

Multicomponent Synthesis of Unsymmetrical Unsaturated N-Heterocyclic Carbene Precursors and Their Related Transition-Metal Complexes**

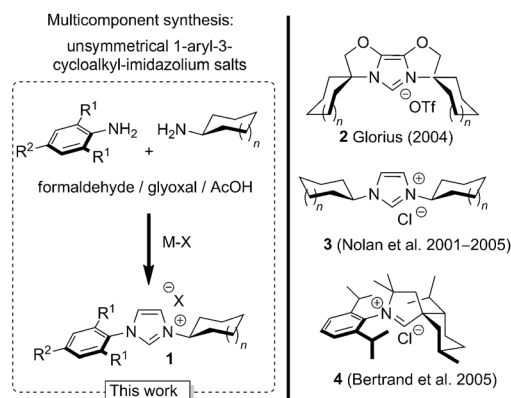
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Abstract: A low-cost, modular, and easily scalable multicomponent procedure affording access in good yields and excellent selectivity (up to 93 %) to a wide range of (a)chiral unsymmetrical 1-aryl-3-cycloalkyl-imidazolium salts is disclosed. Electronic and steric properties of the corresponding unsymmetrical unsaturated N-heterocyclic carbene (U_2 -NHC) ligands were evaluated and evidenced strong electron donor ability, high steric discrimination, and modular steric demand.

In the past two decades, N-heterocyclic carbenes (NHCs) have emerged as powerful ancillary ligands in transition-metal-based catalysis, mainly because of their large steric demand and strong σ -donor character.^[1] Structurally, while a plethora of unsymmetrical saturated NHCs (i.e. imidazolin-2-ylidene; chiral or achiral) have been prepared, the unsymmetrical unsaturated NHCs (i.e. imidazol-2-ylidene) have been drastically limited to trivial N-substituent moieties.^[2] In fact, access to their corresponding imidazolium salt precursors through the quarternization of N-substituted imidazoles were mainly restricted to simple alkyl halides; hindered alkyl or aryl halides are more problematic and often impracticable.^[3] In contrast, the straightforward, inexpensive and largely employed original one-pot procedure of Arduengo et al. appeared to be unsuitable for the synthesis of unsymmetrical imidazolium salts.^[4a,b] In fact, the combination of two different amines (e.g. methyl and *n*-propyl amines) with glyoxal and formaldehyde reacted unselectively and led to the statistical

2:1:1 mixture.^[4c] Unfortunately, and despite the later improvements which could be made by multistep strategies, the scope remained restricted to symmetrical salts.^[1c] In 2008, Fürstner and co-workers reported an elegant strategy for providing various unsymmetrical (a)chiral imidazolium salts having a wide variety of substitution patterns.^[5] Despite its efficiency and flexibility, numerous steps were required, and may limit its use for industrial applications. Furthermore, development of new unsaturated NHC ligands with unprecedented electronic and steric properties would afford access to distinct catalyst behaviors.^[1c] Given the above considerations, convenient methodologies allowing practical synthesis of unsymmetrical N,N'-disubstituted imidazolium salts bearing aryl groups and hindered alkyl groups remain highly desirable.

Herein, we disclose a low-cost, modular, and easily scalable multicomponent procedure leading to good yields and excellent selectivities for a wide range of (a)chiral unsymmetrical 1-aryl-3-cycloalkyl-imidazolium salts **1** (Scheme 1). NHC ligands incorporating a cycloalkyl moiety have recently proved beneficial in the cross-coupling



Scheme 1. Selected examples of NHC precursors bearing a cycloalkyl moiety (right) and synthetic route for the unsymmetrical 1-aryl-3-cycloalkyl imidazolium salts **1** (left). Tf = trifluoromethanesulfonyl.

of sterically demanding substrates because of the induced flexibility of their steric bulk and coordination mode.^[6] Moreover, for unsymmetrical cyclic alkyl amino carbenes (CAACs), wherein the flexibility is combined with a stabilizing bulky substituent, the resulting NHC units have remarkable behaviors.^[7] Therefore, with the dual objective of

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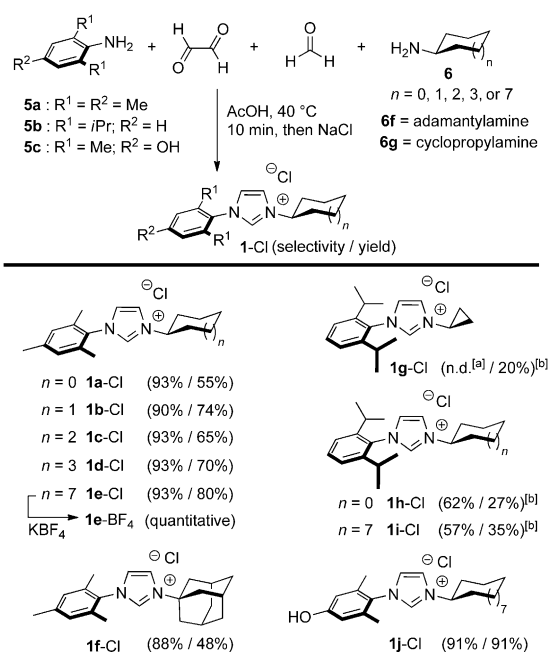
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characterizing and categorizing these unsymmetrical unsaturated NHC (U_2 -NHC) ligands, a large variety of transition-metal (TM) to ligand associations were employed to determine and evaluate the electronic and steric properties of the newly developed ligands.

The quaternization of aryl imidazoles with *sec*-alkyl halides is recognized as a difficult transformation. In fact, our initial attempts to react mesitylimidazole with various cycloalkyl halides failed, thus producing only cycloalkenes and the protonated imidazole after HX elimination. Therefore, we decided to re-investigate the one-pot protocol of Arduengo, involving anilines and cycloalkylamines, with the main objective to reach the exclusive formation of the expected 1-aryl-3-cycloalkyl-imidazolium salts **1**. After several attempts and optimization of the reaction conditions,^[8] we were delighted to observe the formation of the desired 1-mesityl-3-cyclododecyl imidazolium salt **1e-Cl** with high selectivity (93%). Straightforwardly, mesitylamine (**5a**), cyclododecylamine (**6e**), glyoxal, and formaldehyde were mixed in the presence of acetic acid and stirred at 40 °C for few minutes. Subsequent treatment with NaCl and simple precipitation in EtOAc, afforded the imidazolium salt **1e-Cl** in good yield (80%) and excellent purity (Scheme 2).^[9] This protocol was then extended to a variety of cycloalkylamines



Scheme 2. Synthesis of 1-aryl-3-cycloalkyl-imidazolium salts (**1a–h**). Selectivity was determined by ^1H NMR analysis of the crude reaction mixture. [a] Not determined (see the Supporting Information). [b] Performed at 90 °C.

and anilines. In the presence of mesitylamine (**5a**), the unsymmetrical products of the multicomponent reaction were isolated in good yields, ranging from 55% to 80%, and excellent selectivities (90 to 93%). Moreover, the polycyclic adamantylamine **6f** was efficiently employed in this strategy, thus affording the desired imidazolium salt **1f-Cl** with high selectivity and good yield upon isolation. Notably, this salt is

the unsaturated version of the popular unsymmetrical ligand precursor for *Z*-selective ruthenium-based olefin metathesis.^[10] Interestingly, the highly sterically congested 2,6-diisopropylaniline (**5b**), which is considered to be impractical in the original report of Arduengo et al.,^[4] successfully reacted under the present reaction conditions. Nevertheless, the selectivity did suffer from the increased steric bulk, thus affording up to 62% of the desired unsymmetrical imidazolium salt **1h-Cl** and no detectable amount of the 1,3-bis-(2,6-diisopropylphenyl)imidazolium salt (IPr precursor) in the crude reaction mixture. Importantly, this practical process is easily scalable to multigram scale without alteration of the yield (up to 60 g for **1e-Cl**). All these salts were fully characterized including X-ray diffraction studies of single crystals (Figure 1).^[11]

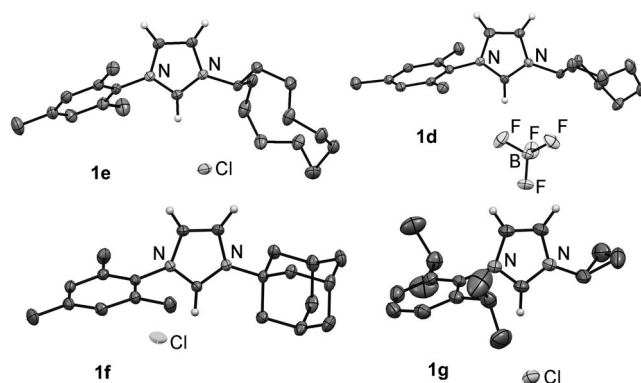
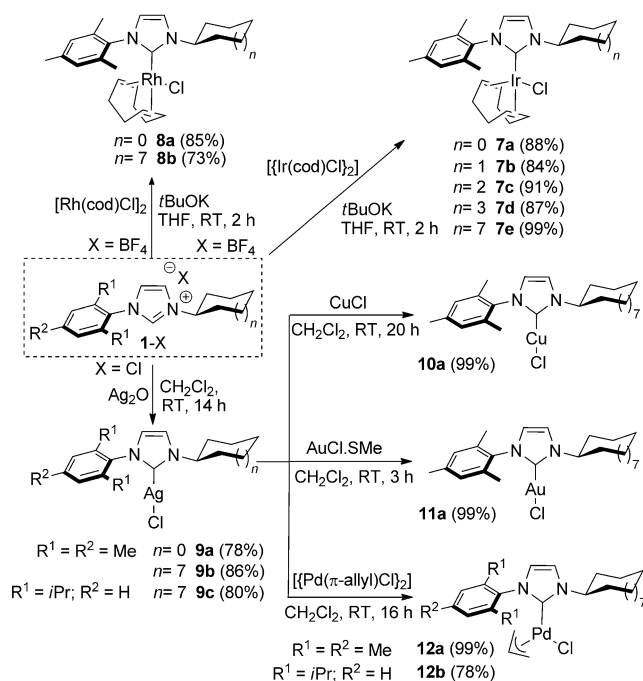


Figure 1. Selection of solid-state structures of 1-aryl-3-cycloalkyl-imidazolium salts from single-crystal X-ray diffraction. Most hydrogen atoms have been omitted for clarity.

Having these salts in hand, we then decided to form the corresponding transition-metal NHC complexes (Scheme 3). Firstly, deprotonation of the tetrafluoroborate salts **1a–e** with *t*BuOK in the presence of $[\text{Ir}(\text{cod})\text{Cl}]_2$ and $[\text{Rh}(\text{cod})\text{Cl}]_2$ afforded, with excellent efficiency, the desired NHC complexes **7** and **8**, respectively, in yields ranging from 73 to 99%. Secondly, the silver complexes **9a**, **9b**, and **9c** were isolated in 78, 86, and 80% yield respectively, after treatment of the imidazolium chlorides **1a**, **1e**, and **1i** with silver oxide. Finally, the transmetalation process involving the silver complex **9a** (or **9c**) and either copper, gold, or palladium salts produced the corresponding NHC complexes **10a**, **11a**, and **12a,b** in excellent yields (78–99%). From the structures, which were unambiguously confirmed by single-crystal X-ray diffraction studies (Figure 2),^[11] examination of the electronic and steric properties of the newly developed unsymmetrical unsaturated NHCs were initiated.^[12]

To measure their electron-donor ability, the $[\text{IrCl}(\text{CO})_2\text{NHC}]$ complexes **13a–e** were synthesized from the complexes **7** and allowed measurement of the average IR stretching frequency of the carbonyl ligands (Scheme 4). According to their calculated Tolman electronic parameter (TEP),^[13] 1-mesityl-3-cycloalkyl-imidazol-2-ylidene ligands display similar electron richness (TEP ranged from 2050.5



Scheme 3. Synthesis of 1-aryl-3-cycloalkyl-imidazol-2-ylidene transition-metal complexes. cod = cyclo-1,5-octadiene.

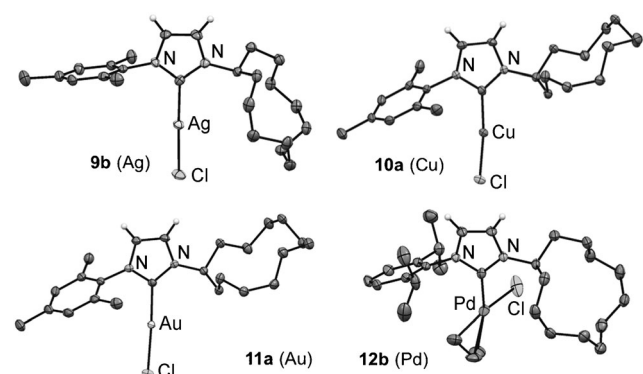
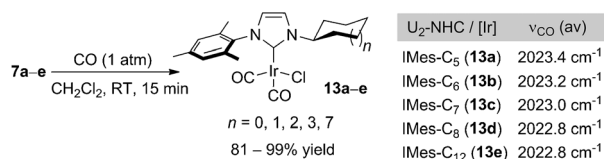


Figure 2. Selection of solid-state structures of 1-aryl-3-cyclododecyl-imidazol-2-ylidene transition-metal complexes from single-crystal X-ray diffraction. Most hydrogen atoms have been omitted for clarity.



Scheme 4. Average IR stretching frequency [$\nu_{\text{CO}}(\text{av})$].

to 2051.0 cm^{-1}) to that of the standard symmetrical diamino-carbenes **14–17** (Figure 3).^[12,14]

The steric properties also play an important role in influencing the catalytic activity of NHC/TM complexes.^[6] Therefore, for the NHC ligand in complexes **9b**, **10a**, and **11a**, we calculated the corresponding percent buried volume ($\%V_{\text{Bur}}$) using the geometry from single-crystal X-ray anal-

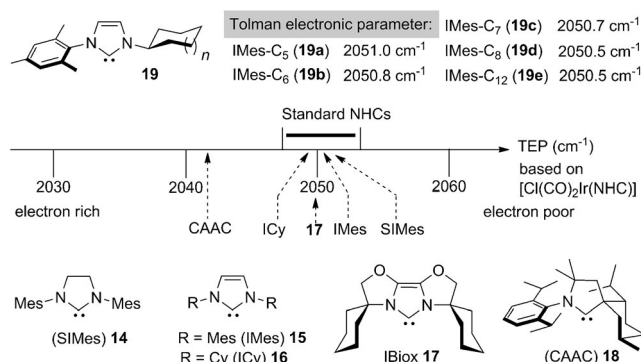


Figure 3. Electronic properties of unsymmetrical 1-mesityl-3-cycloalkyl-imidazol-2-ylidene based on TEP.^[10]

yses.^[15] The resulting $\%V_{\text{Bur}}$ for **10a** (33.6) and **11a** (34.5), which have the cyclododecyl substituent pointing away from the metal, indicated that, despite the presence of the large cycloalkyl group, the overall steric demand is slightly less pronounced than that of the previously reported symmetrical Cu-**15** and Au-**15** analogues (36.3 and 36.5, respectively).^[12] In contrast, for **9b**, which presents the cyclododecyl substituent pointing towards the metal, the overall steric demand (37.6) is more pronounced than that of IMes in the **15**-AgCl complex (36.1).^[12] Interestingly, the steric map views presented in Figure 4 evidenced the high steric discrimination between the

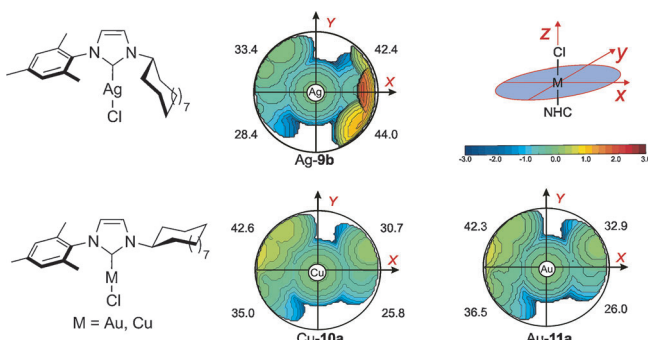
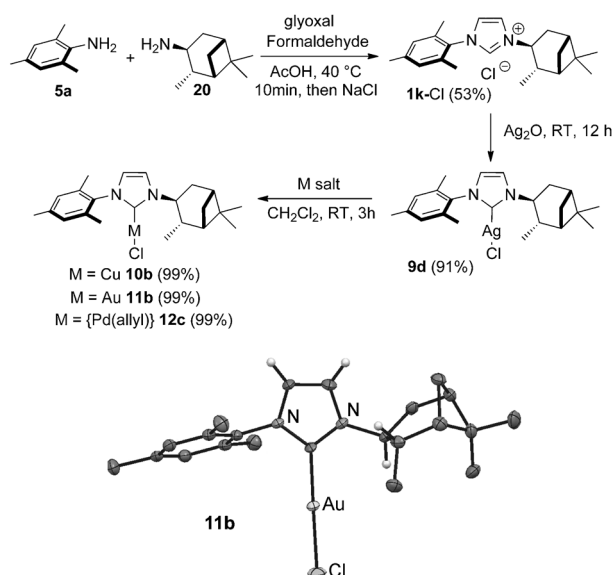


Figure 4. Steric map views of the 1-mesityl-3-cyclododecyl-imidazol-2-ylidene transition-metal complexes **9b**, **10a**, and **11a**.^[14]

flexible aliphatic and bulky aromatic groups and outlined the unsymmetrical environment around the metal center.^[16] Moreover, the difference in conformation observed between **9b** and **11a** demonstrated the highly modular steric demand of U₂-NHC ligands, having a cycloalkyl group which could either shield or liberate a face of the metal center. Therefore, monodentate unsymmetrical 1-aryl-3-cycloalkyl-imidazol-2-ylidene NHCs are able to combine high steric discrimination and flexibility, which is in contrast to traditional C₂-symmetric diaminocarbene ligands.

To demonstrate the broad potential of the described multicomponent procedure, a low-cost synthesis of a new chiral imidazolium salt was considered. With the exception of the multistep procedure reported by Fürstner et al.,^[5] bulky chiral imidazolium salts are only accessible with C₂-symmetry,

which consequently limits electronic and steric modularity of the corresponding chiral NHC ligands and their resulting metal catalysts. As illustrated by the increased interest for chiral monodentate NHC ligands in the recent literature,^[1b,16c] access to new ligand structure is highly desirable. As depicted in Scheme 5, the chiral imidazolium salt **1k-Cl** was success-



Scheme 5. Synthesis of chiral unsymmetrical 1-mesityl-3-isopinocampheyl-imidazol-2-ylidene transition-metal complexes **9d**, **10b**, **11b** (X-ray structure), and **12c** from (+)-isopinocampheylamine (**20**).

fully synthesized in 53 % yield from (+)-isopinocampheylamine (**20**),^[17] a substitution pattern inaccessible by quaternization with a chiral alkyl halide. Subsequently, the silver complex **9d** was isolated in 91 % yield and converted quantitatively into the copper, gold, and palladium complexes (**10b**, **11b**, and **12c**). The structure of 1-mesityl-3-isopinocampheyl-imidazol-2-ylidene gold (**11b**) was confirmed by single-crystal X-ray diffraction studies and evidenced the close proximity of the stereogenic fragment to the metal center, a prerequisite for future applications in enantioselective catalysis (Scheme 5).

To conclude, a straightforward multicomponent methodology has been developed for the synthesis of unsymmetrical unsaturated imidazolium salts from sterically congested anilines and cycloalkylamines. The modularity and the efficiency of this low-cost synthetic route affords access to a broad scope of NHC/metal complexes, which were employed in the evaluation of electronic and steric properties of the carbene ligands (TEP and %V_{bur}). U₂-NHCs displayed high steric discrimination between the flexible aliphatic and bulky aromatic groups and similarly strong σ -donor character relative to the standard symmetrical diaminocarbenes. The newly synthesized organometallics are currently under intensive investigation in our laboratory and their use in catalytic transformations will be reported in due course. It is envisioned that further applications should provide a better understanding of the structure–reactivity relationship associated with the newly developed U₂-NHCs.

Experimental Section

General procedure for the synthesis of chloride imidazolium salts **1a–e-Cl**: The reaction was performed in open vessel under air atmosphere. In a round-bottomed flask were placed 2,4,6-trimethylaniline (10 mmol, 1.0 equiv), cycloalkylamine (10 mmol, 1.0 equiv), and acetic acid (45 mmol, 4.5 equiv). The mixture was then stirred at 40 °C for 5 min (mixture A). In another round-bottomed flask were placed glyoxal (10 mmol, 1.0 equiv, 40 % wt in aqueous solution), formaldehyde (10 mmol, 1.0 equiv, 37 % wt in aqueous solution), and acetic acid (45 mmol, 4.5 equiv), a mixture which was then stirred at 40 °C for 5 min (mixture B). Mixtures A and B were rapidly combined and the resulting mixture was stirred at 40 °C for 10 min then cooled down to room temperature (the selectivity was determined by ¹H NMR analysis of the crude product). Dichloromethane (100 mL) was added and the organic layer was successively washed with water (200 mL) and brine (2 × 100 mL). The combined aqueous layers were extracted with dichloromethane (100 mL). The combined organic layers were dried over magnesium sulfate, filtered, and the volatiles were removed under reduced pressure. Ethyl acetate (20 mL) was added to the crude reaction mixture and the resulting suspension was heated to reflux then cooled down to 0 °C. The solid was filtered and washed with ethyl acetate (3 × 10 mL) then dried under reduced pressure to afford the expected unsymmetrical chloride imidazolium salt as a pale white solid.

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