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COMMUNICATION

The Rabe amination after a century: direct addition of *N*-heterocycles to carbonyl compounds†‡

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A catalytic version of the Rabe electrophilic amination is presented. This kind of reaction was originally employed in 1918 in a key step for the conversion of quinotoxine to quinine. Ketones and α-substituted aldehydes give the corresponding α-aminated carbonyl compounds in moderate yield. α,α-Unsubstituted aldehydes give rise to amino ketones *via* a novel rearrangement.

During the past ten years, the electrophilic amination reaction of carbonyl compounds[1] witnessed enormous advancement. In particular, one of the most widely exploited strategies has been the introduction of a nitrogen moiety *via* the addition of carbonyl compounds to diazodicarboxylates (carbamate-protected diimides), thanks to the pivotal contributions of Evans, List and Jørgensen and co-workers.[2]

The adducts obtained can be converted to biologically and pharmaceutically relevant molecules, such as α-amino acids and β-amino alcohols, and have also been employed in the industrial scale preparation of some pharmaceutically relevant molecules.[3] Whilst these reactions present generally good yields and, in a number of cases, exceptional enantioselectivity, they are not as effective in terms of atom economy. The cleavage of the N–N bond and the carbamate moiety deprotection is not always straightforward.[2b–c]

Amino acids and amino alcohols presenting an *N*-heterocycle moiety are important molecules employed as constrained peptidomimetics and analogues of epinephrine-type drugs.[4]

An attractive complementary strategy to prepare these classes of compounds could be the direct introduction of a heterocyclic moiety in the α-position of carbonyl compounds, *via* the reactive electrophiles *N*-halo amines. These reactive species have sporadically been employed in organic synthesis. Their usage can be traced back to the beginning of the twentieth century in the papers of Rabe.[5] In particular, *N*-bromoquinotoxine was one of the crucial intermediates in Rabe's conversion of quinotoxine to quinine in 1918.[6] This transformation was later exploited by Woodward to claim the first formal synthesis of this natural substance,[7] which has generated significant debate during the recent years. The electrophilic amination step of the Rabe synthesis raised concern among scientists not fully convinced that the authors actually prepared quinine in 1932.[8] In 2001, Stork reported the first "non-formal" synthesis of quinine,[9] casting the doubt that this could indeed be its first total synthesis at all, since not enough experimental detail was provided in the Woodward synthesis. One of his main concerns was the transformation of quinotoxine into quinine.[10] In 2007, Smith and Williams repeated and verified the Rabe synthesis, employing the original conditions of that time, to specifically address this issue.[11] Regardless of the final outcome of this fascinating scientific debate, the amination reaction of carbonyl compounds is an intriguing transformation, which could surely be revisited in modern (asymmetric) synthesis.[12]

We decided to investigate the addition of simply carbonyl compounds to *N*-heterocycles as electrophiles more in detail, since it could also be an effective strategy to access valuable products. We were also interested to test if the "modern" organocatalytic activation mode of carbonyl compounds *via* enamine[13] would allow us to obtain the desired products under transition metal-free and mild conditions and, possibly, in an asymmetric way.

Initially, we tested the addition of acetone **1a** to the cyclic six-membered chlorinated heterocycle **2a**, prepared *via* the addition of NCS to piperidine.[14–15] Interestingly, with the combination of a catalytic amount of L-proline **I** and excess of triethylamine, the reaction proceeded smoothly at rt, giving the desired product **3a** in 63% yield after 24 h (Table 1, entry 1).

The enhanced reactivity of proline-derived enamines in the presence of bases has been documented by us[16a–b] and other authors.[16c–e] Encouraged by this result, we decided to extend the scope of the reaction to other substrates. We selected three classes of ketones: linear ketones **1b–d**, hindered ketones **1e–f** and cyclic ketones **1g–i**. The reaction proceeded in moderate yield (45–58%) with ketones **1b–d** (Table 1, entries 2–4). It should be noticed that the *N*-chloro amines **2a–b** employed as reactants as well as compounds **3** are thermally unstable. Therefore, this can affect the yield of these transformations. The

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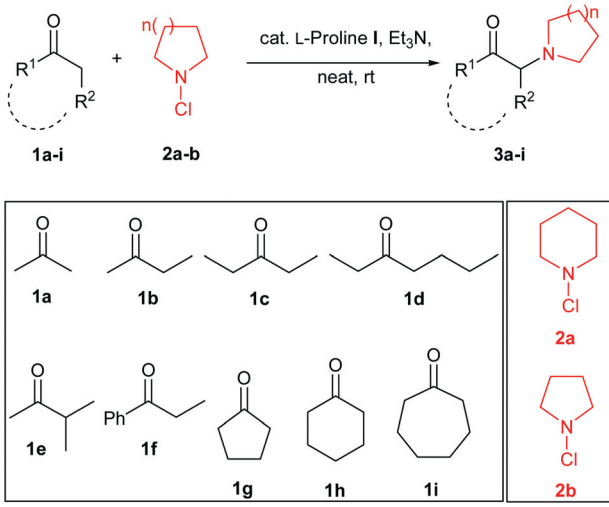
‡ Electronic supplementary information (ESI) available: Experimental procedures and compounds characterization. See DOI: 10.1039/c2ob25595b

Table 1 Organocatalyzed addition of ketones **1a–i** to *N*-chloro heterocycles **2a–b**



Entry[a]	Ketone **1**	Chloro amine (*n*), **2**	Amino ketone R^1, R^2, **3**	Yield[b] (%)
1	**1a**	(2), **2a**	Me, H, **3a**	63
2	**1b**	(1), **2b**	Me, Me, **3b** Et, H, **3b′** **3b**/**3b′** = 1.4 : 1[c]	58
3	**1c**	(1), **2b**	Et, Me, **3c**	35
4	**1d**	(1), **2b**	Me, *n*-Pr, **3d** *n*-Bu, H, **3d′** **3d**/**3d′** = 1 : 1	45
5	**1e**	(1), **2b**	i-Pr, H, **3e**	25
6	**1f**	(1), **2b**	Ph, Me, **3f**	22
7	**1g**	(2), **2a**	$-(CH_2)_3-$, **3g**	38
8	**1h**	(1), **2b**	$-(CH_2)_4-$, **3h**	36
9	**1i**	(1), **2b**	$-(CH_2)_5-$, **3i**	25

[a] Reactions are run employing 200 mg of *N*-heterocyclic amines **2a–b**, 1 mL of ketones **1a–i**, 0.3 equiv. of L-proline **I** and 2 equiv. of Et_3N; reaction times: from 1 to 26 d (see ESI‡ for details). [b] Isolated yield of **3a–i** determined after purification *via* FC. [c] Determined by ^{1}H-NMR.

reported values of reaction times represent for each compound a compromise between conversion and yield. The transformations were left at rt for prolonged reaction times and the temperature has not been raised due to safety concerns.[15] Less satisfactory results were obtained with bulky ketones **1e** and **1f** (25% and 22% respectively, entries 5–6). In these examples, the lower yield is also due to the difficulty of forming the enamine intermediate on such hindered ketones. Finally, we tested cyclic ketones **1g–i** and we were also able to isolate the desired adducts (entries 7–9). In general, most of the examples (entries 6,8,9) were conducted with *N*-chloro pyrrolidine **2b** since it is much more reactive with respect to *N*-chloro piperidine **2a**.

Aldehyde substrates **4a–d** presented a different reactivity. α,α-Disubstituted aldehydes such as hydratropaldehyde **4a** afforded the desired adducts **5a–b** bearing a quaternary stereocenter in moderate to good yield (43–87%) together with the corresponding α-chlorinated products **6a–b** (Table 2, entries 1–2). In this case, the *N*-chloro amines **2a–b** act also as a source of electrophilic chlorine.[17] Isobutyl aldehyde **4b** afforded exclusively the α-aminated compound **5c** with no trace of the α-chlorinated adduct **6c** (entry 3).[18–19]

Aldehydes **4c–d**, presenting a "free" CH_2 moiety in the α-position, showed a different reactivity, giving rise to ketones **3e**, **3j–k** *via* a novel rearrangement (entries 4–6).

We rationalize the formation of ketones **3e**, **3j–k** *via* an intramolecular epoxide **9** formation (*via* adduct **8**) and subsequent 1,2 hydride migration (Scheme 1). The instability of enamine-derived epoxides has been documented.[20]

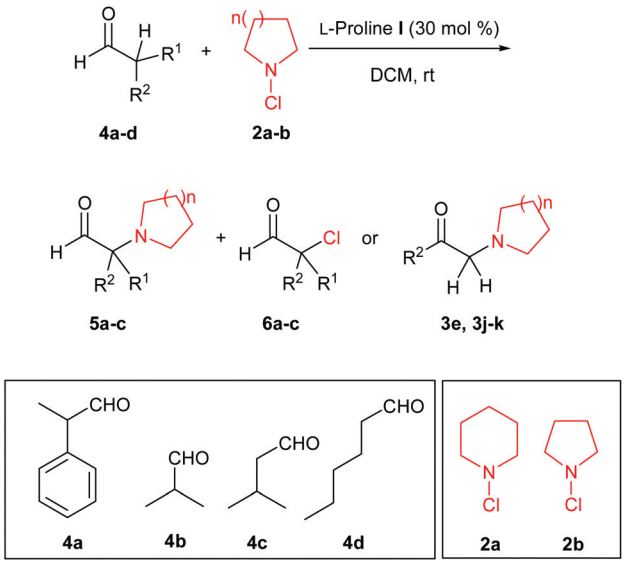
Clearly, developing an asymmetric catalytic version of the Rabe amination would be a challenging but important target. Any attempt to obtain a measurable enantiomeric excess we performed on cyclohexanone **1h** was met with failure. A possible explanation can be the configurational instability of tertiary stereocenters in the α-position with respect to amines and ketones, as reported by Valentin *et al.*[21]

The only substrate that could give products in an enantiomerically enriched form is the α-substituted aldehyde **4a** (Scheme 2).

Despite a vast screening of conditions and catalysts (see ESI‡), we could not achieve any measurable enantioselectivity, except in the case when we conducted the reaction in presence of 4 Å molecular sieves. A similar effect has also been reported by Jacobsen and Yoon[22] and it could be the subject of further studies in our laboratory.

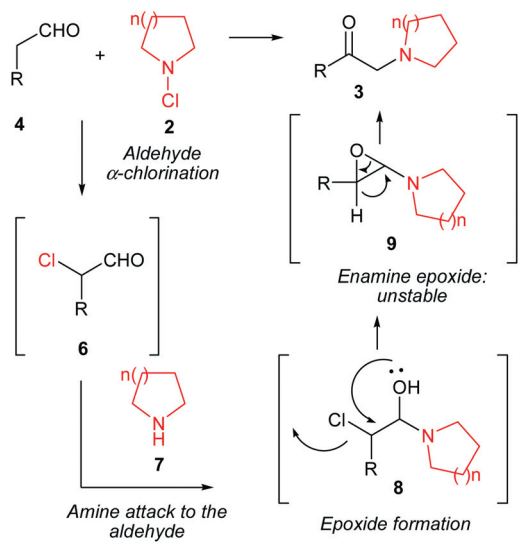
In conclusion, the rediscovery of the Rabe reaction allowed us to report our preliminary results on the direct functionalization of ketones and aldehydes with *N*-chloro amines in mild conditions. In particular, for aldehydes bearing a CH_2 moiety in the α-position, we observed a new rearrangement leading to α-amino ketones. Minimal but measurable enantioselectivity is observed with aldehydes bearing a quaternary stereocenter. Surely, with more extensive screening conditions, the reaction yield could be improved and the reaction time shortened. However, safety

Table 2 Organocatalyzed addition of aldehydes **4a–d** to *N*-chloro heterocycles **2a–b**

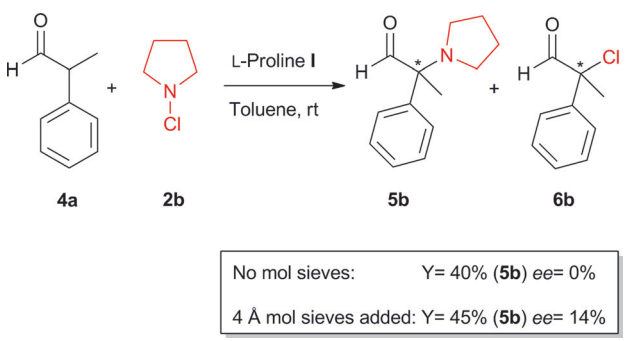


Entry[a]	Aldehyde **4**	Chloro amine (*n*), **2**	Product R^1, R^2, **5**, **6** or **3**	Yield **5**[b] (%)	Yield **6**[b] (%)	Yield **3**[b] (%)
1	**4a**	2, **2a**	Me, Ph, **5a–6a**	43	25	—
2	**4a**	1, **2b**	Me, Ph, **5b–6b**	87	10	—
3	**4b**	2, **2a**	Me, Me, **5c**	25	<5	—
4	**4c**	1, **2a**	H, i-Pr, **3j**	—	—	46
5	**4c**	1, **2b**	H, i-Pr, **3e**	—	—	17
6	**4d**	2, **2a**	H, *n*-Bu, **3k**	—	—	38

[a] Reactions are run employing 50 mg of aldehydes **4a–d**, 1.5 equiv. of *N*-heterocyclic amines **2a–b**, 0.30 equiv. of L-Pro **I** and 1.5 mL of DCM as the solvent; reaction times: 16–240 h (see ESI‡ for details). [b] Isolated yield of **5a–c**, **6a–c**, and **3e**, **3j–k** determined after purification *via* FC.



Scheme 1 Proposed mechanism for the addition of *N*-chloro amines to α,α-unsubstituted aldehydes and their rearrangement to α-amino ketones.



Scheme 2 Enantioselective addition of hydratropaldehyde **4a** to *N*-chloro pyrrolidine.

concerns prevented us from further investigations. We believe that the proof-of-concept contained in this work could be beneficial to the scientific community and in particular to those operating with unstable chloro amines. Hopefully, these preliminary results can also be exploited to develop a more efficient amination reaction with maximum atom economy.

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