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Efficient, Single-Step Access to Imidazo[1,5-*a*]pyridine *N*-Heterocyclic Carbene Precursors

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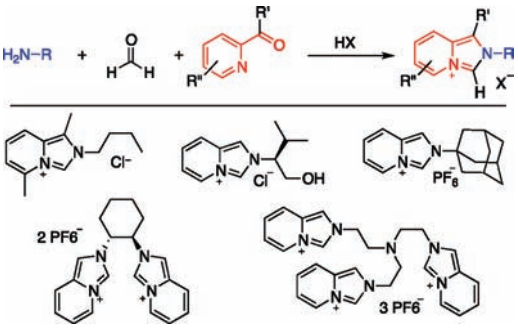
ABSTRACT



The three-component coupling reaction of substituted picolinaldehydes, amines, and formaldehyde to produce imidazo[1,5-*a*]pyridinium ions is reported, providing an efficient method for the preparation of *N*-heterocyclic carbenes (NHCs). Reactions proceed in high yields under mild conditions, allowing the incorporation of diverse functionality and chiral substituents. Higher order condensations are also described that provide access to multidentate NHC ligands useful for a variety of applications.

In the past 20 years, the strong σ-donor capacities, low dissociation rates and unique geometries of *N*-heterocyclic carbenes (NHCs) have made them invaluable ligands for homogeneous catalysis.[1−5] Of particular interest are unsymmetrical NHCs that frame the carbene with differentiated substituents to provide tunable control of metal ligand sphere geometry. Unfortunately, the range of these structures available through straightforward and practical methods is limited. Here, we report a three-component coupling reaction that simplifies the synthesis of imidazo[1,5-*a*]pyridinium salts, providing unprecedented access to variously substituted, chelating, and oligomeric unsymmetrical NHC precursors in a single transformation.

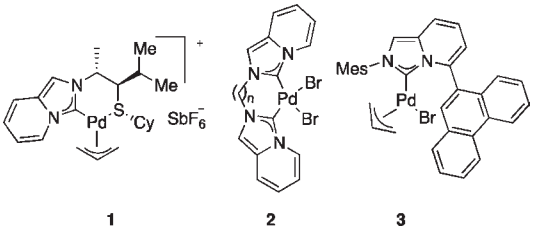


Figure 1. Catalytically relevant complexes of imidazo[1,5-*a*]pyridine-based NHC ligands.

Imidazo[1,5-*a*]pyridine-derived NHCs are well-established in homogeneous catalysis, as exemplified by applications in asymmetric allylic alkylations and Suzuki–Miyaura and related cross-coupling reactions (Figure 1).[6,7] Among the strongest heteroaromatic σ-donors,[7] imidazo[1,5-*a*]pyridine-derived NHCs place substituents directly in the nodal plane of the carbene π-system, facilitating the

(1) Arduengo, A. J.; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361–363.
(2) Crabtree, R. H. *J. Organomet. Chem.* **2004**, *689*, 4083–4091.
(3) Diez-Gonzalez, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612–3676.
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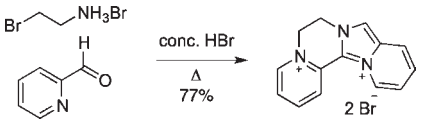
creation of a unique steric environment. General synthetic approaches to these ligands involve alkylations of commercially available imidazo[1,5-*a*]pyridines with reactive electrophiles,[7a] dehydrative cyclizations of *N*-formylpicoline derivatives,[7a] and condensations of picolinealdehyde Schiff bases with activated bis-electrophiles.[7b] The harsh conditions, poor yields, and constrained scope of these methods limit the range of available analogs.

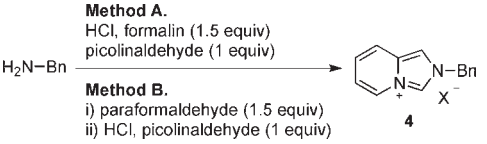
Scheme 1. Campbell's approach to imidazo1,5-*a*]pyridinium ions.[8]



Inspired by the related reports of Campbell[8] and Chakravarty[9] (Scheme 1), we sought to explore condensations of amines with picolinaldehyde and formaldehyde to directly access imidazopyridinium ions. Initial efforts to establish the desired three-component coupling examined the ethanolic reaction of picolinaldehyde with paraformaldehyde and benzylamine in the presence of acid. These transformations involved premixing the amine with paraformaldehyde to avoid double condensations of picolinaldehyde with the amine in a manner analogous to the previously reported reactions (Scheme 1).[8,9] Gratifyingly, rapid reaction was observed at rt to provide salt **4** in 91% isolated yield (Table 1, entry 1). Reaction optimization revealed that using aqueous formaldehyde circumvented picolinaldehyde self-condensation, allowing us to directly combine the reagents in a single reaction without attenuation of yield (Table 1, entry 2). Solvent screens revealed excellent reactivity in a variety of polar solvents with both approaches (Table 1, entries 1−8). Solubility issues in water required the use of polar substrates, but no loss in efficiency was observed (Table 1, entries 7 and 8). Superstoichiometric quantities of acid slowed the reaction, likely impacting the reactivity of the pyridine nitrogen (Table 1, entries 9 and 10). In contrast, substoichiometric quantities of acid revealed the acid as a limiting reagent (Table 1, entries 11 and 12).

Following initial optimizations, we screened several amines to explore the scope of the reaction (Table 2).

Table 1. Initial Optimization[a,b]



entry	equiv acid	solvent	method[a]	yield (%)[b]
1	1.0	ethanol	B	>99
2	1.0	ethanol	A	94
3	1.0	MeCN	B	97
4	1.0	MeCN	A	97
5	1.0	MeOH	B	95
6	1.0	MeOH	A	91
7[c]	1.0	H_2O	B	91
8[c]	1.0	H_2O	A	>99
9	2.0	ethanol	B	71
10	2.0	ethanol	A	85
11	0.5	ethanol	B	34
12	0.5	ethanol	A	25

[a] Method A: Reactions maintained for 2 h with 1.5 equiv of formalin in solvent (0.5 M), anhydrous HCl in ethanol, and 1 equiv of picolinaldehyde. Method B: Benzyl amine was stirred with 1.5 equiv of paraformaldehyde in solvent (0.5 M) for 1−4 h, at which point HCl and 1 equiv of picolinaldehyde were added, and the solutions were maintained at rt for 2 h. [b] Yields determined by ^{1}H NMR spectroscopy with an internal standard (phenol). [c] Reactions performed using aqueous HCl (conc) and ethanolamine in lieu of benzylamine.

The condensation proceeds in excellent yields with simple, functionalized, and sterically encumbered primary amines and anilines. Substrates containing secondary amines, pyridyl moieties, alcohols, thioethers, and esters proceeded with excellent conversions, although substrates bearing an additional basic nitrogen required an additional equivalent of acid (Table 2, entries 1−7). The condensation proceeds at a slower rate in the presence of sterically encumbered amines, requiring prolonged reaction times in some cases (Table 2, entries 8 and 9). Substrates bearing stabilized nitrogens revealed excellent reactivity in the case of electron-rich and -poor anilines (Table 2, entries 10−13). However, no products were observed in reaction attempts with amides or sulfonamides.

Amino acid derived amines exhibited no epimerization during the condensation reaction, facilitating the incorporation of chirality into imidazopyridinium salts (Table 2, entries 6 and 7). Functionalized nonracemic NHCs are powerful tools for homogeneous catalysis,[10] inducing chirality in numerous reactions including hydrogenation, hydrosilylation, and alkylation (among many others).[11] Unfortunately, unsymmetrically functionalized NHCs are generally prepared through a tandem condensation/

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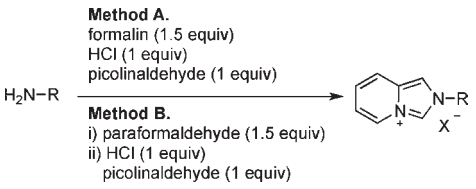
Table 2. Amine Substrate Scope[a,b]



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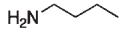
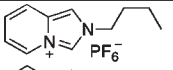
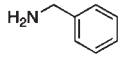
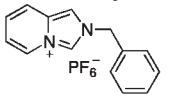
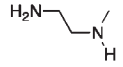
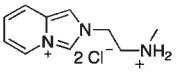
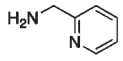
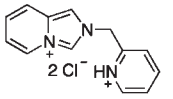
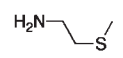
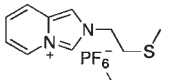
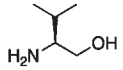
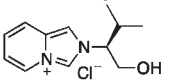
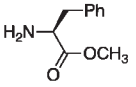
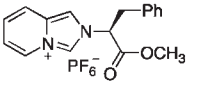
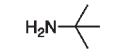
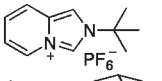
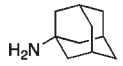
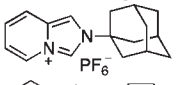
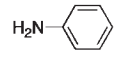
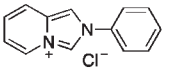
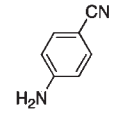
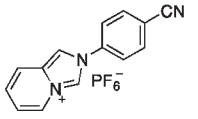
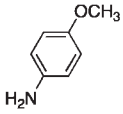
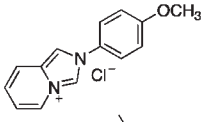
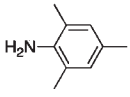
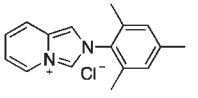
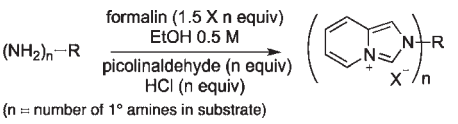
1		A		93
2		A		93
3		B		77[c]
4		B		74[c]
5		A		92
6		A		86
7		A		86
8		B		80[d]
9		B		75[d]
10		A		86
11		B		70
12		A		92
13		A		91

[a] Reactions run as described in Table 1, using varying times (1–12 h) for different amines. [b] Chloride salts isolated through recrystallization or filtration; hexafluorophosphate salts isolated through salt metathesis with KPF_6. [c] Reactions required 2 equiv of HCl. [d] Reactions performed for 4 d.

alkylation aproach, making access to α-chiral compounds of high optical purity both costly and time-consuming.[12] Our procedure simplifies access to these compounds, allowing the incorporation of α-chiral amines without epimerization or loss of chirality in the corresponding NHCs.

(12) (a) Poyatos, M.; Mata, J. A.; Peris, E. *Chem. Rev.* **2009**, *109*, 3677–3707. (b) Corberan, R.; Mas-Marza, E.; Peris, E. *Eur. J. Inorg. Chem.* **2009**, 1700–1716.

Table 3. Bis- and Poly-NHCs[a]



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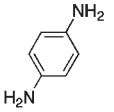
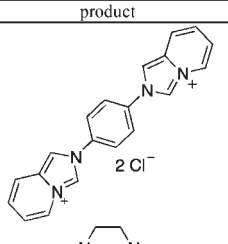
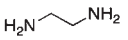
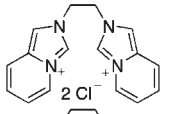
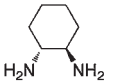
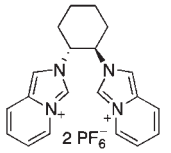
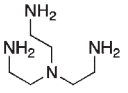
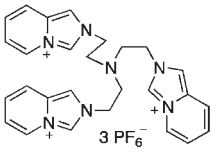
1			81[b]
2			99
3			86[c] 80[c,d]
4			93

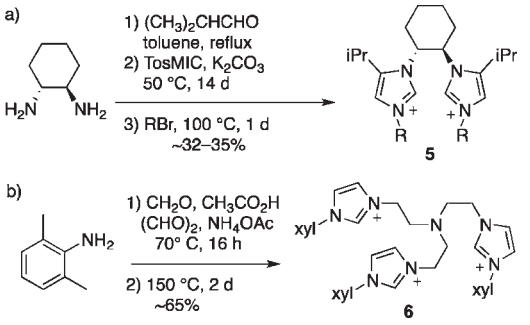
[a] Compounds purified as described in note *b* of Table 2. [b] Reaction performed at 0.35 M in ethanol. [c] Reaction run as described for Method B, Table 1 using 3 equivalents of paraformaldehyde. [d] Reaction performed using the bis-HCl salt of the starting diamine with no additional HCl added.

Reactions of polyamines provide facile access to bis- and tris-NHCs (Table 3). The reaction works exceedingly well with simple diamines, *para*-phenylene diamine, chiral bis-amines, and polyamines. The successful reaction of 1,2-cyclohexyldiamine (Table 3, entry 3) demonstrated our ability to access chiral bis-NHCs possessing two α-stereocenters. Synthesis of the analogous imidazolium salt **5** requires a three-step procedure with the key cycloaddition step involving long reaction times and exhibiting low yields (Scheme 2a).[13] The straightforward synthesis of tris-NHCs such as entry 4 (Table 3) is notable as current approaches center on a harsh alkylation strategy that limits access to these materials (Scheme 2b).[12] Although tris-NHCs remain rare in the literature, they exhibit significant synthetic potential. For example, ligands such as the TIMEN-derived imidazolium NHCs (**6**), developed by Meyer et al., bind first row transition metals (Cu, Fe, Ni, and Co) in a 1:1 fashion, with cobalt complexes of **6** displaying activity in small-molecule activation.[14] Notable exceptions to the polyamine condensations were

(13) Bonnet, L. G.; Douthwaite, R. E.; Hodgson, R. *Organometallics* **2003**, *22*, 4384–4386.

(14) (a) Hu, X. L.; Castro-Rodriguez, I.; Meyer, K. *J. Am. Chem. Soc.* **2004**, *125*, 12237–12245. (b) Hu, X. L.; Castro-Rodriguez, I.; Meyer, K. *J. Am. Chem. Soc.* **2004**, *126*, 13464–13473. (c) Vogel, C.; Heinemann, F. W.; Sutter, J.; Anthon, C.; Meyer, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 2681–2684.

Scheme 2. (a) Representative Synthetic Approach to Chiral Bis-NHCs;[13] (b) Synthesis of the TIMEN Tris-NHC Ligand[14]



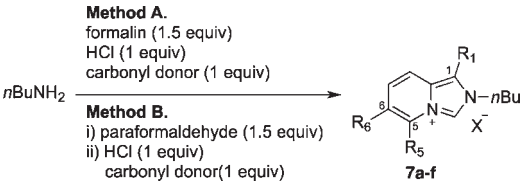
observed for *ortho*-phenylenediamine, which condenses with formaldehyde to produce the corresponding dihydrobenzimidazole, and *meta*-phenylenediamine, which reacted with formaldehyde to produce an intractable red solid. Considering the wealth of commercially available diamines and polyamines, this method allows for the facile construction of a library of imidazo[1,5-*a*]pyridine bis- and poly-NHC analogues.

Reactions of substituted picolinaldehydes and related ketones with *n*-butylamine and formaldehyde further established the scope of this condensation. Electron-rich pyridines react smoothly (Table 4, entry 1); however electron-poor systems led to attenuated yields (Table 4, entry 2). Pyridine substitution at C-5 had no notable effect on reactivity, despite steric interactions introduced by the substituent (Table 4, entry 3). 2-Acetyl-pyridine, 2-benzoylpyridine, and 6-methyl-2-acetyl-pyridine also react well, allowing for placement of substituents at both the 1 and 5 positions. The incorporation of substituents at C5 allows us to increase the effective steric bulk of these ligands. Moreover, substitution at C1 potentially restricts bond rotation at *N*-substituted stereocenters, further rigidifying the system.[15] To the best of our knowledge, this chemistry is the first reported method that provides access to unsymmetrical NHCs that vary in substitution at both sides of the carbene carbon in a single transformation.

One plausible mechanism for this condensation is shown below (Scheme 3). In our mechanistic rationalization, the protonated Schiff base **9** is attacked by picolinaldehyde (**8**), leading to condensation intermediate **10**. Cyclization of **10** occurs through nucleophilic attack of the amine nitrogen onto the aldehyde, and the reaction is driven to completion by an irreversible dehydration to provide aromatic imidazo[1,5-*a*]pyridinium ion **12**. Our proposed mechanism is consistent with observations that both an excess of acid and the use of electron-poor pyridines inhibit the process, as the nucleophilicity of the pyridine is critical to the initial step.

(15) Schmidt, M. A.; Movassaghi, M. *Tetrahedron Lett.* **2007**, *48*, 101–104.

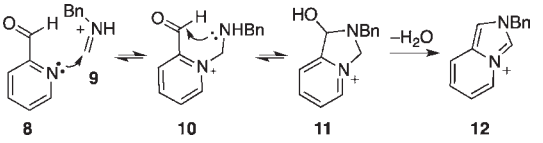
Table 4. Carbonyl Substrate Scope[a,b]



entry	carbonyl donor	method[a]	product	yield (%)[b]
1	5-methoxypicolinaldehyde	A	**7a**	78
2	5-cyanopicolinaldehyde	A	**7b**	43
3	6-methylpicolinaldehyde	A	**7c**	92
4	2-acetylpyridine	B	**7d**	88
5	2-acetyl-6-methylpyridine	B	**7e**	70
6	2-benzoylpyridine	A	**7f**	91

[a] Reactions run as described in Table 1, using varying times (2–12 h) for different amines. [b] Chloride salts were isolated by recrystallization, whereas PF_6 and BPh_4 salts were isolated through salt metathesis with KPF_6 and $NaBPh_4$.

Scheme 3. Proposed Mechanism of Condensation



In conclusion, an efficient method for the general preparation of imidazo[1,5-*a*]pyridine salts has been developed. This method represents a new avenue for directly accessing unsymmetrical NHCs that vary in substitution at both sides of the carbene carbon. Using this chemistry, a library of structurally diverse compounds can be quickly assembled to access new and potentially valuable *N*-heterocyclic carbene ligands. Ongoing studies in our laboratory are directed at developing catalytic systems that incorporate imidazo[1,5-*a*]pyridine based NHC ligands.

Acknowledgment. We acknowledge the financial support of Indiana University.

Supporting Information Available. Experimental procedures and spectral data for all compounds generated through this work. This material is available free of charge via the Internet at http://pubs.acs.org.