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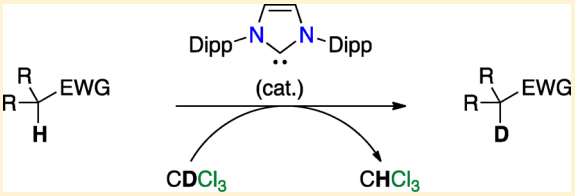
A Stable N-Heterocyclic Carbene Organocatalyst for Hydrogen/Deuterium Exchange Reactions between Pseudoacids and Deuterated Chloroform

Fabien Perez, Yajun Ren, Thomas Boddaert,† Jean Rodriguez,* and Yoann Coquerel*

Aix Marseille Université, Centrale Marseille, CNRS, iSm2 UMR 7313, 13397 Marseille, France

Supporting Information

ABSTRACT: It was observed that the stable and commercially available N-heterocyclic carbene (NHC) 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, the so-called IDipp, catalyzes hydrogen/deuterium exchange reactions between pseudoacids and chloroform-d_1, while the analogous saturated NHC 1,3-bis(2,4,6-trimethylphenyl)imidazolin-2-ylidene, the so-called SIMes, is inefficient for the same transformation. Experimental and computational DFT studies allowed these differences of reactivity to be attributed to the relative stability of the corresponding azolium−trichloromethyl anion ion pairs: in the former case, the complex evolves toward dissociation of the ions to produce an aromatic azolium cation and a basic trichloromethyl anion, while in the latter case, it evolves by ion recombination to give the product of formal carbene C−H insertion into the C−H bond of chloroform. These results provide a rationale for some early intuitions and observations of Wanzlick, Arduengo, and others on the reactivity of NHCs with chloroform as well as a simple organocatalytic method for the deuteration of pseudoacids ($pK_{a,DMSO}$ = 14−19) with chloroform-d_1.

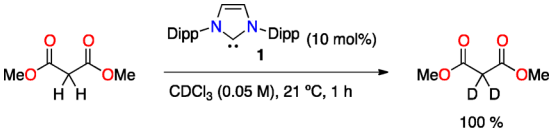


INTRODUCTION

N-heterocyclic carbenes (NHCs) have explosively moved from the status of understudied laboratory curiosities to routine molecular objects in organometallic chemistry and catalysis over the past two decades.[1−3] On the one side, NHCs are excellent σ-donating ancillary ligands in transition-metal complexes with a multitude of applications,[4−7] and on the other side, free NHCs have also found a number of applications as organocatalysts.[8,9] Organocatalysis with NHCs can involve either their ambiphilic properties to trigger catalytic "umpolung" reactivity of aldehydes and enals,[10,11] their Lewis base properties for nucleophilic activation, or also their Brønsted base properties for applications requiring a proton shuttle.[12−14] Of course, the reactivity profiles of the various classes of NHCs are very dependent on their intimate electronics and sterics.[15,16]

In the course of our studies on NHC-catalyzed (hetero-) Michael additions using NHCs as catalytic proton shuttles,[17−20] we fortuitously observed that the stable and commercially available NHC 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IDipp, **1**) efficiently catalyzes the hydrogen/deuterium exchange reaction between dimethyl malonate ($pK_{a,DMSO}$ = 15.9[21]) and deuterated chloroform (Scheme 1). This intriguing NHC-catalyzed H/D exchange reaction was further examined both experimentally and computationally, which allowed us to rationalize previous experimental observations and our own ones as well as to gain further insight into the Brønsted base properties of NHCs and their insertion reactions into the C−H bonds of pseudoacids.

Scheme 1. IDipp-Catalyzed H/D Exchange Reaction between Dimethyl Malonate and $CDCl_3$ (Dipp = 2,6-Diisopropylphenyl)



RESULTS AND DISCUSSION

The NHC-catalyzed H/D exchange reaction between pseudoacids and deuterated chloroform was examined with several prototypical pseudoacids (Table 1 and Figure 1) ranging from easily enolizable/deprotonable substrates such as 2-nitro-1-phenylethanone ($pK_{a,DMSO}$ = 7.7; entry 1) to weakly acidic compounds such as propionitrile ($pK_{a,DMSO}$ = 32.5; entry 12). The reactions were periodically monitored by ^{1}H NMR spectroscopy until no significant change was observed (equilibrium). Overall, and as shown in Figure 1, it was observed that the NHC IDipp (**1**) could efficiently catalyze the hydrogen/deuterium exchange reaction of deuterated chloroform only with moderately acidic substrates ($pK_{a,DMSO}$ = 14−19) and that the reaction was shut down with the tested substrates having $pK_{a,DMSO}$ values equal to or lower than 10 (entries 1 and 2) and higher than 29 (entries 11 and 12).

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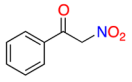
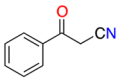
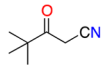
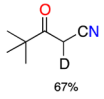
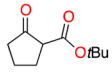
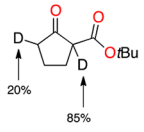
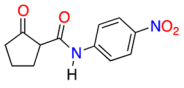
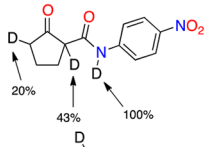
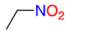
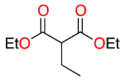
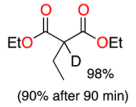
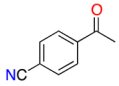
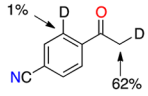
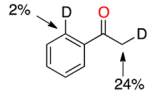
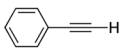
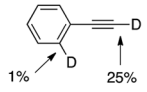
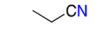
Table 1. IDipp-Catalyzed Hydrogen/Deuterium Exchange Reaction between Various Pseudoacids and Deuterated Chloroform[a]

entry	substrate	p$K_{a\mathrm{DMSO}}$	deuterium incorporation
1		7.7[b]	no deuteration
2		10.2[b]	no deuteration
3		12.0[c]	 67%
4		Cα–H: 14.0[c] Cγ–H: 25.0[c]	 20% 85%
5		Cα–H: 10.6[d] N–H: 16.0[d] Cγ–H: 24.5[c]	 20% 43% 100%
6		16.7[e]	 100%
7		19.0[c]	 98% (90% after 90 min)
8		22.0[f]	 1% 62%
9		24.7[e]	 2% 24%
10		28.8[e,g]	 1% 25%
11		29.5[h]	no deuteration
12		32.5[i]	no deuteration

[a]The reactions were performed in $CDCl_3$ (0.05 M) at 21 °C with **1** (10 mol %) for 48 h (entries 1–5, 7, and 12), 1 h (entry 6), or 43 h (entries 8–11). [b]From ref 22. [c]From ref 23. [d]From refs 24 and 25. [e]From ref 26. [f]From ref 27. [g]From ref 28. [h]From ref 29. [i]From ref 30.

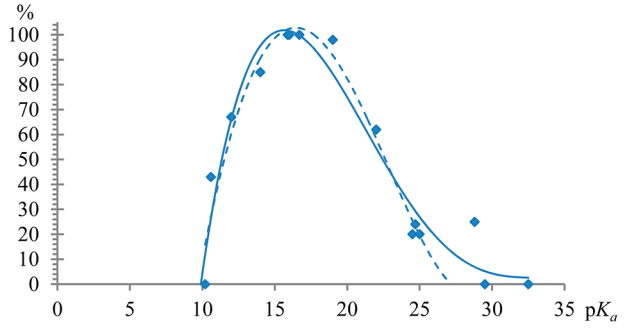


Figure 1. Trend line of H/D exchange with $CDCl_3$ using the NHC catalyst IDipp (**1**) against p$K_{a,\mathrm{DMSO}}$ values (data from Scheme 1 and Table 1). The solid line accounts for all of the experiments, and the dotted line accounts for all of the experiments except Table 1, entry 10.

The other well-known stable and commercially available NHCs SIMes (**2**) and the so-called "Ender's carbene" **3**,[31] as well as the organic Brønsted base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), were tested as catalysts for the H/D exchange reaction of chloroform-d_1 with dimethyl malonate (Figure 2).

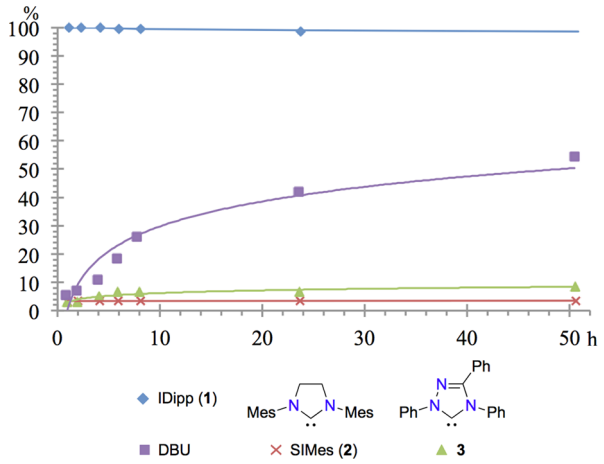
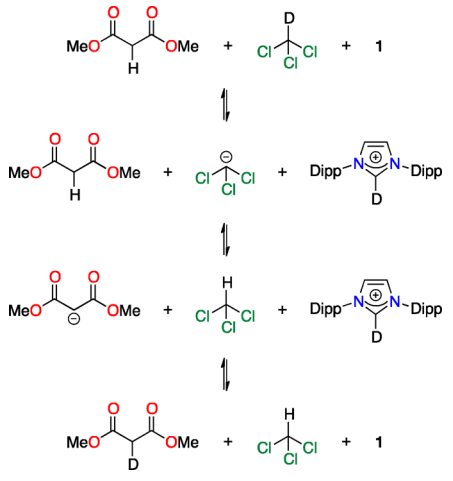


Figure 2. H/D exchange reactions with the NHC catalysts **1**–**3** and DBU using dimethyl malonate in $CDCl_3$ (0.1 M) with 2 mol % catalyst.

In sharp contrast to the reaction with IDipp (**1**), the reactions with SIMes (**2**) and NHC **3** were found to produce only very small amounts of the H/D exchange product. However, the reaction with DBU led to a significant H/D exchange (ca. 50%) after 50 h.

From this set of data and the fact that chloroform is a weak Brønsted acid (p$K_{a,\mathrm{aq}}$ = 24[32]), it was logically concluded that the above NHC-catalyzed H/D exchange reaction between chloroform-d_1 and pseudoacids with **1** proceeds by deprotonation of chloroform-d_1 with NHC **1** to form a catalytic amount of the deuterated azolium cation[33] and the basic trichloromethyl anion (Scheme 2). The latter would deprotonate the pseudoacid substrate to form chloroform, and a deuterium atom would be transferred from the deuterated azolium cation to the pseudoacid anion. Overall, NHC **1** (p$K_{a,\mathrm{aq}}$ of the corresponding azolium cation = 21.1[34]) would operate as a

Scheme 2. Postulated Mechanism of the NHC-Catalyzed H/D Exchange Reaction



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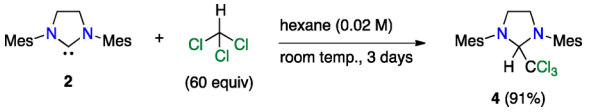
catalytic deuterium atom shuttle in this reaction, and the same should hold true for the H/D exchange reaction catalyzed by DBU (Figure 2). If this is indeed the case, one should question why the moderately less basic NHC **3** ($pK_{a,aq}$ of the corresponding azolium cation = 16.8[35]) and, more strikingly, the slightly more basic NHC **2** ($pK_{a,aq}$ of the corresponding azolium cation = 21.3[34]) are not efficient catalytic deuterium atom shuttles in this reaction. While the lower Brønsted basicity of NHC **3** compared with IDipp (**1**) could very significantly slow the deprotonation of chloroform-d_1 and thus the overall H/D exchange process, the reaction with SIMes (**2**) should be at least operative if not accelerated compared with the reaction with IDipp (**1**) unless another competitive reaction occurs in the case of SIMes (**2**). This is obviously the case.

In 1999, Arduengo and co-workers reported the insertion reaction of the NHC SIMes (**2**) into the C−H bond of chloroform to afford the insertion product **4** in good yield after 3 days in hexane (Scheme 3).[36] As to the mechanism of this

Scheme 3. C−H Insertion Reaction of SIMes (2) with Chloroform (from ref 36)



reaction, the authors noted that it is consistent with a stepwise pathway initiated by the deprotonation of chloroform with **2**; however, evidence for the formation of the free CCl_3^- anion that would be formed by a fully stepwise process was not observed, and it was concluded that "there may be some degree of concertedness to these insertions". In the case of the NHC-catalyzed H/D exchange reaction between chloroform-d_1 and pseudoacids with catalyst **2**, the quantitative and irreversible formation of **4**-d_1 would explain why the catalytic activity of **2** is rapidly shut down after the beginning of the reaction. But it should nevertheless be noted that in our case a fraction of the dimethyl malonate substrate was actually rapidly deuterated (ca. 3% after 1 h; see Figure 2), pointing out the possible generation of the free CCl_3^- anion in the early stages of the reaction (before equilibrium is reached). Beside this, in their pioneering work directed at the isolation of stable carbenes, Wanzlick and co-workers used the reverse reaction, namely, the 1,1-elimination of chloroform from 1,3-diphenyl-2-(trichloromethyl)imidazolidine, which resulted in the production of the corresponding carbene dimer, probably via the transitory NHC analogue of **2**, 1,3-diphenylimidazolin-2-ylidene.[37−39] Also, more recently, Waymouth, Hedrick, and co-workers used the 1,1-elimination of chloroform from **4** to produce the NHC **2** in solution.[40] They also questioned the mechanism of the reaction and noted that it "is consistent with a concerted elimination of $HCCl_3$ ... rather than a stepwise ionic mechanism".

Intrigued by these apparently contradictory results, we embarked on a theoretical computational study with the intention to rationalize the sharp difference in reactivity between the two structurally very similar NHCs IDipp (**1**) and SIMes (**2**) in the H/D exchange reaction and possibly to elucidate the actual mechanism of the C−H insertion reaction of SIMes (**2**) with chloroform. The reactions of the NHCs **1** and **2** with chloroform were investigated using DFT with the B3LYP functional and the extended 6-311++G** basis set to account for polarization and diffusion on all atoms, along with the IEFPCM solvation model for chloroform. It was found that the reaction of **2** with chloroform produces the C−H insertion product **4** by a *formally* stepwise mechanism (Figure 3), and we

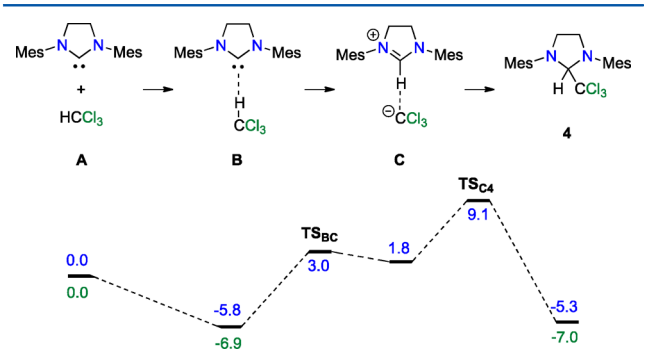


Figure 3. Detailed mechanism and energy profile of the reaction of SIMes (**2**) with chloroform in chloroform (blue) and energies of the stationary points **A**, **B**, and **4** in *n*-hexane (green). The energy profile was obtained by DFT calculations at the B3LYP/6-311++G** level of theory (free energies at 25 °C including ZPE corrections in kcal/mol with the IEFPCM solvation model); see the Supporting Information for details.

were not able to identify a transition state that could account for a truly concerted pathway. The system **2** + $CHCl_3$ without interaction (**A**) spontaneously evolves to the stabilized Brønsted pair **B** (−5.8 kcal/mol). Then the proton exchange step producing the zwitterionic Brønsted pair **C** can occur via TS_{BC} with a relatively low energy barrier (+3.0 kcal/mol from **A**). From **C**, the C−H insertion product **4** is then formed with a reasonable energy barrier (+9.1 kcal/mol from **A**) and a stabilization of the system of −5.3 kcal/mol relative to **A** (−7.1 kcal/mol relative to **C**). These calculations indicate that the Brønsted pair **B** and the C−H insertion product **4** are roughly isoenergetic and are most probably in equilibrium at room temperature with a small preference for **B**. However, under the reaction conditions using chloroform as both the substrate and the solvent, this equilibrium is virtually entirely shifted to the C−H insertion product **4**, thus fully justifying the rapid loss of activity of NHC **2** in the studied H/D exchange reaction. The isolation of **4** from **2** + $CHCl_3$ as depicted in Scheme 3 questioned the validity of our computational data, indicating that **B** is slightly more stable than **4** in chloroform. In order to address this specific point, the geometries and energies of both **B** and **4** were recalculated modeling *n*-hexane as the solvent, and **4** was found to be slightly more stable than **B** (energy values in green in Figure 3), which nicely fits with the experimental results reported by Arduengo and co-workers (where both a long reaction time and a large excess of $CHCl_3$ were required). Overall, the present computational study sheds some light on the actual mechanism of the reaction **2** + $CHCl_3$ → **4** (and the reverse reaction). Our conclusion on this matter is that the mechanism of this reaction is best regarded as a *formally* stepwise mechanism with indeed "some degree of concertedness", as proposed early-on by Arduengo and co-workers, due to the existence of the weakly stabilized, fleeting zwitterionic intermediate **C**.

A similar series of calculations was performed for the reaction of the NHC IDipp (**1**) with chloroform (Figure 4). The energy profiles of the proton exchange reactions of the NHCs **1** and **2** with chloroform reflect their very similar Brønsted basicities (compare **A** → **B** → **C** with **D** → **E** → **F**) and also the slightly

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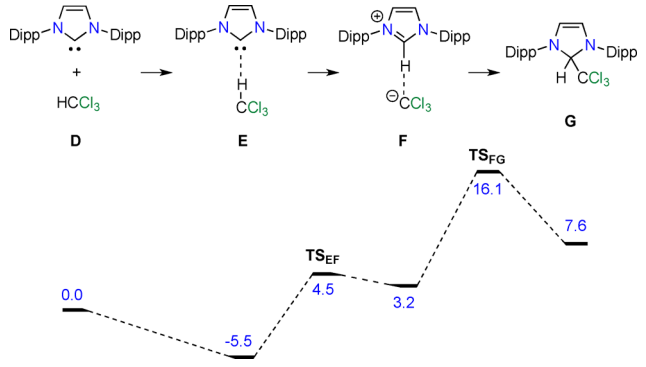
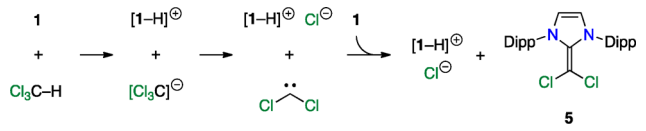


Figure 4. Detailed mechanism and energy profile of the reaction of IDipp (**1**) with chloroform in chloroform. The energy profile was obtained by DFT calculations at the B3LYP/6-311++G** level of theory (free energies at 25 °C including ZPE corrections in kcal/mol with the IEFPCM solvation model); see the Supporting Information for details.

more basic character of **2** compared with **1** (ΔE_{BC} = 7.6 kcal/mol vs ΔE_{EF} = 8.7 kcal/mol). With IDipp (**1**), the possible C−H insertion product **G** was found to be significantly less stable than the two Brønsted pairs **E** and **F**, which corresponds to a negligible amount of **G** at equilibrium. Moreover, the conversion of **F** into **G** requires a relatively high activation energy (+16.1 kcal/mol from **D**), and if it occurs, the formation of **G** should be slow and quickly reversible. The unfavored formation of the C−H insertion product **G** reflects, at least in part, the aromaticity of the azolium cation in **F**. Thus, in the presence of a large excess of chloroform, the system **1** + $CHCl_3$ (**D**) should exist predominantly as intermediate **F** at equilibrium, liberating some amount of free CCl_3^- anion. The α-elimination of a chlorine atom from the free CCl_3^- anion is known to produce the electrophilic dichlorocarbene. Thus, in the absence of any other proton source, solutions of IDipp (**1**) in $CHCl_3$ should produce some amount of dichlorocarbene, which would rapidly react with additional **1** to form the heterodimeric product **5** (Scheme 4).[41] In practice, a signal

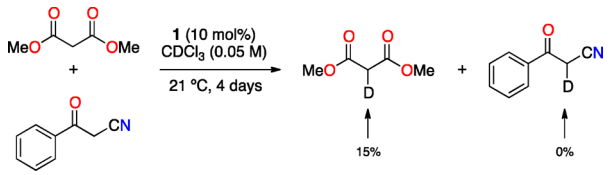
Scheme 4. Formation of the Heterodimeric Compound 5



attributed to the product **5** and its isotopes was detected by mass spectrometry analysis of a chloroform solution of IDipp (**1**) that was allowed to stand at room temperature, probing the formation of the free CCl_3^- anion (see the Experimental Section). Similarly, diluted solutions of IDipp (**1**) in chloroform-d_1 at equilibrium should produce largely the corresponding deuterated azolium cation[33] $[\mathbf{1}–D]^+$ and the free CCl_3^- anion, both of which are responsible for the observed H/D exchange reaction.[42] Accordingly, the ^{13}C NMR analysis of a solution of **1** in chloroform-d_1 showed no detectable amount of **1** (or **1**-d_2[42]) after a few hours.[43]

As shown in Table 1 and Figure 1, the H/D exchange reaction between chloroform and pseudoacids catalyzed by IDipp (**1**) is efficient only with substrates having $pK_{a,DMSO}$ values in the 14−19 range. With poorly acidic substrates (e.g., entries 11 and 12 in Table 1), the trichloromethyl anion catalytically generated by the deuterium atom exchange reaction between **1** and chloroform-d_1 is not basic enough to deprotonate the substrate and continue the H/D exchange reaction at a significant rate. Similarly, the poor to nonexistent catalytic activity of IDipp (**1**) with more acidic substrates (e.g., entries 1 and 2) is attributed to the largely favored protonation of the NHC catalyst **1** by the acidic substrate at equilibrium. Indeed, under the conditions of our study, the almost quantitative (ca. 96−99%) formation of the azolium cation $[\mathbf{1}–H]^+$ could be detected by ^1H NMR spectroscopy in the case of entries 1 and 2 (at 10.22 and 9.89 ppm, respectively, for the H atom at C2), indicating that protonation by the substrate occurred faster than the H/D exchange reaction with chloroform-d_1. Taking advantage of the pK_a-dependent efficiency of the NHC-catalyzed H/D exchange reaction with IDipp (**1**) and chloroform-d_1, we questioned whether the selective deuteration of dimethyl malonate could be possible in the presence of a more acidic substrate. A somewhat selective deuteration was indeed observed for the N−H proton in the secondary β-keto amide substrate of entry 5 in Table 1. In the presence of a catalytic amount of IDipp (**1**), a 1:1 solution of dimethyl malonate and 3-oxo-3-phenylpropanenitrile in chloroform-d_1 did show the selective deuteration of dimethyl malonate, but at a very low rate (Scheme 5). Actually, 94%

Scheme 5. Selective Deuteration of Pseudoacids



of the introduced amount of NHC catalyst **1** was found by ^1H NMR analysis to exist in its $[\mathbf{1}–H]^+$ azolium form, accounting for the observed very low rate. Overall, despite the fact that the range of substrates is somewhat limited, the organocatalytic H/D exchange method discussed herein has some practical value, especially considering that $CDCl_3$ is a cheap and widely available deuterium atom source. An obvious practical bottom line to this study is that chloroform-d_1 should, of course, be avoided as a solvent for NMR experiments involving free NHCs.

CONCLUSION

In summary, efficient NHC-catalyzed H/D exchange reactions between pseudoacids having $pK_{a,DMSO}$ values of 14−19 and chloroform-d_1 were observed when the stable NHC 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene (IDipp, **1**) was used as a catalyst, thereby providing an original organocatalytic method for the deuteration of pseudoacids. The excellent organocatalytic activity of **1** was attributed to its ideally suited deuterium-shuttling properties for the studied system, involving a stable azolium−trichloromethyl anion Brønsted pair. The structurally similar NHC 1,3-bis(2,4,6-trimethylphenyl)-imidazolin-2-ylidene (SIMes, **2**), despite exhibiting almost identical Brønsted basicity as **1**, is an incompetent catalyst for the same transformation. A theoretical study indicated that the reaction of NHC **2** with chloroform actually produces a fleeting azolinium−trichloromethyl anion Brønsted pair that rapidly rearranges into the product of insertion of the NHC into the C−H bond of chloroform, shutting down the deuterium-shuttling activity of **2**. These results provide a rationale for

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some early intuitions and observations of Wanzlick, Arduengo, and others on the reactivity of NHCs with chloroform.

EXPERIMENTAL SECTION

General Methods. Reagents and catalysts were weighed in air at room temperature, and all of the reactions were conducted under an argon atmosphere in sealed reaction vessels. $CHCl_3$ and $CDCl_3$ used in this study were stored over a bed of 4 Å molecular sieves and solid K_2CO_3. Unless stated otherwise, all of the chemicals were obtained from commercial sources and used as received. The substrates in entries 4 and 5 in Table 1 were prepared by described methods.[44] ^1H NMR spectra were recorded in $CDCl_3$ at 294 K at 300 or 400 MHz using the residual nondeuterated solvent as an internal standard (δ = 7.26 ppm). $^{13}C\{^1H\}$ NMR spectra were recorded in $CDCl_3$ at 294 K at 75 or 100 MHz using the deuterated solvent as an internal standard (δ = 77.16 ppm).

Data in Scheme 1, Table 1, and Figure 1. To a solution of the pseudoacid substrate (0.10 mmol) in $CDCl_3$ (2.0 mL) was added IDipp (**1**) (4 mg, 0.01 mmol). The resulting solution was stirred at 21 °C and periodically monitored by ^1H NMR spectroscopy (single-scan experiments) until no significant change was observed. The percentage of deuterium incorporation was determined by measuring the decrease in the integration of the signal corresponding to the enolizable/deprotonable position compared with an internal standard present on the substrate (a nonexchangeable position).

Data in Figure 2. To a solution of dimethyl malonate (57 μL, 0.50 mmol) in $CDCl_3$ (5.0 mL) was added the NHC catalyst **1**−**3** or DBU (0.01 mmol). The resulting solution was stirred at 21 °C and periodically monitored by ^1H NMR spectroscopy over 50 h. The percentage of deuterium incorporation was determined by measuring the decrease in the integration of the signal corresponding to the enolizable position (δ = 3.39 ppm) compared with an internal standard present on the substrate (the methyl groups).

Data in Scheme 4. A 0.01 M solution of IDipp (**1**) in $CHCl_3$ was allowed to stand overnight at 21 °C. The analysis of this solution (highly diluted in MeOH) by mass spectrometry (ESI+) expectedly showed a very largely major ion at m/z 389.3 corresponding to the azolium cation $[\mathbf{1}-H]^+$ but also ions at m/z 471.2 (100%), 472.2, 473.2, 474.2, 475.2, and 476.2, an isotopic pattern corresponding to the isotopic distribution of the cation $[\mathbf{5}-H]^+$ of formula $C_{28}H_{37}Cl_2N_2^+$ (see the Supporting Information).

Data in Scheme 5. To a 1:1 solution of dimethyl malonate (11 μL, 0.10 mmol) and 3-oxo-3-phenylpropanenitrile (15 mg, 0.10 mmol) in $CDCl_3$ (2 mL) was added IDipp (**1**) (4 mg, 0.01 mmol), and the resulting solution was stirred at 21 °C for 4 days. ^1H NMR analysis of the reaction mixture revealed 15% deuterium incorporation at the methylene position of dimethyl malonate and no deuterium incorporation in 3-oxo-3-phenylpropanenitrile.

ASSOCIATED CONTENT

Supporting Information

Geometries of all stationary points of the theoretical computational study, selected computed structural parameters, details of the H/D exchange reaction at the 4 and 5 positions in **1**, and a copy of the mass spectrum of **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Authors

*E-mail: jean.rodriguez@univ-amu.fr.

*E-mail: yoann.coquerel@univ-amu.fr.

Present Address

[†]T.B.: CP3A Organic Chemistry Group, ICMMO (UMR CNRS 8182), Université Paris Sud, 15 rue Georges Clémenceau, 91405 Orsay Cedex, France.

Notes

The authors declare no competing financial interest.

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