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One-Pot Synthesis of Unsymmetrical N-Heterocyclic Carbene Ligands from *N*-(2-Iodoethyl)arylamine Salts

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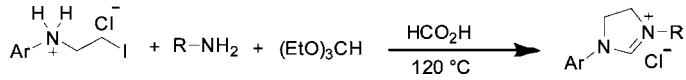
ABSTRACT



An approach that provides symmetrical, unsymmetrical, and asymmetric N-heterocyclic carbene (NHC) ligands is reported. Reaction of iodoethanol with aniline provides *N*-(2-iodoethyl)arylamine salts that are then converted to the corresponding iodide. Reaction with aliphatic or aromatic amines followed by triethyl orthoformate was used to provide 26 different NHC ligands.

The discovery of new catalysts is often limited by the availability of new ligands. Consequently, the development of chemistry that provides access to new ligand types is critical. N-Heterocyclic carbenes (NHCs) have been shown to provide transition metal complexes that have improved reactivity and stability over their analogous phosphine complexes.[1−3] An approach for the synthesis of symmetrical, unsymmetrical, and chiral NHC ligands has been developed.

Since their original disclosure by Öfele in 1968[4] and their initial isolation by Arduengo,[5] NHC ligands have been shown to be effective as ligands on transition metal complexes that catalyze a number of reactions. The Heck reaction,[6] Suzuki and Sonogashira couplings,[7,8] aryl amination,[9,10] amide α-arylation,[11] hydrosilylation,[12] Kumada coupling,[13] hydrogenation,[14,15] hydroformylation,[16] alkyne coupling,[17] olefin cyclopropanation,[18] arylation of aldehydes,[19] and olefin metathesis[20] are all reactions that, in many cases, have been catalyzed by NHC complexes with greater efficiency than the usual phosphine complexes.

In addition to being used as ligands on catalytically active transition metals, the NHC functional group has been very useful in a wide variety of different reactions catalyzed by nucleophilic activation.[21,22] As organocatalysts, NHC ligands

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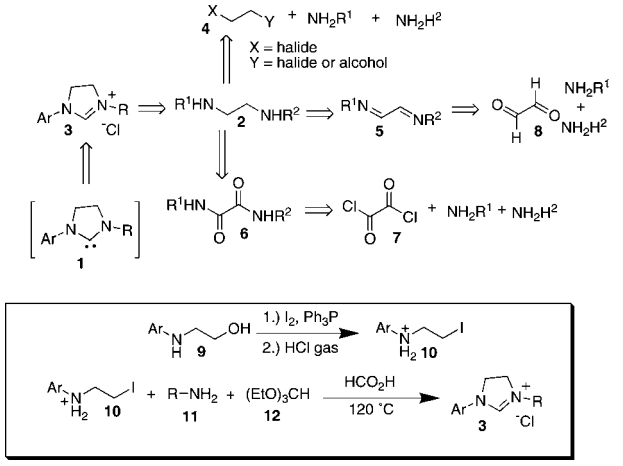
have recently been used for a variety of reactions such as transesterification/amidation,[23,24] living ring-opening polymerization,[25,26] homoenolate,[27−29] and nucleophilic substitution of fluorobenzene, in addition to the widely studied benzoin condensation[30] and Stetter reaction.[31]

The synthesis of NHC ligands (**1**) is generally achieved by formation of a diamine (**2**) followed by reaction with an ortho ester to form the carbene precursor imidazolinium salt (**3**).[32] The necessary diamines are generally synthesized by either alkylation of a dihalide (**4**) or formation of an imine (**5**) or amide (**6**) followed by reduction. Reaction of oxalyl chloride (**7**) with amines, to form a bisamide (**6**), or formation of bisimines (**5**) from the reaction of glyoxal (**8**) and amines, followed by exhaustive reduction, are related approaches (Scheme 1). Typically, the problem with these methods is the reduction step, which can limit the types of groups that can be on the amine. It can also be difficult to synthesize unsymmetrical NHC ligands by this approach.

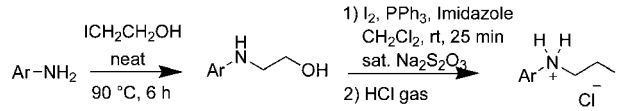
Scheme 1



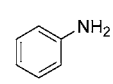
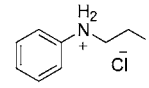
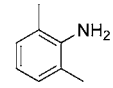
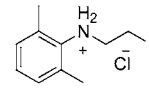
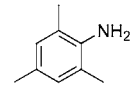
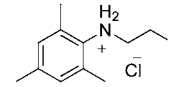
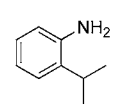
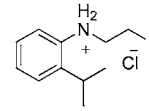
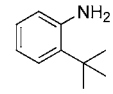
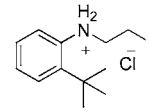
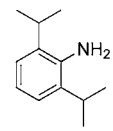
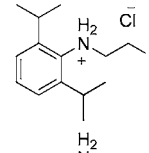
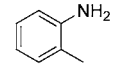
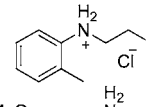
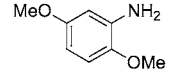
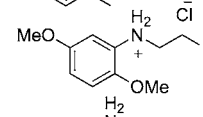
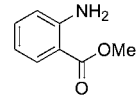
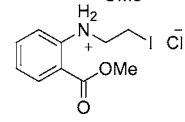
We envisioned a procedure where conversion of the amino alcohol (**9**) to an iodide followed by reaction with an amine and then trapping with an ortho ester would result in the formation of N-heterocyclic carbene precursor imidazolinium salt.

The necessary amino iodides are accessible by a simple two-step process from an amine and 2-iodoethanol (Table 1). The first step is solvent-free substitution at the iodide which is followed by reaction with triphenylphosphine and iodine to provide the amino iodide.[26] Treatment with gaseous hydrochloric acid provides the desired salt in excellent yields. The approach has been used to synthesize nine different iodoamine salts from a series of substituted anilines. The method appears to be quite general, working on amines ranging from aniline to highly hindered amines such as 2,6-diisopropylaniline (Table 1, entry 6). Surprisingly, we did not observe any formation of the competitive dialkylation of aryl amines even in the case of unhindered amines (entries 1 and 2, Table 1). We have synthesized multigram quantities of the necessary salts by this method. It should be noted

Table 1. Synthesis of *N*-(2-Iodoethyl)aryl Amine Salts[a]



13 9 10

entry	Ar	product	yield (%)
1		 **10a**	88
2		 **10b**	88
3		 **10c**	86
4		 **10d**	94
5		 **10e**	88
6		 **10f**	87
7		 **10g**	85
8		 **10g**	91
9		 **10i**	69

[a] Overall yield starting from aryl amine.

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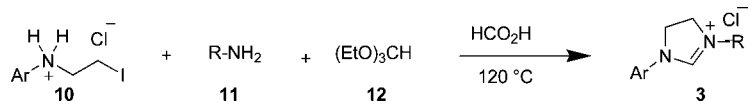
Table 2. Synthesis of Imidazolinium Salts[a]



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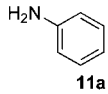
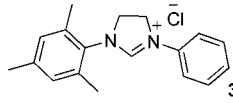
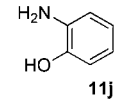
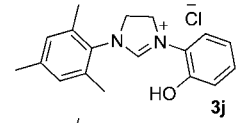
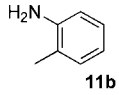
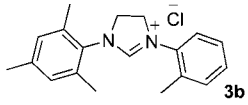
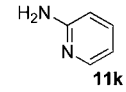
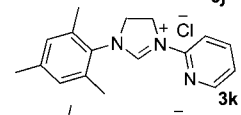
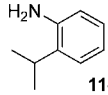
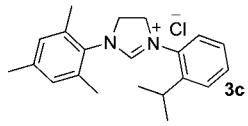
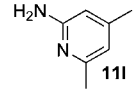
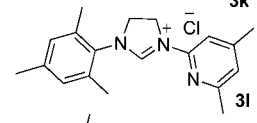
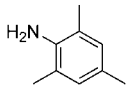
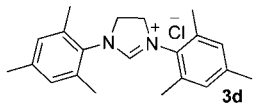
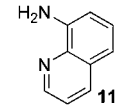
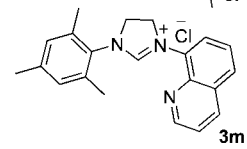
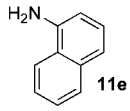
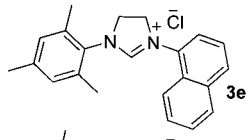
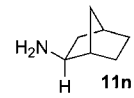
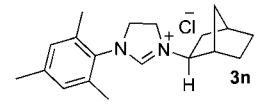
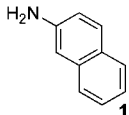
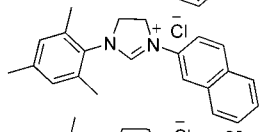
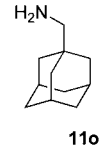
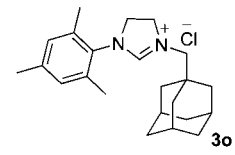
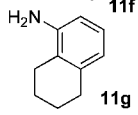
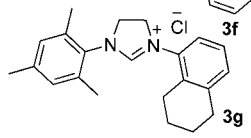
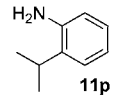
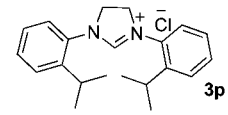
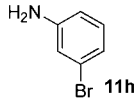
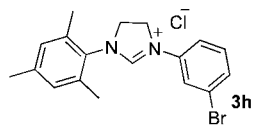
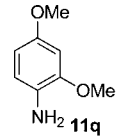
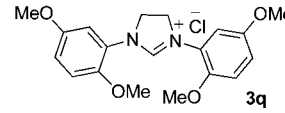
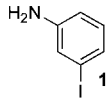
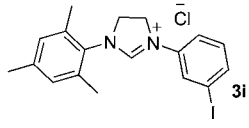
1	 11a	 3a	76	10	 11j	 3j	65
2	 11b	 3b	71	11	 11k	 3k	72
3	 11c	 3c	62	12	 11l	 3l	94
4	 11d	 3d	83	13	 11m	 3m	83
5	 11e	 3e	72	14	 11n	 3n	72
6	 11f	 3f	77	15	 11o	 3o	89
7	 11g	 3g	60	16	 11p	 3p	68
8	 11h	 3h	72	17	 11q	 3q	80
9	 11i	 3i	67				

[a] Reaction conditions: 10 mol % of HCO_2H and 2 equiv of $(EtO)_3CH$ were used with respect to 1 equiv of *N*-(2-iodoethyl)arylamine salt and primary amine, respectively, in neat conditions.

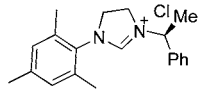
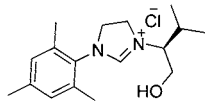
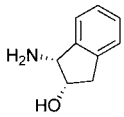
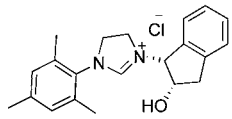
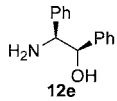
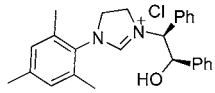
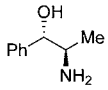
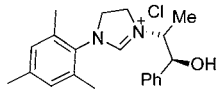
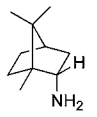
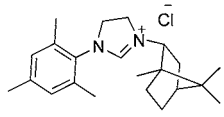
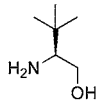
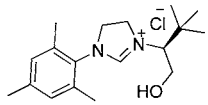
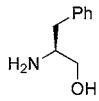
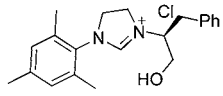
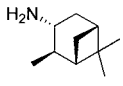
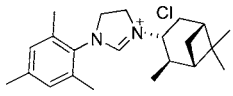
that, if one so desires, the intermediate amino iodides can be isolated without resorting to forming their salts. We have found the salts to be easy to isolate and stable over long periods of time. When they are desired, the free amines can be generated from the salts by reaction with triethylamine.

The synthesis of NHC ligands uses the iodides, such as **10**, as a key intermediate. While similar to the reported methods using iodoethanol,[33] it allows for the facile one-step synthesis of a collection of NHC precursor imidazolinium salts. Through reaction of a single salt with an ensemble of amines, this approach allows for the rapid synthesis of a series of symmetrical and unsymmetrical NHC ligands.

The mesitylene salt was chosen as our test case since it was felt that it would be one of the more difficult examples. As can be seen in Table 2, other *N*-(2-iodoethyl)aryl amine salts work equally well. Reaction with a number of aromatic and aliphatic amines provides a collection of imidazolinium salts (Table 2). Fourteen of the unsymmetrical ligands in Table 2 (entries 1−3 and 5−15) were synthesized from the

(33) Leuthaeusser, S.; Schmidts, V.; Thiele, C. M.; Plenio, H. *Chem.−Eur. J.* **2008**, *14*, 5465–5481.

Table 3. Synthesis of Chiral Imidazolinium Salts

entry	R		product		yield (%)
1		**11r**		**3r**	29
2		**11s**		**3s**	32
3		**11t**		**3t**	56
4	 **12e**	**11u**		**3u**	50
5		**11v**		**3v**	66
6		**11w**		**3w**	76
7		**11x**		**3x**	31
8		**11y**		**3y**	35
9		**11z**		**3z**	62

mesitylene iodide (**10c**), and three symmetrical NHC ligands were prepared from the **10c**, **10d**, and **10h** amine salts (Table 2, entries 4, 16, and 17). The reaction sequence also runs well with other amino iodides.

The route has also been used to synthesize chiral unsymmetrical NHC ligands. A series of chiral amines and α-amino alcohols were treated with ammonium salts to form chiral N-heterocyclic carbene ligands in moderate to good yields (Table 3).

This approach is compatible with a number of potentially reactive groups and gives access to chiral and achiral bidentate N-heterocyclic carbene ligands with *β*-amino alcohols, 8-amino quinoline, 2-aminophenol, and 2-aminopyridine derivatives as amine sources. The noteworthy feature is there is no need to protect the alcohol or pyridine groups.

We have scaled up the synthesis of a number of these ligands and are in the process of screening them against a variety of different reactions, both metal and nucleophilically catalyzed including asymmetric catalysis.

In summary, an approach to provide an expedient route to a variety of different N-heterocyclic carbene (NHC) ligands is presented. The key to this route is the use of a stable amino iodide salt that can then be reacted with a variety of different amines in the presence of triethylorthoformate. This potential one-pot method gives access to symmetrical, unsymmetrical, and chiral bidentate NHC ligands.

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

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