Lewis Acid/Hexafluoroisopropanol: A Promoter System for Selective ortho-C-Alkylation of Anilines with Deactivated Styrene Derivatives and Unactivated Alkenes

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Shengdong Wang,[a] Guillaume Force,[a] Régis Guillot,[a] Jean-François Carpentier,[b] Yann Sarazin,[b] Christophe Bour,[a] Vincent Gandon*[,a,c] and David Lebœuf*[,d]

[a] Institut de Chimie Moléculaire et des Matériaux d'Orsay (ICMMO), CNRS UMR 8182, Université Paris-Saclay, Bâtiment 420, 91405 Orsay, France.

[b] Univ. Rennes, CNRS UMR 6226, Institut des Sciences Chimiques de Rennes (ISCR), 35000 Rennes, France.

[c] Laboratoire de Chimie Moléculaire (LCM), CNRS UMR 9168, Ecole Polytechnique, Institut Polytechnique de Paris, route de Saclay, 91128 Palaiseau cedex, France.

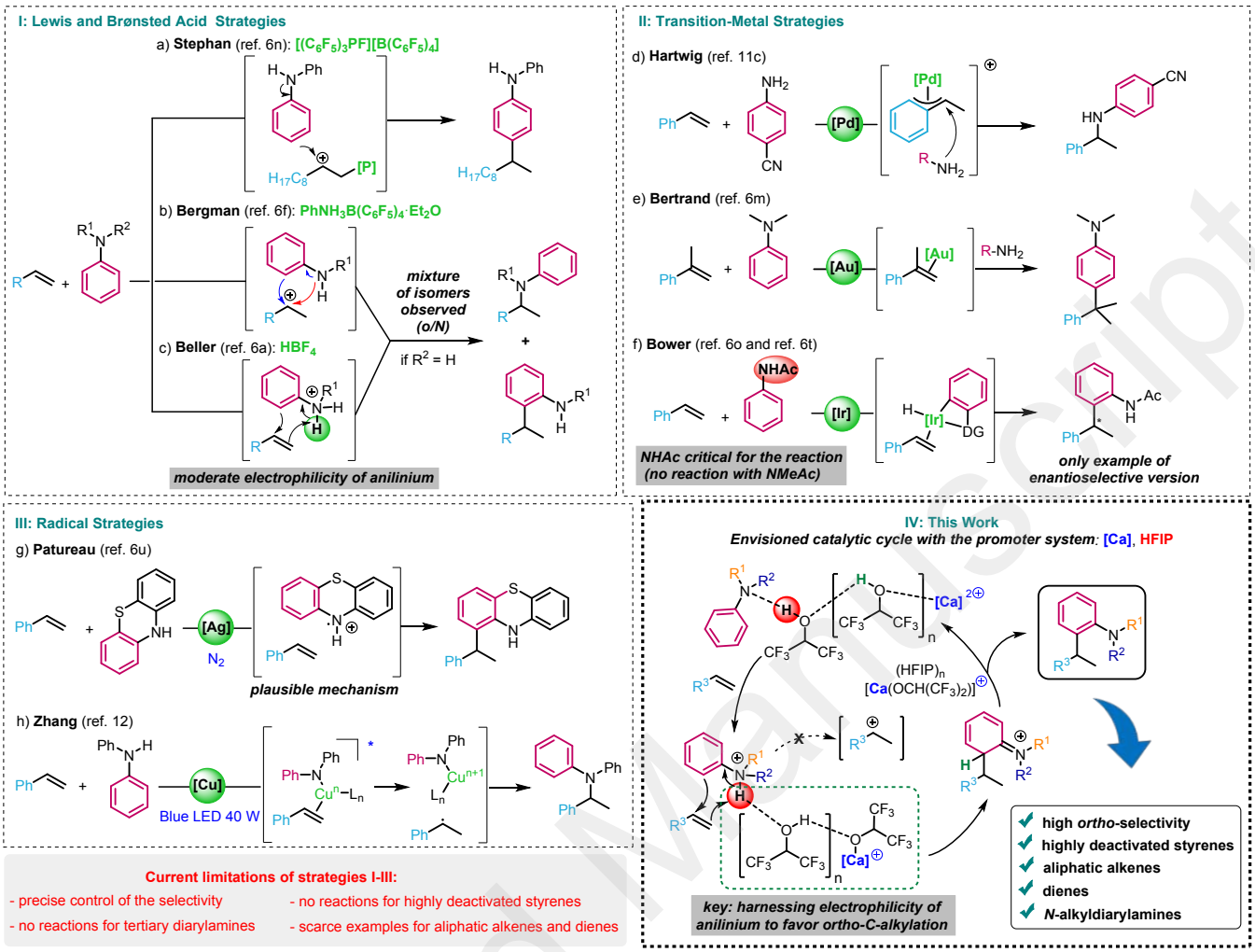
[d] Institut de Science et d'Ingénierie Supramoléculaires (ISIS), CNRS UMR 7006, Université de Strasbourg, 8 allée Gaspard Monge, 67000 Strasbourg, France.

KEYWORDS alkenes, anilines, hexafluoroisopropanol, Lewis acid, ortho-C-alkylation

ABSTRACT: Aniline derivatives are frequently encountered in molecules of industrial relevance such as dyes or antioxidants, which make the development of synthetic methods for the functionalization of these privileged structures highly sought-after. A general protocol for the hydroarylation of electronically diverse alkenes with anilines would be ideal to provide densely functionalized compounds. Yet, this transformation has been underexplored compared to more traditional hydroarylation of unactivated alkenes because of the significant challenges associated with the control of the selectivity and its substrate tolerance. Herein, we describe a selective, versatile and user-friendly *ortho*-C-alkylation of anilines with alkenes that hinges on the beneficial combination of a Lewis acid (Ca(II)) and hexafluoroisopropanol as a solvent. This protocol allows for the extension of this transformation to highly deactivated styrenes and demonstrates a remarkable improved reactivity regarding aliphatic alkenes, styrene derivatives and dienes. In addition, DFT computations were performed which, combined with experimental observations, suggest a nearly concerted mechanism that impart the *ortho*-selectivity.

Diarylamines, and generally simple anilines, are prevalent building blocks in organic synthesis. They offer a wide variety of applications, including pharmaceuticals, agrochemicals, and functional organic materials.[1] Besides, they can be rapidly converted into acridinium derivatives,[2] which have emerged as powerful catalysts for photoredox transformations.[3] Within this context, the identification of synthetic methods to increase the molecular complexity and diversity of these compounds has been thoroughly investigated over the last decades. Among them, the hydroarylation of unactivated alkenes with anilines represents arguably an ideal process: an atom- and step-economic transformation featuring feedstock alkenes and anilines to form key C–C bonds in an efficient manner.[4] Despite many studies outlined in Scheme 1,[5-7] the intrinsic limitations associated with this transformation have still to be addressed, including its unpredictable selectivity (*ortho*-C alkylation/*para*-C alkylation/hydroamination), its incompatibility with highly deactivated styrenes and *N*-(alkyl or aryl) diarylamines and its limited reactivity regarding aliphatic alkenes. In particular, the dearth of reports regarding highly deactivated styrenes[8] that incorporate strong electron-withdrawing groups is detrimental to discovering new applications, as such substrates may impart original properties to the compounds prepared through non-covalent interactions (π-anion, lone pair-π or π-π interactions).[9] In the realm of hydroarylation of unactivated alkenes, a traditional approach involves the use of a Lewis or Brønsted acid, which typically triggers the formation of a stabilized carbocation species and a subsequent trapping by (hetero)arene nucleophiles.[4] Yet, this strategy often leads to both *ortho*- and *para*-products, limiting its applicability. The problem becomes even more pronounced in the case of anilines, which can also undergo hydroamination reactions (Schemes 1a-1c).[10] To account for the formation of the *ortho*-alkylated product, Beller and coworkers alluded to a concerted mechanism that would differ from that of a typical proton-catalyzed hydroarylation (Scheme 1c).[6a] However, in the case of Lewis and Brønsted acid-based strategies, the transformation led to uneven selectivities between *ortho*-C alkylation and hydroamination depending on the promoter system used (from 1:0 to 0:1),[6a,6c-6l,6n] suggesting competing reaction pathways. To date, the iridium-catalyzed enantioselective *ortho*-alkylation of acetanilides described by the group of Bower can be considered as a reference in terms of selectivity (Scheme 1f);[6o,6t] yet, no highly deactivated styrene was investigated, a specific directing-group was required, and tertiary anilines were incompatible with the reaction conditions. In

Scheme 1. Hydroarylation and hydroamination of olefins with aniline derivatives.



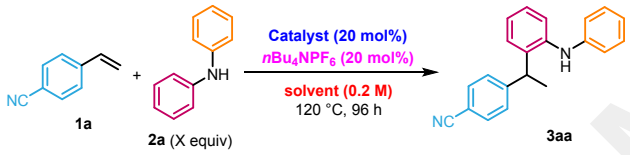
contrast, transition-metal-catalyzed reactions are more prone to produce hydroamination adducts[11] or give rise to *para*-selectivity in the absence of directing groups (Schemes 1d-1e).[6m,6q] Visible-light photoredox protocols are curbed with similar limitations (Schemes 1g-1h).[12]

Our recent studies demonstrated that the use of HFIP as a solvent[13] paired with a Lewis or Brønsted acid enables the activation of highly unreactive olefins.[8f,14] Conceptually, the role of the catalyst in these examples is not to directly activate the nucleophile or the electrophile, but, instead, to augment the acidity of a H-bond network of HFIP molecules.[8f,14a] In search of a reliable and selective *ortho*-C-alkylation of anilines with olefins and inspired by the work of Beller, we reasoned that, under highly acidic conditions, anilines would provide an anilinium cation, which could react through a 6-membered transition state to generate the targeted *ortho*-alkylated product exclusively. This is where the use of HFIP would be paramount for the success of the transformation as it may sufficiently harness the acidity of the anilinium to even react with highly deactivated substrate, in contrast with the use of common solvents.[15] Importantly, the strategy could be applied irrespective of the nature of the aniline (primary, secondary or tertiary). Additionally, since the aniline would act as a buffer, even dienes and styrene derivatives, which typically generate oligomers in HFIP,[16] could be tolerated. Herein, we disclose our findings regarding this transformation with a special emphasis on highly deactivated styrenes and their synthetic applications. This approach provides an amenable and broadly applicable method to break the stalemate on the selective *ortho*-C-alkylation of anilines. The mechanistic considerations are further supported by DFT computations. Moreover, this study shows how the nature of the substrates can dictate the *ortho/para* selectivity.[17]

At the outset, we examined the feasibility of this concept by investigating the inherent reactivity of highly deactivated 4-cyanostyrene **1a** with diphenylamine **2a**[6u] (4 equiv.) in the presence of the promoter system that we previously described for hydrofunctionalizations: $Ca(NTf_2)_2/n Bu_4NPF_6$ (20 mol%)[18] in HFIP (0.2M) (Table 1). With respect to this system, the role of the ammonium salt of weakly coordinating hexafluorophosphate is to promote an anion metathesis to form the heteroleptic salt $Ca(NTf_2)(PF_6)$, which is more prone to activate the H-bond network of HFIP than the sole $Ca(NTf_2)_2$.[19] Although the reaction required a prolonged heating at 120 °C for 4 d to proceed to full conversion, the targeted compound **3aa** was obtained as a sole product in an excellent yield of 92% (entry 1). The

structure of **3aa** was further confirmed by X-ray analysis (Figure 1). Reactions with reduced number of equivalents of diphenylamine **2a** still yielded **3aa**, albeit in lower yields (entries 2-4).[20] On the other hand, we found that the reaction was significantly affected by the catalyst loading as the yield decreased to 55% in the presence of 10 mol% of catalyst (entry 5). Importantly, no reaction was observed by conducting the transformation in common solvents (entries 6-8), while **1a** remained intact. Besides, reactions in solvent mixtures to decrease the amount of HFIP employed gave inferior results (entries 9-11). While reactions in the presence of $Ca(NTf_2)_2$ occurred with the highest yields, $Ca(NTf_2)_2$ is not pivotal in the process; reactions in the presence of a wide series of Lewis and Brønsted acids also furnished product **3aa** in high yields (55-87%) (entries 12-17), indicating that HFIP is the true cornerstone of the reaction. Given the results obtained, $Ca(NTf_2)_2$ has the major advantage to be easy to handle when compared to $HNTf_2$, which is highly hygroscopic and becomes rapidly deliquescent. Of note, the sole presence of HFIP is not sufficient to mediate the reaction (entry 18). The robustness of this reaction was also evaluated on a scale-up experiment (5 mmol) and **3aa** could be synthesized on a 1.33 g scale (89%).

Table 1. Reaction optimization for the formation of diarylethane **3aa**.[a]



entry	catalyst	solvent	X	yield [%][d]
1	$Ca(NTf_2)_2$	HFIP	4	92
2	$Ca(NTf_2)_2$	HFIP	3	89
3	$Ca(NTf_2)_2$	HFIP	2	78
4	$Ca(NTf_2)_2$	HFIP	1	75
5[b]	$Ca(NTf_2)_2$	HFIP	4	55
6	$Ca(NTf_2)_2$	1,2-DCE	4	NR
7	$Ca(NTf_2)_2$	toluene	4	NR
8	$Ca(NTf_2)_2$	$MeNO_2$	4	NR
9	$Ca(NTf_2)_2$	1,2-DCE/HFIP (3:1)	4	43
10	$Ca(NTf_2)_2$	toluene/HFIP (3:1)	4	60
11	$Ca(NTf_2)_2$	$MeNO_2$/HFIP (3:1)	4	23
12[c]	$HNTf_2$	HFIP	4	87
13[c]	HOTf	HFIP	4	87
14	$Sc(OTf)_3$	HFIP	4	80
15	$Cu(OTf)_2$	HFIP	4	55
16	$Bi(OTf)_3$	HFIP	4	83
17	$Al(OTf)_3$	HFIP	4	85
18	-	HFIP	4	NR

[a] Reactions performed in a sealed tube. [b] Reaction in the presence of $Ca(NTf_2)_2$ (10 mol%) and nBu$_4$NPF$_6$ (10 mol%). [c] Reaction in the absence of nBu$_4$NPF$_6$. [d] Yields of isolated **3aa**. NR = no reaction.

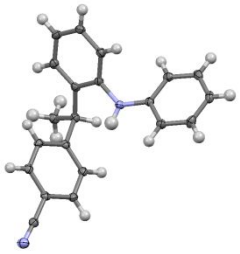
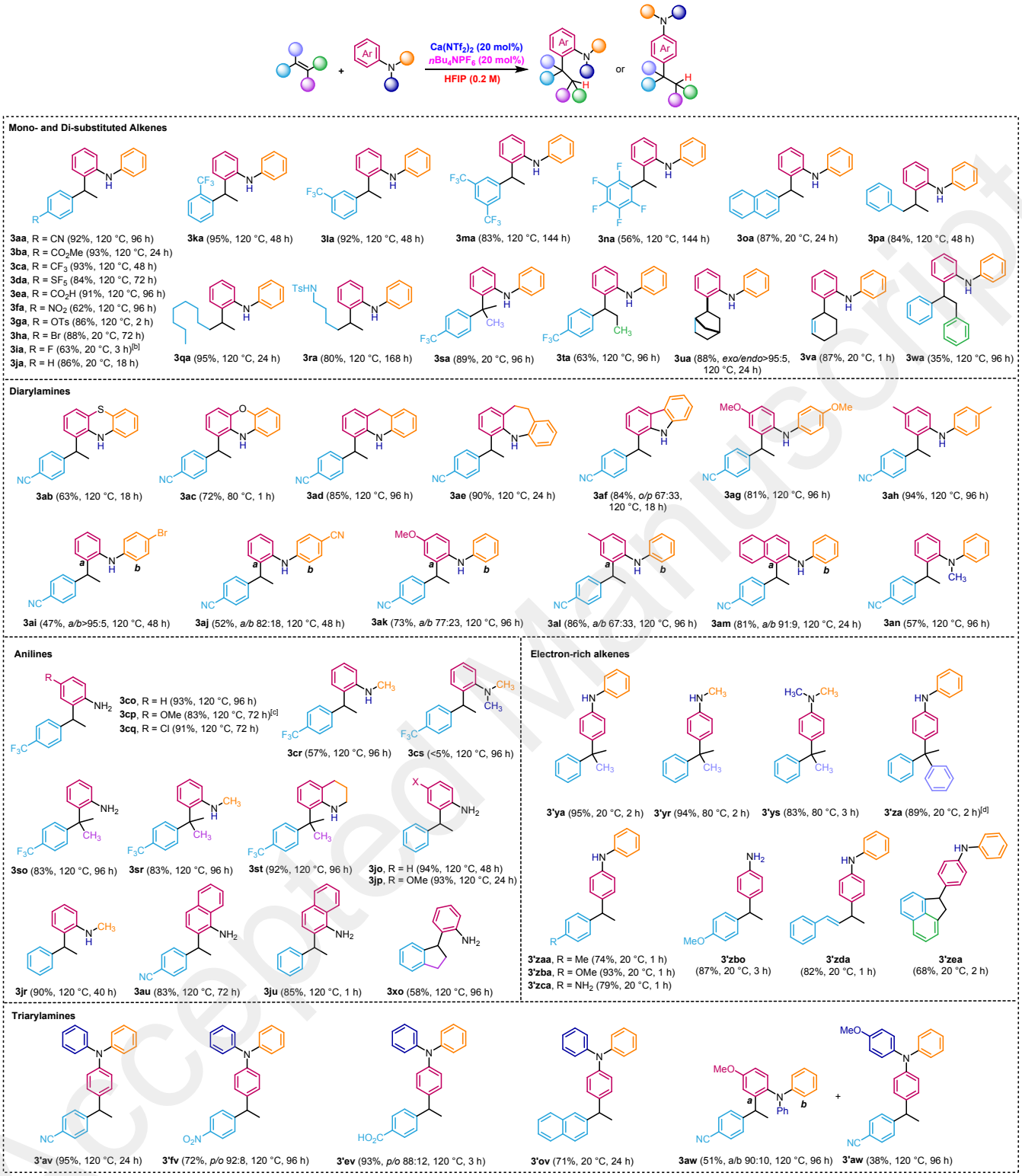


Figure 1. ORTEP drawing of compound **3aa**. Thermal ellipsoids are shown at 50% probability level.

With the identified reaction conditions, we sought to explore the generality of the protocol with a large range of alkene and aniline derivatives (Scheme 2). Initially, we focused our efforts on the reactivity of different styrene derivatives bearing distinct electronic properties and substitution patterns. The reaction proved to be compatible with a large variety of strong electron-withdrawing groups to yield the corresponding products in good to excellent yields (**3aa**-**3ga** and **3ka**-**3na**, 56-95%). Substituents at *ortho*-, *meta*- and *para*-positions were well tolerated. However, in the case of even more deactivated substrates such as **1m** and **1n**, the reaction required 6 d for the styrene to be fully consumed. The reaction could also be expanded to styrenes bearing moderate electron-withdrawing groups (**1h** and **1i**) and even unsubstituted styrene **1j**, which is typically prone to undergo oligomerization in HFIP,[16] confirming the role of buffer of the amine in the reaction to preclude the side-process. These transformations could be conducted under milder reaction conditions (20 °C), which represents a notable improvement when compared to previous reports that required higher temperatures (up to 160 °C).[6] Furthermore, aliphatic alkenes (**1p**-**1r**) were competent substrates for the reactions, forming the products in 80-95% yields. Even a substrate incorporating an additional functional group (**1r**) that may engage in an intramolecular process reacted in a target fashion. It should be emphasized that, in all reactions studied, no products arising from the isomerization of the double bond were observed. The reaction was also not limited to mono-substituted styrenes: both α- and β-methylstyrenes **1s** and **1t** afforded the products in 89% and 63% yields, respectively. Reactions of cyclic alkenes such as norbornene **1u** and 1,3-cyclohexadiene **1v** gave also excellent results (88% and 87% yields). Finally, we examined the reactivity of hindered styrenes such as (*E*)-stilbene **1w**, which led to compound **3wa** in a moderate yield (35%).[21]

Next, we evaluated a broad range of diarylamines in a model reaction with 4-cyanostyrene **1a**. Initially, we investigated symmetrical diarylamines (**3ab**-**3ah**). In addition to diphenylamine **2a**, this catalytic process was applied to prepare a number of frameworks of interest such as phenothiazine (**3ab**, 63%), phenoxazine (**3ac**, 72%), dihydroacridine (**3ad**, 85%) or iminodibenzyl (**3ae**, 90%). One exception was carbazole **2f**, which furnished both *ortho*- and *para*-products in a combined yield of 84% (*o*/*p* 67:33). An important feature of this protocol is also the use of dissymmetrical diarylamines. We noticed that, by relying on the electronic properties of the aryl rings with electron-donating or electron- withdrawing groups, it was possible to execute the reaction with a good control of the selectivity,

Scheme 2. Scope and limitations of the C-alkylation of anilines with olefins.[a]



[a] Reactions performed in a sealed tube. [b] *o/p* 88:12. [c] *o/N* 93:7. [d] *ortho*-product obtained in 7% yield.

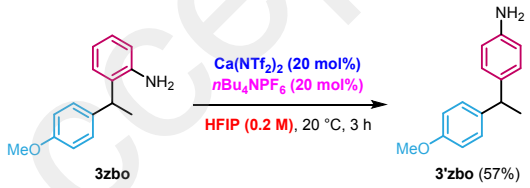
ranging from 67:33 to > 95:5. Gratifyingly, engaging the tertiary diarylamine **2n** in the reaction gave **3an** in 57% yield.

We also studied the title process with primary anilines, *N*-alkyl anilines and 1-naphthylamine, which were previously found to form hydroamination products along the targeted compounds in well-documented Lewis and Brønsted acid catalysis.[6a,6c-6l,6n] Here, they reacted with highly deactivated styrenes to generate exclusively *ortho*-products in high yields (up to 93%). Similarly, the reaction between styrene and aniline derivatives afforded the targeted products (up to 94%). One limitation of our method was the reactivity of a highly basic aniline such as *N,N*-dimethylaniline **2s**, which

proved to be unreactive under standard reaction conditions. The results are in agreement with the hypothesized mechanism, where the reduced electrophilicity of the corresponding anilinium compared to those previously studied along with the low nucleophilicity of styrene **1c** is prohibitive for the reaction to occur.

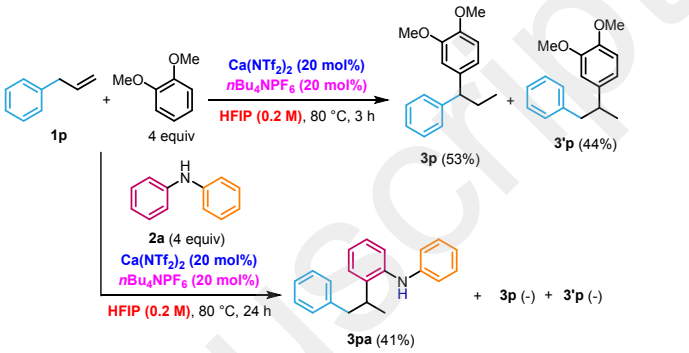
We noted that the electron density of the alkene is another key factor in this transformation. Indeed, when α-methylstyrene **1y** was employed instead of electron-deficient styrene **1s**, we observed a complete switch of the selectivity from *ortho* to *para*, independently of the aniline used. These results hint at a different mechanism with electron-rich alkenes, which would first involve the protonation of the alkene with the formation of highly stable carbocation under the reaction conditions and a subsequent electrophilic aromatic substitution. Similarly, other electron-rich alkenes such as 1,1-diphenylethylene **1z**, 4-methylstyrene **1za**, 4-methoxystyrene **1zb**, 4-aminostyrene **1zc**, (*E*)-1-phenyl-1,3-butadiene **1zd** and acenaphthylene **1ze** delivered the *para*-products in high yields (68-93% yield). On the other hand, introducing an electron-withdrawing group on oxygen (**1g**) allows to restore the *ortho*-selectivity (**3ga**, 86%). The use of triphenylamine **2v** led also to the generation of *para*-adducts (**3'av**, **3'ev**, **3'fv** and **3'ov**) (71-95% yields). Our assumption is that the reactivity of **2v** might be directly linked to the p*Ka* of its conjugated acid Ph_3NH^+ (p*Ka* = –3.9) in comparison to the ones of $Ph_2NH_2^+$ (p*Ka* = 0.8) and $PhNH_3^+$ (p*Ka* = 4.6).[22] Indeed, Ph_3NH^+ should protonate the alkene more easily than $Ph_2NH_2^+$ or $PhNH_3^+$ and, in that case, an electrophilic aromatic substitution would occur. This trend could be partly counterbalanced through electronic effects by introducing an electron-donating group (4-MeOPh)Ph_2NH^+, p*Ka* ~ –2.4)[23] to form the *ortho*-C-alkylated product **3aw** in 51% yield. However, we cannot exclude that the *ortho*-alkylation may also take place and that the increased stability of the carbocation intermediate may facilitate the retro-alkylation to eventually generate the more stable *para*-alkylated product. Indeed, when compound **3zbo**[6h] was subjected to the reaction conditions, we observed its conversion into *para*-product **3'zbo**, albeit in a moderate yield (57%) (Scheme 3).

Scheme 3. Possibility of a rearrangement from *ortho*- to *para*-product.



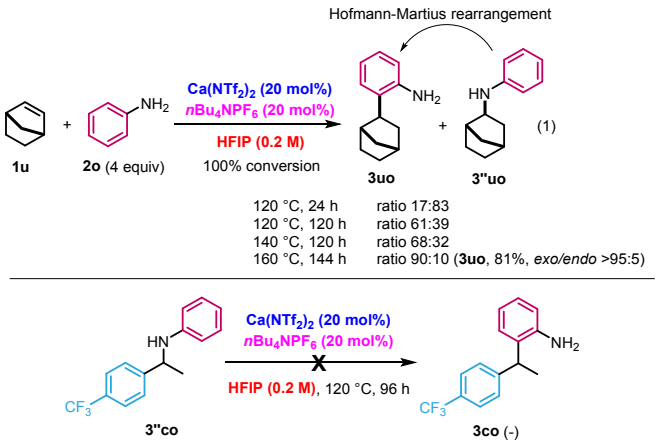
The overall excellent *ortho*-selectivities observed led us to examine in more detail the mechanism governing this transformation, notably its potentially concerted nature. As mentioned above, no isomerization product was obtained in the case of aliphatic alkenes, which seems in agreement with a plausible concerted mechanism for the formation of the targeted products. To confirm this hypothesis, we conducted the hydroarylation of allylbenzene **1p** with 1,2-dimethoxybenzene under standard conditions (Scheme 4), which delivered compound **3p** as a major product, resulting from an isomerization/hydroarylation sequence in a typical proton-catalyzed process. On the other hand, when the same reaction was conducted in the presence of **2a**, the reaction provided **3pa** as a sole product, while neither **3p** nor **3'p** was detected. Besides, when the protonation of the alkene occurred in the case of electron-rich alkenes, we noted that only the formation of the *para*-products was observed.

Scheme 4. Reactivity of aliphatic alkenes



Secondly, although the hydroaminated adduct was not detected in the previous examples, we cannot rule out the possibility that a Hofmann-Martius rearrangement,[24] which consists in the rearrangement of *N*-alkylated aniline into the *ortho*-C-alkylated aniline, occurred during the reaction. Indeed, in the case of norbornene **1u**, we could observe the formation of the hydroamination product **3'uo** along with **3uo** (Scheme 5). Upon prolonged heating at 160 °C, **3'uo** could be mostly converted into **3uq** (81%). We also prepared in parallel the secondary amine **3''co**[11a] and subjected it to the reaction conditions. After 96 h, **3''co** remained fully intact, indicating that this reaction pathway is unlikely to take place in the case of highly deactivated styrenes.

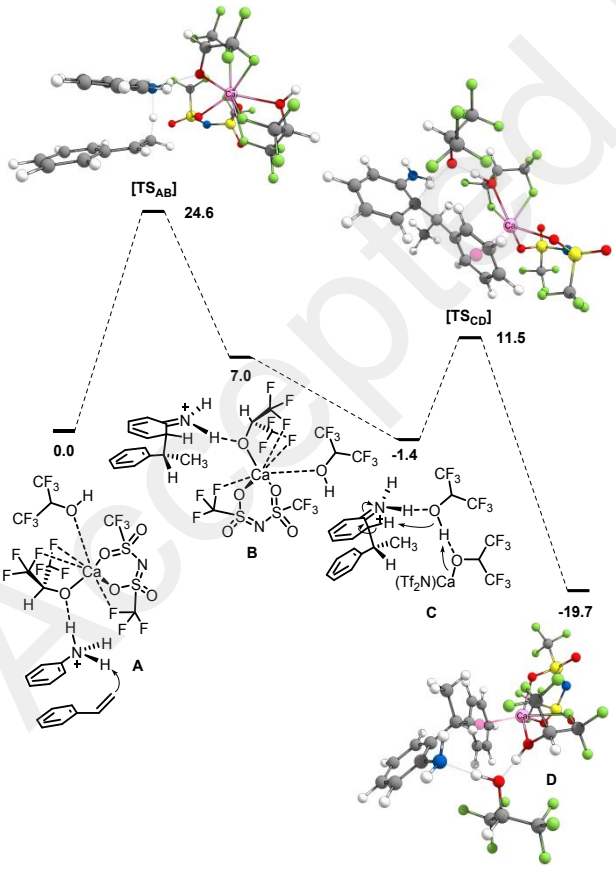
Scheme 5. Possibility of a Hofmann-Martius rearrangement.



To shed more light on the reaction mechanism, we studied the reaction of aniline with styrene by DFT computations, performed at the M06-2X/6-311+G(d,p) level of theory. The values discussed below are Gibbs free energies at 393.15 K (ΔG_{393} kcal/mol), which include a solvent correction. A detailed discussion is presented in the Supporting

Information and only the main conclusions are summarized here. As mentioned above, the $Ca(NTf_2)_2/nBu_4NPF_6$ is likely to generate $Ca(NTf_2)(PF_6)$.[19] Thus, the $Ca(NTf_2)^+$ ion has been used in the computations. In agreement with our previous computational studies on calcium-catalyzed reactions in alcoholic media, a direct activation of the substrates by $Ca(NTf_2)^+$ proved to be inefficient.[8f,14a,19c] Simple H-bonded $(HFIP)_n$ clusters (n = 1, 2, 3) also led to prohibitively high energy barriers. We then studied various combinations of $Ca(NTf_2)^+$ and HFIP molecules (up to three). The lowest energy was obtained with one $Ca(NTf_2)^+$ and two HFIPs (Scheme 6). Once HFIP is ligated to the calcium center, its acidity is strengthened, and it spontaneously protonates aniline to give adduct **A**.[25,26] N-to-C proton transfer requires 24.6 kcal/mol of free energy of activation. The resulting carbocation (not shown) collapses to the Wheland-type intermediate **B**, located at 7.0 kcal/mol. The formation of **B** can thus be considered as nearly concerted. The deprotonation could be modeled directly from **B**, but a lower energy path was obtained from the more stable isomer **C**, lying at -1.4 kcal/mol on the free energy surface. In **C**, it is HFIP that is bound to the ammonium instead of the calcium alcoholate. This new arrangement of the fragments benefits from a π-arene calcium interaction,[27] which lowers the deprotonation barrier (**[TS_{CD}]**, 11.5 kcal/mol) and provides the final π-arene calcium complex **D**, more stable than **A** by 19.5 kcal/mol.

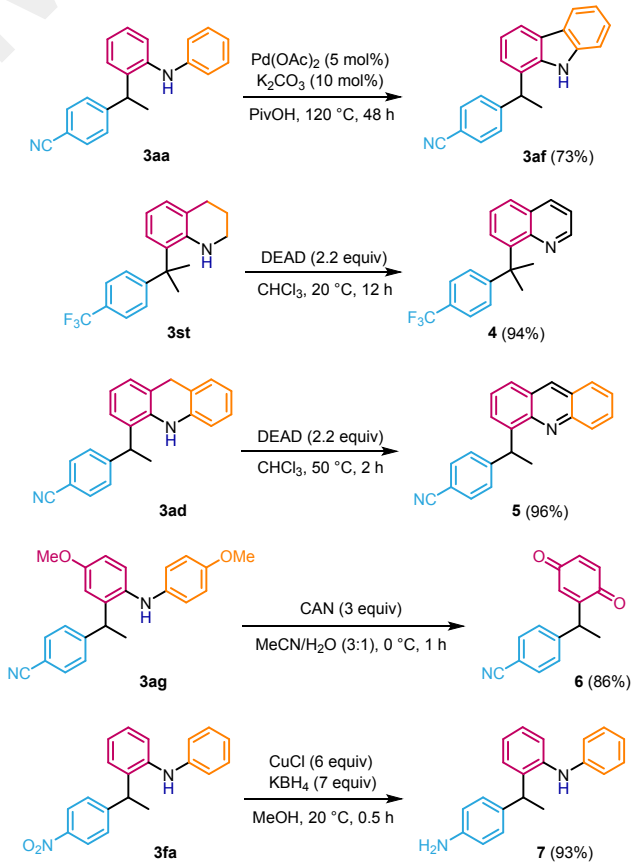
Scheme 6. Simplified free energy profile (ΔG_{393}, kcal/mol) of the $[Ca(NTf_2)(HFIP)]^+$-triggered *ortho*-*C*-alkylation of aniline with styrene.



The *N*-alkylation was also calculated, and it was found to require 1.6 kcal/mol more free energy of activation than going to the *ortho*-*C*-alkylation transition state (see the Supporting Information). We can thus conclude that the *N*-alkylation/Hofmann-Martius pathway, which could also explain the formation of the *ortho*-*C*-alkylation product, should be a minor process with aniline and styrene compared to the *ortho*-*C*-alkylation proposed in Scheme 5. It should also be noted that the *para*-alkylation transition state was found much higher in energy than **[TS_{AB}]** (39.9 kcal/mol). Thus, at least with primary anilines, and in line with the experimental results, the *para*-alkylation seems unlikely compared to the *ortho*-alkylation pathway. Overall, this set of computations shows that the $Ca(NTf_2)^+$/HFIP mixture provides an acidic medium able to protonate aniline and facilitate a proton transfer to styrene which, although not thermodynamically favored, is triggered by the virtually concomitant formation of the C-C bond and a facile deprotonation of the Wheland intermediate. This process can only take place in the *ortho* position, hence the regioselectivity observed with primary amines.

From a synthetic perspective, those compounds were engaged in several derivatizations to build useful frameworks that could be tedious to prepare otherwise (Scheme 7). Because the reaction of carbazole led to a mixture of products, we tested an approach to circumvent this issue. A simple Pd-catalyzed oxidative C–C bond formation of **3aa** gave access to carbazole **3af** in 73% yield.[28] Another envisaged application was to engineer a

Scheme 7. Derivatizations of the *ortho*-C-alkylated compounds.



dehydrogenation of tetrahydroquinoline **3su** and dihydroacridine **3ad** in the presence of diethyl azodicarboxylate (DEAD).[29] In this way, formal *ortho*-C-alkylated products of quinoline (**4**) and acridine (**5**) were delivered in 94% and 96% yields, respectively. Of note, quinoline and acridine are unreactive under our standard conditions. In the same vein, because the benzylation of quinone is challenging,[30] we used our strategy as a relay to access such type of products (**6** in 86% yield) through the oxidation of **3ag** in the presence of cerium ammonium nitrate (CAN). Moreover, the primary aniline **7** could be obtained by reduction of **3fa** in 93% yield,[31] while it could not be accessed starting from 4-aminostyrene **1zc**.

In conclusion, we have devised a general and efficient method to accomplish the selective *ortho*-C-alkylation of aniline derivatives, which is enabled by the partnership of a Lewis acid and hexafluoroisopropanol as a solvent. This transformation displays broad functional group tolerance and high selectivities, while using inexpensive feedstocks. In contrast to previous strategies, this method is not only applicable to electron-rich and moderately electron-poor styrenes, but could also be extended to highly deactivated styrenes, aliphatic alkenes and dienes. It further buttresses the utility of hexafluoroisopropanol in organic synthesis to develop hitherto unsolved transformations. Additionally, we emphasized that the nature of the aniline and the alkene had a major impact on the *ortho/para* selectivity of the reaction.

ASSOCIATED CONTENT

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

AUTHOR INFORMATION

Corresponding Authors

* dleboeuf@unistra.fr

* vincent.gandon@universite-paris-saclay.fr

Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENT

We gratefully thank the ANR (ANR-17-CE07-0003 funding for SW and ANR-16-CE07-0022 funding for GF), the CNRS, Ecole Polytechnique and Université Paris-Saclay for the support of this work. We used the OCCIGEN high performance cluster of the CINES.

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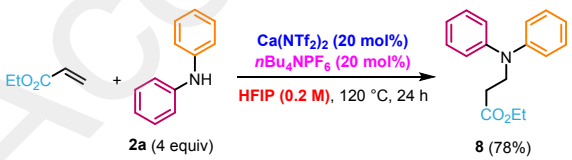

2a (4 equiv) **8** (78%)

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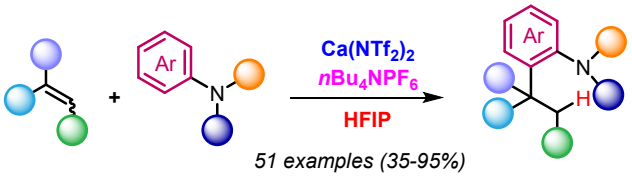
SYNOPSIS TOC



51 examples (35-95%)

- **Excellent *ortho*-C selectivity**
- **Use of previously unreactive substrates**
- **High yields and gram-scale**
- **Functional group tolerance**
- **Mechanism supported by DFT computations**