamidation step at the expense of the scope with reactions often limited to terminal alkenes.[4-6] But, one of the major advantages of our methodology is its compatibility with a large variety of *N*-protecting groups, ranging from sulfonyl to (alkoxy)carbonyl and carbamoyl (Table 3), which was a recurrent issue in intramolecular hydroamidations with Lewis and Brønsted acids.[5,6] In each case, the desired pyrrolidine was obtained in good to high yields (up to 95%), without having to resort to precious metals, whose use, incidentally, is often limited to the hydroamidation of terminal alkenes. Regarding our exploration studies, the only exception was the *N*-*tert*-butyloxycarbonylamino alkene **3h**. Indeed, we noticed that, during the course of the reaction, the protecting group was partially cleaved to generate the corresponding free amine, precluding the hydroamidation because of a presumed strong coordination to calcium. However, replacing the *N*-*tert*-butyloxycarbonyl group by the less sensitive fluorenylmethyloxycarbonyl group proved to be beneficial for the restoration of the reactivity (**4g**, 88% yield). Of note, the use of common solvents such as toluene, nitromethane and 1,2-dichloroethane was ineffective with substrates **4d-4i**. It is also worth mentioning that the tosyl group from **4a** can be easily removed in the presence of magnesium powder in methanol (under sonication) to provide 2-phenylpyrrolidine **4j** in 85% yield (see Supporting Information for details).

Table 3. Influence of *N*-protecting groups on the reactivity.



[a] Reaction in the presence of $Ca(NTf_2)_2$ (10 mol%) and nBu_4NPF_6 (10 mol%). Boc = *tert*-butyloxycarbonyl. Fmoc = fluorenylmethyloxycarbonyl.

Interestingly, the reaction could also be extended to the substrate **5**, featuring the presence of two electron-withdrawing groups on the nitrogen, to give the corresponding lactam derivative **6** in 53% yield (Equation 1).

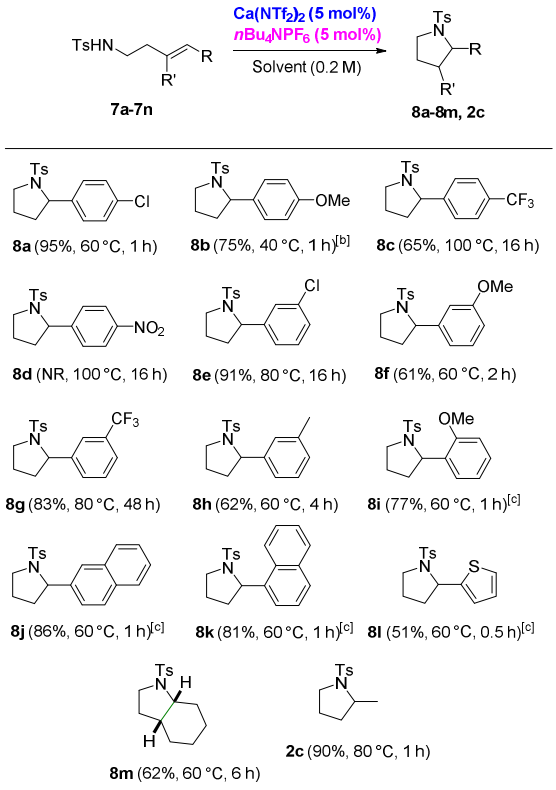


(1)

The substitution pattern at the alkene moiety was then evaluated (Table 4). To our delight, the reaction was tol-

erant to a large variety of functional groups (alkyl, naphthyl and (hetero)aryl) with yields ranging from 51% to 96%. In particular, we succeeded to achieve the hydroamidation in the presence of a strong electron-withdrawing group such as CF_3 in good yields, albeit at a slower reaction rate. On the other hand, the *p*-nitrophenyl analogue **7d** failed to provide **8d**. Regarding the reactivity, we noticed that the hydroamidation was extremely dependent on the electronic nature of the functional groups. For instance, in the presence of electron-richer groups, our standard reaction conditions in HFIP proved to be detrimental to the reactivity (see Supporting Information for details). However, this problem could be circumvented by using a 1:3 combination of HFIP and toluene in order to soften the reaction conditions, with the exception of compound **8b**, which required the sole use of toluene as a solvent. We also found that we could access bicyclic framework such as **8m** in 62% yield.

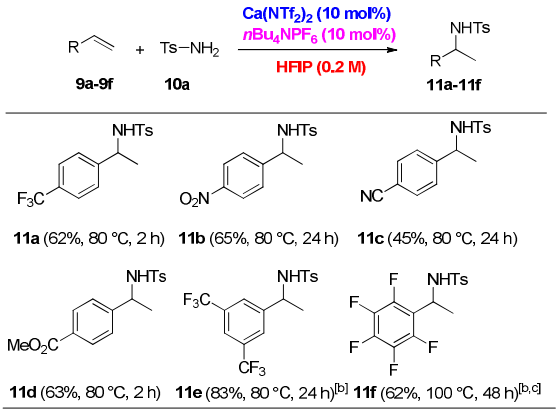
Table 4. Influence of alkene substitution on the reactivity.[a]



[a] Reactions conditions: *N*-tosylaminoalkenes **7a-7m** in HFIP (0.2 M) in the presence of $Ca(NTf_2)_2$ (5 mol%) and nBu_4NPF_6 (5 mol%) at the indicated temperature. [b] Reaction performed in toluene. [c] Reaction performed in toluene/HFIP (3:1).

Encouraged by these results, we turned our attention to intermolecular hydroamidations of alkenes, focusing on a less reactive class of compounds, namely electronically deactivated styrene derivatives (Table 5). To date, the hydroamidation of these types of compounds is unprecedented. Gratifyingly, by using an excess of *p*-toluenesulfonamide **10a** (3 equiv) in the presence of 10 mol% of $Ca(NTf_2)_2$/nBu_4NPF_6, we succeeded to synthesize the desired *N*-benzyl sulfonamides **11a-11d** in good yields, while the formation of the desired products was not observed in other solvents (toluene, nitromethane and 1,2-dichloroethane). On the other hand, in the case of even more deactivated styrenes (**10e** and **10f**), we found out that using an excess of styrene derivative led to better yields.

Table 5. Scope of intermolecular hydroamidation of alkenes.[a]



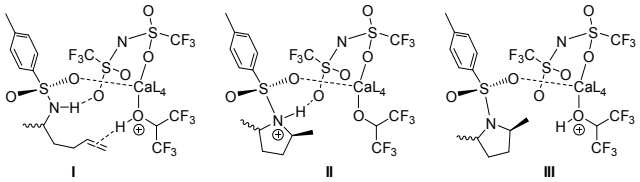
[a] Reactions conditions: *N*-tosylamine derivative **10a** (3 equiv) and alkene **9** (1 equiv) in HFIP (0.2 M) in the presence of $Ca(NTf_2)_2$ (10 mol%) and nBu_4NPF_6 (10 mol%) at the indicated temperature. [b] *N*-tosylamine derivative **10a** (1 equiv) and alkene **9** (3 equiv). [c] $Ca(NTf_2)_2$ (20 mol%) and nBu_4NPF_6 (20 mol%).

The mechanisms involved in Lewis acidic salt-catalyzed processes are still not fully understood. In many cases, the reactions are quenched or strongly slowed down in the presence of a proton scavenger, which suggests that hidden Brønsted acid catalysis is taking place.[15] However, it is also clear that the metal is indispensable, since the direct use of Brønsted acids is often not as efficient as with the metal salt.[15c] Another important point is that the reaction of $Ca(NTf_2)_2$ with nBu_4NPF_6 produces $[Ca(NTf_2)]^+[PF_6]^-$[12] rather than species in which both NTf_2 ligands would have been replaced, such as $[Ca]^{2+}[PF_6]_2^-$.[16] The NTf_2 ligand is actually a polybasic fragment (through its nitrogen atom and its sulfonyl oxygens) that should not be neglected.[17] The study of the reaction mechanism by means of DFT computations offered us a unique opportunity to relate the metal, the NTf_2 ligand, and protons coming from HFIP. The calculations were carried out using the Gaussian 09 software package.[18] The results presented are ΔG_{298} in kcal/mol obtained at the M06-2X/6-31+G(d,p) level of theory. The solvation model based on density (SMD) was used to take the solvent effect into account, using the parameters of 2-propanol, except ε set at the HFIP value of 16.7.[19] Compound **1a** was used as model substrate. Since $Ca(NTf_2)_2$ is known as an 8-coordinate tetrahydrate in the solid state,[20] and since no special precautions are taken when using it, water molecules were used to fill the coordination sphere of calcium. It is important to stress first that the activation of the C=C bond with calcium to trigger the cyclization failed. On the other hand, we succeeded in modeling the cyclization after introducing one HFIP molecule as ligand to calcium and using its proton as activator (Table 6).

The ligation of the substrate to the $(NTf_2)Ca^+$ moiety is actually achieved at a tosyl oxygen as in **I**. A non-covalent interaction between the alkene and the OH group also contributes to freeze the conformation of the substrate (the maximum electron density found in this area is $\rho_{max} \sim 0.02$ e.Å^{-3} for each case studied). However, a third association between the substrate and the $(NTf_2)Ca^+$ moiety is also required. Provided the NTf_2 ligand is oriented so as to establish a strong NH---OS hydrogen bond, the N-C bond formation to give ammonium **II** could

be achieved by HFIP-to-alkene proton transfer and concomitant attack of the nitrogen atom.

Table 6. Computed free energies.[a]



I II III

Entry	L_4	Dias	$\Delta G^{\ddagger}_{298}$ (**II-I**)	ΔG_{298} (**II-I**)	ΔG_{298} (**III-I**)
1	4 H_2O	*trans*	33.9	6.5	-13.6
2	4 H_2O	*cis*	34.3	6.7	-15.8
3	HFIP/ 3 H_2O	*trans*	32.5	0.5	-8.4
4	HFIP/ 3 H_2O	*cis*	32.7	4.5	-14.8
5	**2 HFIP/ 2 H_2O**	***trans***	**27.3**	**-1.2**	**-35.6**
6	2 HFIP/ 2 H_2O	*cis*	31.4	4.6	-46.9

[a] kcal/mol, L = H_2O.

However, a quite high free energy of activation of 33.9 kcal/mol was computed to obtain the *trans* product (entry 1). The transformation yielded a calcium hydroxide in an endergonic fashion (ΔG_{298} 6.5 kcal/mol). The transfer of the ammonium proton to the hydroxide to regenerate HFIP led to **III**, which is more stable than **I** by 13.6 kcal/mol. Forming the *cis*-product through this mechanism proved slightly more demanding in free energy of activation (entry 2, $\Delta G^{\ddagger}_{298}$ 34.3 kcal/mol). With 2 HFIP molecules, $\Delta G^{\ddagger}_{298}$ decreased slightly (entries 3 and 4). While the formation of the *cis* product remained endergonic, that of the *trans* became virtually thermoneutral. With 3 HFIP molecules (entries 5 and 6), $\Delta G^{\ddagger}_{298}$ decreased significantly (27.2 vs 31.4 kcal/mol). The formation of the *trans* ammonium even became exergonic (-1.2 kcal/mol vs 4.5 kcal/mol for the *cis* ammonium). The transition state leading to the *trans* ammonium is displayed in Figure 1.

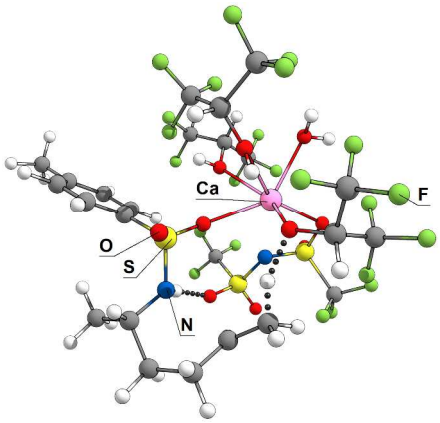


Figure 1. Geometry of the computed transition state corresponding to the *trans* cyclization (one water molecule omitted for clarity)

These results rationalize why HFIP is an appropriate solvent for the title transformation. Once ligated to calcium, it will become able to protonate the alkene. This is especially true if the calcium center is not too electronically enriched, i.e. with other HFIP molecules in its coordination sphere rather than water molecules. Another important point is that the cyclization does not take place if the NTf_2 ligand is not oriented so as to interact with the NH group. The length of the forming N-C bond is still long in the transitions state (2.51 Å with 3 HFIP), but the NH---OS interaction contributes to its rigidification. Overall, in such a model, a coordination site is required on the EWG at the nitrogen, which can be found in any of the examples reported herein, and the substrate is confined through a triple association with the $(NTf_2)Ca(HFIP)_n^+$ fragment. The metal has two roles: it unites the substrate, the NTf_2 ligand and HFIP, and it strengthens the acidity of the latter, which proved to be crucial to activate styrenes usually unreactive towards hydroamidation. To some extent, $(NTf_2)Ca(HFIP)_n^+$ can be compared to a metal-templated hydrogen bonding bifunctional organocatalyst.

Conclusions

In summary, we have devised a novel catalytic strategy to forge valuable nitrogen-containing derivatives through the hydroamidation of unactivated alkenes. In particular, we used the remarkable properties of HFIP as a solvent in combination with a catalytic Ca(II)-based Lewis acid to activate challenging substrates and, therefore, trigger a hydroamidation process. This methodology proved to be general and versatile, while expanding the boundaries of the hydroamidation. Further investigations are on-going to apply this catalytic system to other transformations.

ASSOCIATED CONTENT

SUPPORTING INFORMATION

Experimental procedures and characterization data of all new compounds (including NMR spectra), and DFT computations. This material is available free of charge via the Internet at http://pubs.acs.org/

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Authors' Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing interest.

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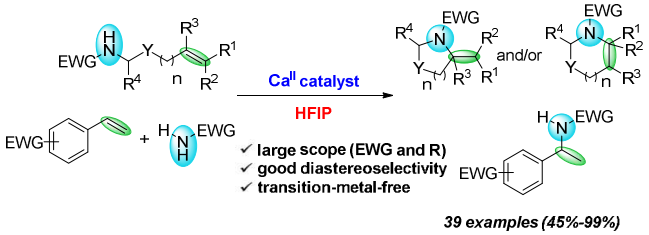
EWG
R4
R3
R1
R2
Y
n
Ca[II] catalyst
HFIP
and/or
large scope (EWG and R)
good diastereoselectivity
transition-metal-free
39 examples (45%-99%)