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Sterically demanding imidazolinium salts through the activation and cyclization of formamides†

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A new protocol was developed for the synthesis of sterically demanding imidazolinium salts. This procedure was adopted for the synthesis of seven NHC salts, including ones that were demonstrated to be inaccessible using the conventional orthoformate ester type cyclization method.

N-heterocyclic carbenes (NHCs) have become ubiquitous as ligands for transition metal catalyzed transformations and as organocatalysts.[1] The impressive performance of the first (*Pd-PEPPSI-IPr*, **1**) and second (*Pd-PEPPSI-IPent*, **3**) generation of *PEPPSI*-precatalysts in cross-coupling reactions prompted us to further examine the effect of sterics of NHC-ligands on catalysis. Our own research into palladium–NHC precatalysts supports theories in the literature that steric bulk of the NHC ligand is of great importance to catalyst activity.[2] "Flexible bulk"[3] from the 3-pentyl groups in *Pd-PEPPSI-IPent* was instrumental in promoting certain reactions that were previously reported as "challenging" in the literature.[4] For some reactions, *Pd-PEPPSI-SIPr* showed comparable activity to *Pd-PEPPSI-IPr* but at lower temperature.[5] Analogously, in an attempt to perform cross-coupling at even lower temperatures than have been achieved using *Pd-PEPPSI-IPent*, we turned our attention to the synthesis of its saturated analogue **4** (Fig. 1).

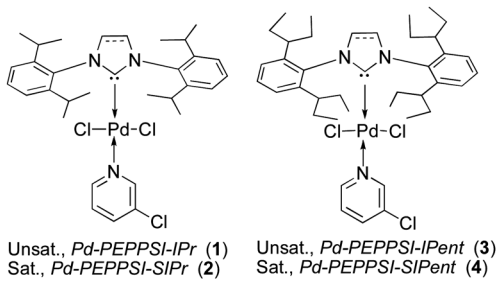
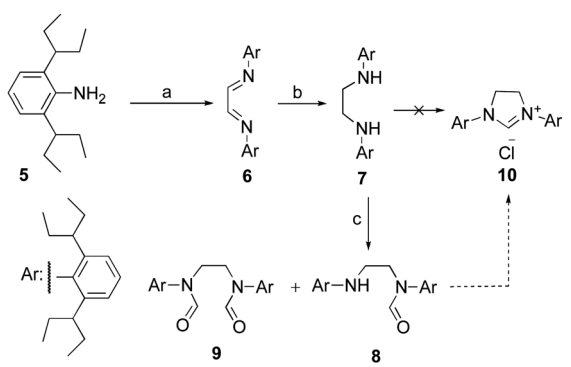


Fig. 1 First and second generations of *Pd-PEPPSI* complexes.

A limited number of saturated NHC salts are commercially available and their reported syntheses are sparse. This may be due to the challenge associated with their synthesis, especially when the groups on the forming saturated imidazolinium core are large.[6] Conversely, syntheses of unsaturated NHC salts often enjoy the advantages from the proximal rigid disposition (*cis*) of cyclizing ends and the energy-gain upon formation of an aromatic compound during the cyclization process.[7] During the synthesis of the saturated version, the high degrees of freedom about the C–C single bond becomes a major hurdle, which is exacerbated by larger substituents which destabilize the pseudo *cis* arrangement required for cyclization.

Our approach began with formation and subsequent reduction of bis-imine **7** using aniline **5**.[8] Surprisingly, treatment of **7** with HCl and an orthoformate ester led only to the formation of a mixture of mono-formamide (**8**) and bis-formamide (**9**). Similarly, precipitation of the bis-ammonium dichloride salt and subsequent addition of an orthoformate ester gave the same result. Treatment of other, less bulky bis-amines with either set of conditions is known to produce exclusively the imidazolinium chloride salt. Nonetheless, the formation of mono-formamide **8** was not unproductive as it could serve as a precursor to the desired imidazolinium salt (Scheme 1). After optimization, formamide **8** was isolated in 54% yield when **7** was treated with acetic formic anhydride (AFA).[9]



Scheme 1 *Reagents and conditions*: (a) $(HCO)_2$ 40% in H_2O, HCO_2H, EtOH, 70 °C, 24 h, 75%; (b) $NaCNBH_3$, AcOH, Et_2O, EtOH, rt, 4 h quantitative; (c) $HC(OEt)_3$, HCl in dioxane, 1,4-dioxane, microwave heating at 140 °C for 45 min, 3 : 1 **8/9**, 41% yield of **8**.

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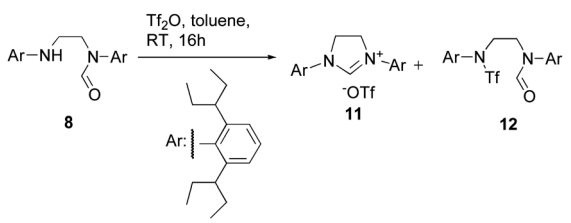
† Electronic supplementary information (ESI) available: Experimental procedures and NMR data are available for compounds **6–9**, **11**, **17–32**. See DOI: 10.1039/c2cc36329a

Formamides are known decomposition products of NHCs, and precedence exists for the inter-conversion between the two species.[10] Less bulky mono-formamides could be cyclized to the corresponding imidazolinium salts simply by treatment with neat Brønstead acid.[11] However, conversion of **8** to the corresponding imidazolinium salt using various acidic protocols was unsuccessful even at an elevated temperature. Evidently, the protonation of the formamide carbonyl does not overcome the energy barrier for the intramolecular attack by a sterically bulky amine nucleophile. Alternatively, covalent activation of amide groups has been shown to be a versatile and effective strategy for the formation of carbon–carbon and carbon–heteroatom bonds.[12]

The same strategy has been used for the synthesis of various cyclic and acyclic formamidinium salts,[13] and similar protocols have been used in the preparation of triazolium[14] and oxazolinium[15] salts. The most general and relevant application of the formamide activation strategy to generate imidazolium salts utilized $POCl_3$. However, all reported examples involved an sp^2 hybridized nitrogen nucleophile, which subsequently generated an aromatic imidazolium ring.[16] We opted to activate the formamide *via* the formation of covalent bonds to cyclize formamide **8** to the corresponding imidazolinium salt.

Treatment of mono-formamide **8** with Tf_2O did produce the desired imidazolinium triflate salt (**11**), although once again the steric bulk slowed the intramolecular attack on the triflylimminium triflate moiety and **12** was produced alongside the desired imidazolinium salt (Scheme 2). Presence of the strong electrophile Tf_2O in the presence of the amine resulted in an alternative, irreversible reaction pathway to give the N-triflated sulfonamide (**12**). A closer look at the reactivity pattern revealed that formation of the desired salt (**11**) was deterred when the reaction was performed under strictly anhydrous conditions with freshly distilled Tf_2O and toluene. Perhaps N-triflation becomes favoured over desired O-triflation under anhydrous conditions while a trace of water can produce triflic acid (from Tf_2O) that mutes the nucleophilicity of the nitrogen lone pair. However, we recognized the detrimental effect of an unregulated amount of water on the stability of intermediates such as triflylimminium triflate **14**. Consequently, we added a stoichiometric amount of "dry" TfOH prior to the addition of Tf_2O to sequester the lone pair of the free amine and yet maintain an anhydrous environment, thus setting the stage for the Vilsmeyer–Haack reaction. This strategy necessitated a suitable base that could free-base the amine but would not attack the triflylimminium triflate electrophile. After some investigation DIPEA (Hünig's base) was found to be optimal for the cyclization, irrespective of steric encumbrance around the core of the final salt. This reaction sequence produced the desired imidazolinium triflate salt and avoided the formation of any N-triflated byproduct. Purification of the imidazolinium salt from other species was found to be trivial since the removal of toluene and the addition of hexanes resulted in the exclusive precipitation of the imidazolinium salts (NHC salts) and DIPEA ammonium triflate salts. Any formamide that was unreacted or was regenerated following hydrolysis of the triflylimminium triflate intermediate **14**, was recovered in the mother liquor. Prolonged reaction times did not lead to full conversion, resulted rather in a more complex reaction mixture that complicated purification.

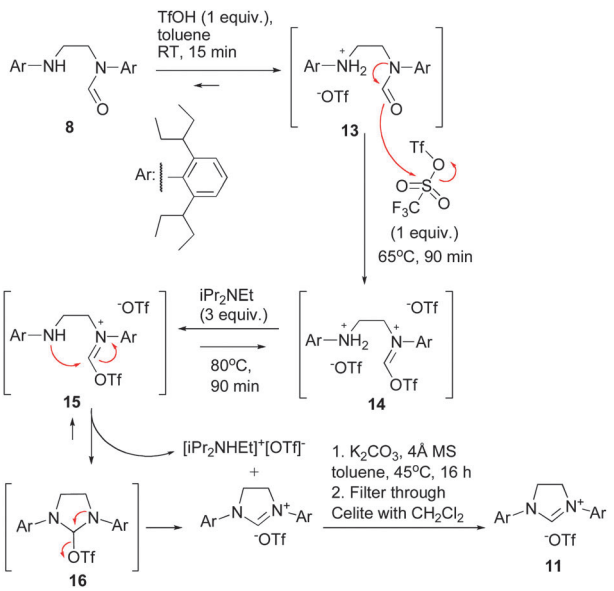


Scheme 2 Triflic anhydride-promoted cyclization of formamide **8**.

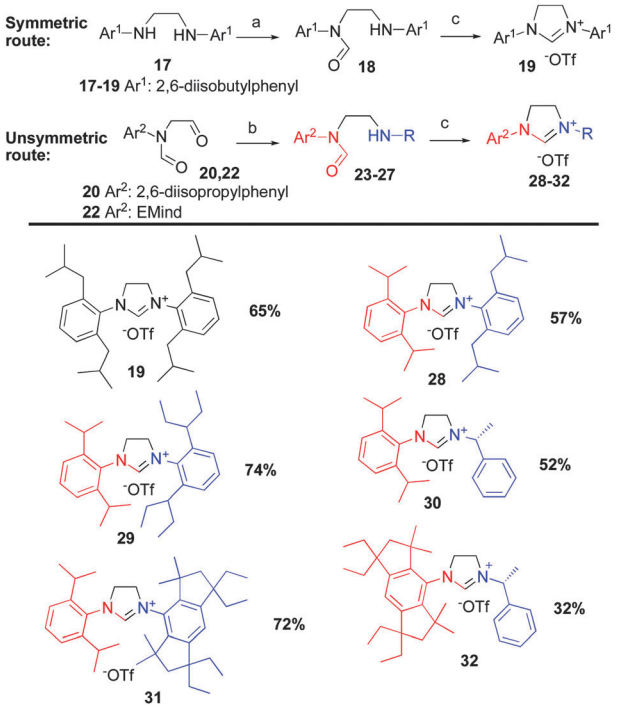
Generally, separation of trialkyl ammonium and imidazol(in)ium salts is difficult to achieve by crystallization. Aqueous washes are often required that may decompose the imidazolinium salt and necessitate additional steps for drying the product.[17] As a consequence, we developed a unique procedure to purify of the imidazolinium salt away from the Hünig's salt contaminant. Treatment of the mixture of salts with an equal weight of K_2CO_3 and crushed 4 Å molecular sieves at 45 °C in toluene for 16 h produced, in quantitative recovery, clean imidazolinium salt. The origin of the purification may stem from selective deprotonation of the ammonium salt and subsequent hydrogen bonding or ion–dipole interactions between the free amine and the Zeolite framework.[18] The protocol was found to be general for the purification of the DIPEA ammonium triflate salt from various imidazolinium salts and facilitated the formation of **11** in 64% yield from **8** (Scheme 3).

While symmetric bis amine **17** was also successfully formylated (**18**) and cyclized (**19**), following the work of Fürstner *et al.* we were able to modify the route towards the synthesis of unsymmetric imidazolinium salts through precursors **20** and **22**.[15] Production of chiral NHC salts with this protocol is of special interest to us since high enantiocontrol can be achieved in a number of transformations where bulk is moved close to the reaction site, which in this case would be at the metal center.[19] We were able to synthesize several NHC salts **28–32** *via* their appropriate precursors **23–27**, ranging in steric bulk, and were even able to incorporate the highly hindered EMind aniline (**21**) bearing two *ortho* tertiary carbons (Scheme 4).[20]

The formamide activation strategy was shown to be general for the preparation of alkyl- and aryl-substituted imidazolinium



Scheme 3 Process for formation/purification of imidazolinium salt **11**.



Scheme 4 *Reagents and conditions*: (a) AFA, CH_2Cl_2, rt, 2 h, 57% yield. (b) i. RNH_2, ^tBuOH, toluene, p-TSA, microwave heating at 100 °C for 1 h; ii. $Na(CN)BH_3$, AcOH, ^tBuOH, CH_2Cl_2, rt, 16 h, 33–58% yield. (c) i. TfOH, toluene, rt, 15 min; ii. Tf_2O, 65 °C, 90 min; iii. iPr_2NEt, 80 °C, 90 min; iv. K_2CO_3, 4 Å MS, toluene, 45 °C, 18 h.

salts and is readily scalable due to the novel purification strategy (*vide supra*). Careful choice of reagents ensures that only one counteranion is present in the reaction mixture so that precipitation of the product is facile and determination of the yield is unambiguous. Importantly, the imidazolinium salt obtained is suitable for metal complexation reactions where the presence of different counter anions can affect the yield, kinetics of formation, and purity of the final product (*e.g.*, for Ru-complexes).[21] Alternatively, the use of $POCl_3$, while sometimes effective for the cyclization step, generates a number of possible counteranions that complicate analysis and require tedious purification.[22]

The formamide activation strategy facilitates cyclizations that are too challenging for the orthoformate ester cyclization protocol and thus allows the formation of more sterically demanding NHC salts. Methods were developed to synthesize symmetric and unsymmetric formamide precursors for the cyclization step, that led to alkyl- and aryl-substituted imidazolinium salts in pure form that are ready for metal ligation.

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