Convenient, scalable and flexible method for the preparation of imidazolium salts with previously inaccessible substitution patterns†

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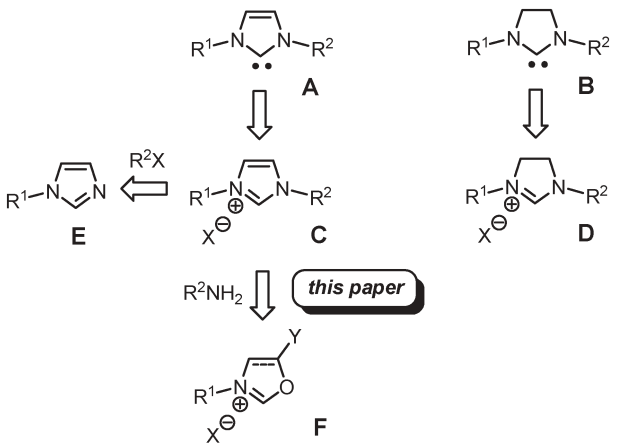
A high yielding and modular approach to *N*,*N*′-disubstituted imidazolium salts is described, providing access to substitution patterns that are beyond the reach of established methodology.

Over the course of the last decade, *N*-heterocyclic carbenes (NHC's) have gained a prominent role in catalysis due to the favorable properties that they impart as ancillary ligands on many transition metal templates,[1] and because of their ability to act as powerful organocatalysts in their own right.[2] Most studies focused on *N*,*N*′-disubstituted imidazol-2-ylidenes **A** and their 'saturated' analogues **B**, which are usually prepared by deprotonation of the corresponding imidazolium or imidazolinium salts **C** and **D**, respectively (Scheme 1).

Although the tremendous success of these 2-electron donor ligands has led to a huge number of structural variants, it is surprising to find that several obvious and seemingly trivial substitution patterns are as yet unknown. Most strikingly, unsymmetrical imidazolium salts bearing two different aryl groups on their N-atoms have not been described. Even the number of unsymmetrical imidazolium salts with one *N*-aryl- and one *N*-alkyl-group is still fairly small and essentially restricted to those having *primary* *N*-alkyl substituents.[3,4] These limitations stem from the commonly practised synthesis routes, which rely on *N*-substitutions of appropriate imidazole precursors **E**. Such



Scheme 1 Formation of NHC's by deprotonation of (dihydro)imidazolium salts and retrosynthetic analysis for the latter.

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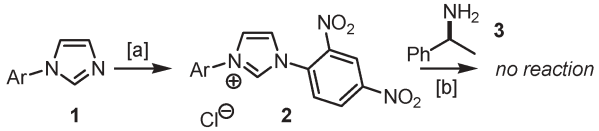
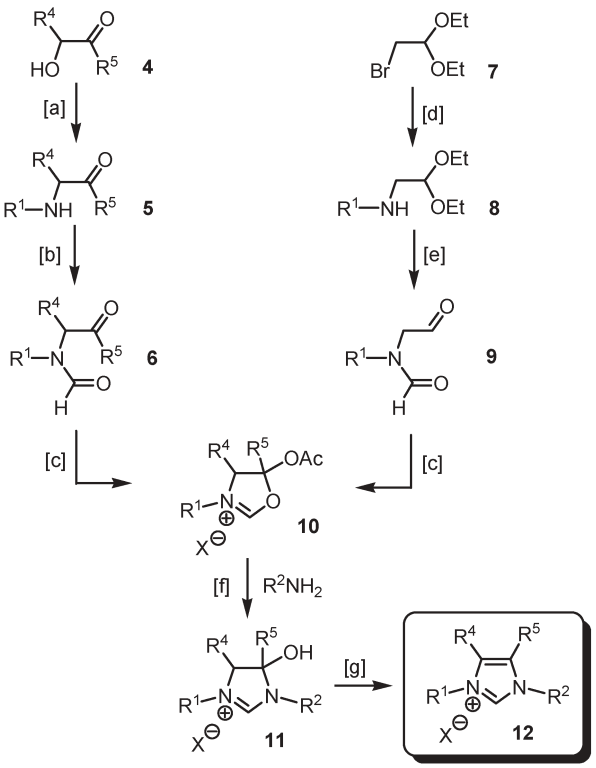
† Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data of all new compounds; crystal data for the structures shown in Fig. 1–3. See DOI: 10.1039/b604236h

transformations work well with reactive halides R^2X but are difficult or even impossible with aryl halides,[5] *tert*-alkyl halides, and even many *sec*-alkyl halides, in particular if they are chiral and non-racemic. To aid further (organometallic) catalyst design,[6] a more general method for the preparation of unsymmetrical *N*,*N*′-disubstituted imidazolium salts is therefore highly desirable. As part of our ongoing studies on the synthesis, structure and use of metal–NHC complexes,[7–10] we developed such a method that opens access to a wide variety of substitution patterns that are beyond reach otherwise. In addition to being highly modular, this novel protocol is practical, scalable, and high yielding, allowing for a convenient molecular editing of every substituent on the imidazolium backbone and even of the escorting counterion.

As outlined in Scheme 1, this novel route to unsymmetrical *N*,*N*′-disubstituted imidazolium salts is based on a heterocycle-interconversion strategy. In a first attempt, a variant of the Zincke reaction was considered,[11] but the envisaged replacement of the dinitrophenyl moiety of imidazolium salt **2** even with the fairly nucleophilic phenethylamine **3** did not proceed (Scheme 2). Encouraged by previous examples of the formation of *N*-aryl-triazolium salts from 1,3,4-oxadiazolium precursors, though mostly low yielding under the conditions reported in the literature,[12] we envisaged the use of oxazolinium salts **F** as more reactive substrates for the same purpose. Such compounds turned out to be easily accessible by a short sequence of readily scalable operations (Scheme 3): first, the acid catalyzed reaction of a (commercially available) α-hydroxyketone of type **4** with the amine R^1–NH_2 of choice under azeotropic removal of water afforded the α-aminoketones **5** which were *N*-formylated prior to treatment with acetic anhydride in the presence of a strong mineral acid such as aqueous HBF_4 or $HClO_4$. Surprisingly, the ensuing cyclization stopped at the intermediate acetal stage **10** and did not lead to the expected aromatization with formation of an oxazolium salt.[13] Compounds **10** could be conveniently precipitated with Et_2O and processed without further purification. The constitution of these synthetic intermediates was evident from their NMR data and was unambiguously confirmed by the crystal structure analysis of one representative case (Fig. 1).‡ Access to the 4,5-unsubstituted series was equally facile, involving *N*-alkylation of R^1–NH_2 with



Scheme 2 *Reagents and conditions*: [a] 1-chloro-2,4-dinitrobenzene, toluene, 50 °C; [b] phenethylamine **3**, toluene, reflux.



Scheme 3 *Reagents and conditions*: [a] R^1NH_2, HCl cat., toluene, Dean–Stark; [b] MeC(O)OC(O)H; [c] Ac_2O, HX (1.15 eq.); [d] R^1NH_2, *n*BuLi, then bromide **7**; [e] (i) HCOOH, Ac_2O, THF, 0 °C; (ii) HCOOH; [f] R^2NH_2, toluene; [g] Ac_2O, HX cat., *or*: HX (1 eq.), *cf.* Table 1.

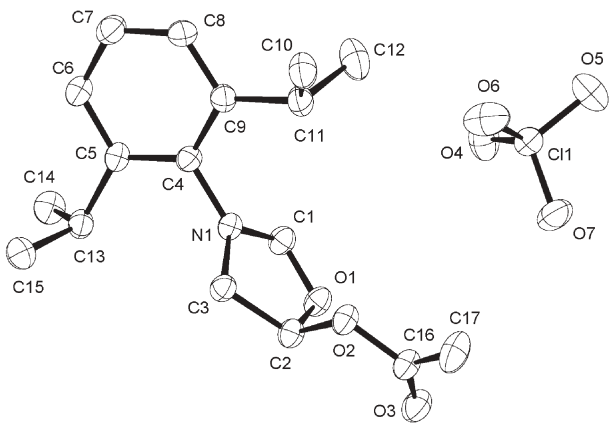


Fig. 1 Molecular structure of **10** (R^1 = 2,6-di-isopropylphenyl, $R^4 = R^5$ = H) from single crystal X-ray structure determination. Anisotropic displacement parameter ellipsoids are shown at 50% probability and hydrogen atoms have been omitted.

commercial bromoacetaldehyde diethylacetal **7** to give product **8** which was then processed analogously.

Gratifyingly, reaction of the oxazolinium adducts **10** with a second amine of choice R^2–NH_2 proceeded smoothly, affording the hydroxylated imidazolinium salts **11** that precipitated from the reaction mixture in all cases investigated, thus making the work up again very straightforward. The constitution of this novel type of heterocycle featuring a labile hemiaminal motif was confirmed by the crystal structure depicted in Fig. 2.‡

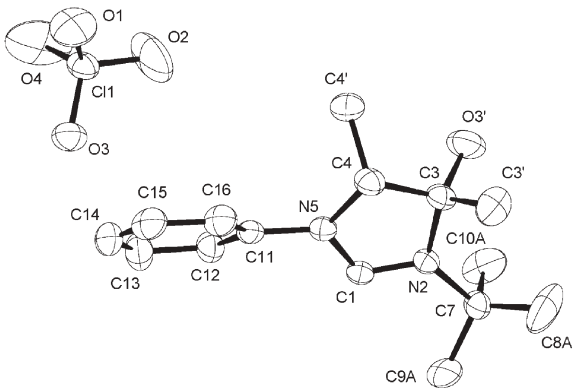


Fig. 2 Molecular structure of **11** (R^1 = Ph, R^2 = *t*-Bu, $R^4 = R^5$ = Me) from single crystal X-ray structure determination. Anisotropic displacement parameter ellipsoids are shown at 50% probability and hydrogen atoms have been omitted. The *tert*-butyl group is disordered over two positions at a ratio of 40 : 60.

Compound **11** was then suspended in toluene and reacted with Ac_2O and a catalytic amount of HX at 80 °C. After evaporation of the solvent, the residue was triturated with Et_2O and the resulting suspension sonicated in a cleaning bath for *ca.* 20 min to give the desired imidazolium salts **12** as solids that can be conveniently filtered off. As can be seen from Table 1, the isolated yields obtained over the entire sequence were good to excellent for a variety of cases.

Most noticeable is the fact that the method accommodates variously substituted anilines as well as secondary and tertiary amines as the reaction partners, thus giving access to imidazolium salts that are inaccessible by any of the established routes; the structure of a representative example falling into this category is depicted in Fig. 3.‡ Even very weakly nucleophilic anilines as well as sterically hindered amines still provide satisfactory results. We therefore believe that this practical methodology should find widespread use and invites applications to the preparation of structurally novel types of carbene precursors. Investigations along these lines together with applications of such ligands in catalysis will be reported shortly.

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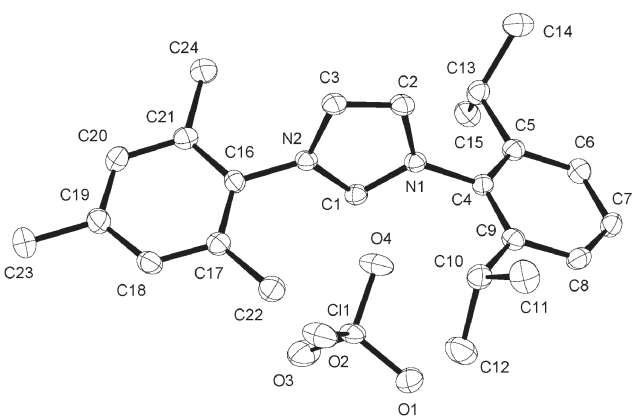
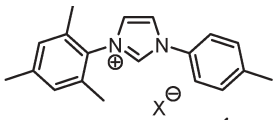
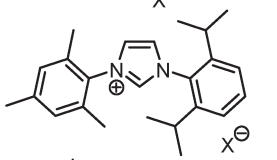
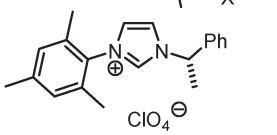
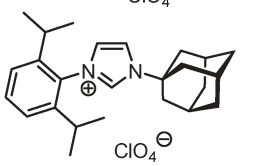
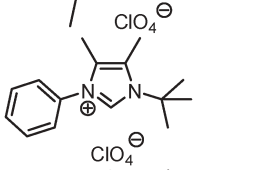
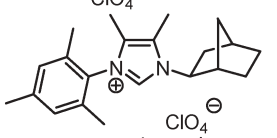
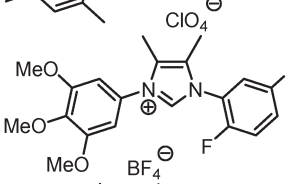
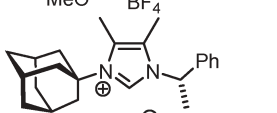
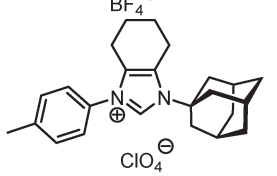


Fig. 3 Molecular structure of **12** (R^1 = mesityl, R^2 = 2,6-di-isopropylphenyl, $R^4 = R^5$ = H) from single crystal X-ray structure determination. Anisotropic displacement parameter ellipsoids are shown at 50% probability and hydrogen atoms have been omitted.

Table 1 Unsymmetrical *N*,*N*′-disubstituted imidazolium salts prepared by the method depicted in Scheme 3

Entry	Product	Yield[a]
1		64% (X = BF_4)
2		59% (X = ClO_4)
3		75% (X = BF_4)
4		91% (X = ClO_4)[b]
5		64%
6		82%
7		91%
8		84%[c]
9		31%
10		59%
11		88%

[a] Refers to the overall yield of the reaction sequence shown in Scheme 3 from compound **6** (or **9**) to the final product. [b] Using mesitylamine as R^2NH_2; 73% yield using 2,6-di-isopropylphenylamine as R^2NH_2. [c] In racemic form.

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Notes and references

‡ CCDC 602504–602506. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b604236h

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3 Exceptions are known for special ligand architectures, *cf.*: (*a*) F. Glorius, G. Altenhoff, R. Goddard and C. W. Lehmann, *Chem. Commun.*, 2002, 2704; (*b*) M. Alcarazo, S. J. Roseblade, A. R. Crowley, R. Fernández, J. M. Brown and J. M. Lassaletta, *J. Am. Chem. Soc.*, 2005, **127**, 3290; (*c*) H. Seo, H. Park, B. Y. Kim, J. H. Lee, S. U. Son and Y. K. Chung, *Organometallics*, 2003, **22**, 618.

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5 An interesting alternative for the *N*-arylation of imidazoles is the reaction with aryne intermediates; however, this method is not suitable for the preparation of unsymmetrical imidazolium salts bearing two *N*-aryl groups, *cf.*: H. Yoshida, S. Sugiura and A. Kunai, *Org. Lett.*, 2002, **4**, 2767.

6 (*a*) In this context it is worth noting that several transformations are known in which catalysts with unsaturated carbene ligands **A** perform significantly better than those with saturated NHC's of type **B**; for representative examples see ref. 10 and the following: J. W. Sprengers, J. Wassenaar, N. D. Clement, K. J. Cavell and C. J. Elsevier, *Angew. Chem., Int. Ed.*, 2005, **44**, 2026; (*b*) in contrast to the prevailing assumption, recent experimental data indicate that unsaturated NHC's might be even stronger electron donors than their saturated counterparts, see: R. Dorta, E. D. Stevens, N. M. Scott, C. Costabile, L. Cavallo, C. D. Hoff and S. P. Nolan, *J. Am. Chem. Soc.*, 2005, **127**, 2485.

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13 Formation of oxazolium salts from α-aminoketones with triethyl orthoformate was claimed in a patent, *cf.*: DD 254 0902 A1. In our hands, however, this procedure is less clean and hence inferior to the route *via* the formamide described herein.

