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Synthesis of Electronically Diverse Tetraarylimidazolylidene Carbenes via Catalytic Aldimine Coupling

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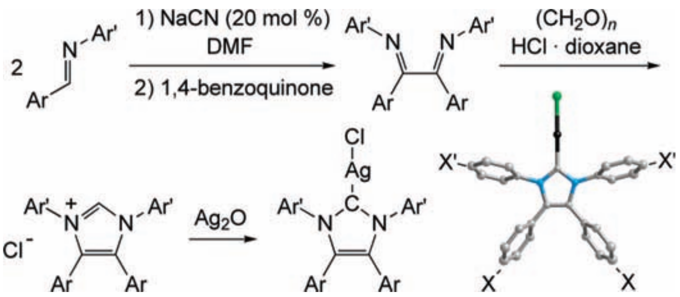
ABSTRACT



A new method for synthesizing symmetrical N-heterocyclic imidazolium salts is described. Catalytic coupling of aldimines with cyanide followed by oxidation gives α-diketimines, which can then be cyclized with formaldehyde in acidic media. This two-step procedure requires no chromatography and allows the synthesis of electronically diverse 1,3,4,5-tetraarylimidazolylidene carbenes.

The recent popularity of N-heterocyclic carbenes (NHCs) stems primarily from their utility as ancillary ligands (e.g., phosphine analogues) in organometallic complexes and as metal-free agents for organocatalysis.[1] Hundreds of free and metal-coordinated N-heterocyclic imidazolylidene carbenes have been reported, but 4,5-diaryl substituted heterocyclic imidazolylidene carbenes are relatively rare. One example is that reported by Arduengo et al., who synthesized the prototypical 1,3,4,5-tetraphenylimidazol-2-ylidene from 1,3,4,5-tetraphenylimidazol-2-thione.[2] Although some insights into the impact of 4,5-substituents have been reported,[3] improved synthetic methods for such carbenes are necessary for their comprehensive understanding.

Our group first demonstrated application of the *intra*molecular cyanide-catalyzed aldimine coupling reaction as a general route for making heterocycles.[4] Herein, we report the scope and generality of an *inter*molecular aldimine coupling reaction followed by cyclization with formaldehyde for preparing a wide variety of 1,3,4,5-tetraaryl substituted

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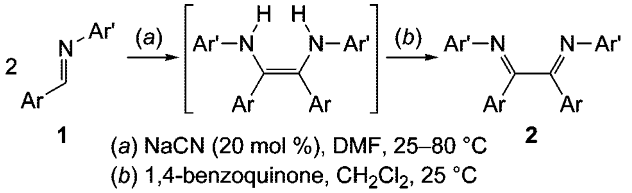
NHCs. Although the intermolecular cyanide-catalyzed aldimine coupling reaction of aromatic Schiff bases was first studied in 1928,[5] few reports since then have applied this reaction toward further synthesis. Our success with the intramolecular variant prompted us to further investigate more practical uses of cyanide-catalyzed aldimine coupling, and it soon became apparent that NHC synthesis could readily be accomplished by reviving the original intermolecular method. Somewhat related to our approach, Kison and Opatz have recently reported the synthesis of highly substituted unsymmetrical 1,2-diamines and 1,2-diimines via cross-coupling of α-aminonitriles with *N*-sulfonylimines—leading to imidazolium salts and imidazolylidenes.[6]

Our approach employing aldimine coupling reactions may be superior for preparing α-diketimine substrates because the corresponding α-diketones generally condense with the second amine equivalent only under rather stringent reaction conditions.[7] Furthermore, it is well-known that the cognate cyanide-catalyzed benzoin condensation is quite sensitive to the aromatic aldehyde substrates and further oxidation of benzoin to make α-diketone compounds requires relatively harsh conditions.[4a,8]

Sixteen aromatic aldimines with varying *C*-aryl and *N*-aryl substituents were prepared and subjected to cyanide-catalyzed C−C coupling conditions (Table 1, **1a**−**1p**). The aldimine substrates were combined with 20 mol % of NaCN catalyst in dry DMF, and the conversion to intermediate ene-diamines was monitored by ^{1}H NMR spectroscopy. Following subsequent oxidation with 1,4-dibenzoquinone, most substrates afforded the targeted diketimines (**2a**−**2h**, **2k**, **2l**, **2n**).

The results from Table 1 delineate the scope of the aldimine coupling strategy. The reaction is halted by the phenolic functionality (**1o**). Compounds **1i** and **1m** both gave a mixture of products, indicating that this methodology is intolerant of the nitro functionality. What little product that was observed in these reactions indicated that a mixture of cyanide addition products was likely produced, both with and without oxidation. Nonetheless, several electron-poor substrates reacted favorably, as demonstrated by **2c**, **2d**, **2f**, **2k**, and **2l**. The very electron-rich **1j** likely cannot form the initially required carbanion which is necessary to react in the benzoin condensation-like mechanism. This is consistent with diminished stability of the benzyl anion, generally thought to be the nucleophilic intermediate generated following cyanide addition to the aldimine and subsequent tautomerization.[9] In general, the reaction appears to work well for both electron-rich and electron-poor rings that are between the nitro and amino extremes but generally gives higher yields for electron-poor rings. Additionally, steric bulk tends to slow or stop the reaction, as demonstrated by the naphthyl (**1n**) and mesityl (**1p**) substrates.

Table 1. Cyanide-Catalyzed Aldimine Coupling Reactions to Prepare Symmetrical α-Diketimines[a]



entry	Ar	Ar′	temp (°C)	time (h)	yield (%)[b]
1a	Ph	Ph	25	24	54
1b	4-MeC$_6$H$_4$	Ph	25	40	78
1c	4-FC$_6$H$_4$	Ph	25	20	67
1d	4-CF$_3$C$_6$H$_4$	Ph	25	20	65
1e	4-MeOC$_6$H$_4$	Ph	25	24	57
1f	Ph	4-FC$_6$H$_4$	25	22	51
1g	4-MeC$_6$H$_4$	4-MeC$_6$H$_4$	80	36	40
1h	Ph	4-MeOC$_6$H$_4$	80	24	28
1i	4-NO$_2$C$_6$H$_4$	Ph	25	24	-[c]
1j	4-NMe$_2$C$_6$H$_4$	Ph	80	120	-[d]
1k	4-CF$_3$C$_6$H$_4$	4-MeC$_6$H$_4$	25	18	31
1l	4-CF$_3$C$_6$H$_4$	4-MeOC$_6$H$_4$	25	24	55
1m	4-MeC$_6$H$_4$	4-NO$_2$C$_6$H$_4$	80	48	-[c]
1n	1-naphthyl	Ph	25	24	9[e]
1o	2-OH,3-MeOC$_6$H$_3$	4-MeC$_6$H$_4$	25	24	-[d]
1p	Ph	2,4,6-Me$_3$C$_6$H$_2$	25	24	0

[a] The reaction was conducted under N$_2$; the crude coupling product was isolated first then oxidized with 1,4-benzoquinone (see the Supporting Information). [b] Isolated yield. [c] Imine starting materials were unreactive; some unidentified products were produced. [d] Trace amount of reaction (<5%) observed by ^{1}H NMR; no isolation was attempted. [e] The NMR yield at about 90% purity was 30%; starting material could not efficiently be removed from the product by crystallization.

Although Becker discussed the effect of reaction conditions on the aldimine coupling reaction in 1970,[9b] his principal characterization method was fluorescence spectroscopy. Our studies allow additional understanding since NMR readily shows the intermediates that form before oxidation and more conclusively quantifies the products. While the initial ene-diamine coupling products were claimed by Becker to be oxidized easily in air,[9b] **1a** in DMF with 20% NaCN under dry air—employing a variety of temperature and solvent conditions—for 24 h resulted in, at most, a 9:1 mixture of ene-diamine to α-diimine. 1,4-Benzoquinone was found to be a competent oxidant for converting the ene-diamines to α-diimines; for example, one equivalent (relative to **1a**) provided the diimine **2a** within minutes (monitored by NMR), while simply stirring the reaction open to air afforded **2a** in only 50% yield after 24 h. 1,4-Benzoquinone failed as an in situ oxidant to convert the ene-diamine to diimine—apparently because of unwanted reaction with sodium cyanide. However, we found that simple dilution of the reaction mixture with dichloromethane followed by extraction with water is sufficient to remove NaCN and DMF, which allowed us to skip isolation of the ene-diamine intermediate.

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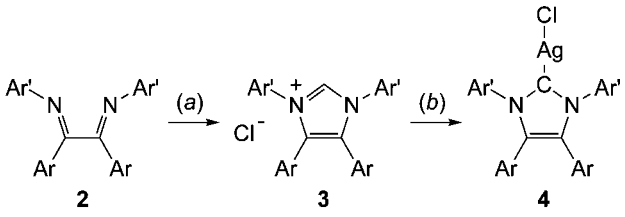
Our results are consistent with Becker's conclusion that DMF is a good solvent for aldimine coupling. Our previous study on the ring-closing of dialdimines to form heterocycles showed that *intramolecular* aldimine coupling also performs well in MeOH or the biphasic CH_2Cl_2/H_2O system using Bu_4NI as a phase transfer agent. Ethanol is a common solvent for the benzoin reaction; however, no *intermolecular* aldimine coupling could be achieved using NaCN in alcohols or in the biphasic $CH_2Cl_2/H_2O/Bu_4NI$ system for those substrates attempted (**1a** and **1g**). For several substrates (**1a**, **1c**, **1e**, and **1g**), the reaction was sensitive to air, water, (including wet DMF not previously dried over $MgSO_4$), or even residual MeOH—lowering the yield or altogether preventing reactivity. Alternative solvents were not explored for the remaining substrates.

As imidazolium salts are important precursors for NHC synthesis, several different procedures have been reported for converting α-diimines to imidazolium salts. Arduengo[10] originally reported a strategy for cyclizing α-diimines with formaldehyde equivalents which has been fruitful in generating a variety of imidazolium salts. From the diimines **2a**−**2h**, we modified Noels' procedure[11] (based on Arduengo's strategy) to prepare imidazolium chlorides by reaction with paraformaldehyde and anhydrous HCl. Our yields, albeit low, are similar to those previously reported via this method (Table 2). The imidazolium salts **3a**−**3h** have been synthesized, purified, and fully characterized by NMR, mass spectrometry, and, in the case of **3d**, single-crystal X-ray analysis (see the Supporting Information).

Table 2. Formation of Tetraarylimidazolium Salts and Tetraaryl N-Heterocyclic Silver Carbenes



(*a*) $(CH_2O)_n$, HCl · dioxane, toluene, 40 °C
(*b*) Ag_2O, CH_2Cl_2, 40 °C

entry	**2**→**3** time (h)	yield **3** (%)[a]	δ ^{1}H **3** CH[b]	yield **4** (%)[a]	Ag−C (Å)[c]
a	12	22	10.81	80	2.079
b	18	33	10.85	-	-
c	18	12	9.85	75	2.087
d	18	16	9.78	-	-
e	12	32	10.58	55	2.051
f	18	33	10.88	88	2.070
g	36	29	10.63	-	-
h	24	31	10.58	80	2.079

[a] Isolated yields. [b] ^{1}H NMR shift of the imidazolium ring proton. [c] Determined by X-ray crystallography (see the Supporting Information).

NHCs can be directly prepared by deprotonation of the imidazolium chloride salt with KO^{t}Bu using the typical method reported in the literature.[10−12] Free carbene compounds from **3b** and **3e** have thus been prepared and characterized by ^{1}H and ^{13}C NMR spectroscopy. The carbene carbons can be verified with peaks resonating around 220 ppm in the ^{13}C NMR spectra.

Alternatively, the imidazolium chloride salts can be directly transformed into the silver(I) chloride carbene species by refluxing with silver oxide in methylene chloride. Silver carbene complexes **4a**, **4c**, **4e**, **4f**, and **4h** were targeted for synthesis because of their electronically diverse substituents. These complexes were prepared and isolated as colorless needles which are neither air nor moisture sensitive. X-ray crystallography confirmed the anticipated structures, and these are illustrated in Figure 1.

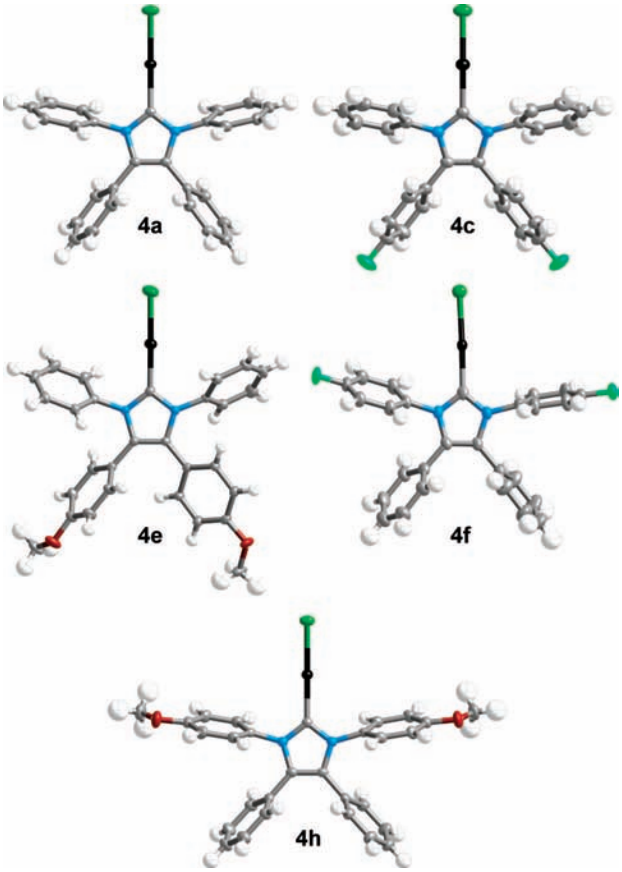


Figure 1. Silver carbene complexes **4a**, **4c**, **4e**, **4f**, and **4h** depicted with 50% probability ellipsoids.

Although silver NHCs are useful for transmetalation to generate other organometallic species, they have few inherent uses.[13] We sought a catalytically active system bearing classical NHCs that could be modified to include our novel carbenes for comparative investigations. Both the electronic

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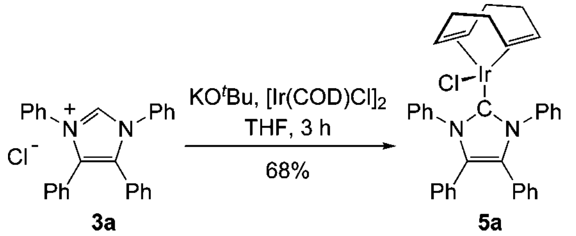
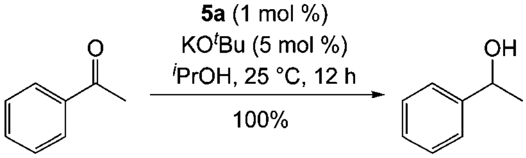
and steric characteristics of Ir(1,5-cyclooctadiene)NHC systems have been very extensively studied in the literature in recent years by Crabtree and Nolan.[3,14] Routes to generate these species are also well established. Scheme 1 shows our initial strategy to generate the complexes parallel to the method of Crabtree. Our preliminary studies have shown that we can synthesize iridium complex **5a** in 68% yield—importantly, with no chromatographic isolation steps.

Scheme 1. Strategy for the Synthesis of Ir(COD)NHC Chloride Complexes from Imidazolium Salts



The catalytic activity of iridium NHC complexes is well-known.[15] One of the simplest systems for assessing catalytic activity is transfer hydrogenation.[16] In the application of **5a**, we have found very good catalytic activity in the transfer hydrogenation of acetophenone to α-hydroxyethylbenzene (Scheme 2), as 100% conversion is obtained in 12 h and, separately, a turnover frequency (TOF) of 41 h^{-1} is obtained in the first hour. This compares well with most iridium NHC complexes, although some are known to have a TOF of 150−174 h^{-1} for acetophenone.[17] However, the comparison is notably more favorable considering that our procedure is rather simple. It does not require heating (to 80 °C) or dynamic removal of acetone. Also, our catalyst has the longevity to attain 100% conversion, whereas catalyst mortality has limited most previous efforts to about 70−90% conversion.

Scheme 2. Initial Studies of Transfer Hydrogenation Using Ir[COD](tetraphenylNHC) Chloride (**5a**)



In conclusion, we have extended our intramolecular cyanide-catalyzed aldimine coupling strategy to the intermolecular coupling of several readily available, electronically variable diarylaldimines. The functional group tolerance of this reaction was fairly broad and has allowed the synthesis of a novel family of electronically diverse tetraarylimidazolylidene carbenes. The silver chloride carbenes are readily generated as air-stable compounds. In addition, metalation of the imidazolium salts is facile and can form catalytically useful iridium NHC complexes, which we have applied to transfer hydrogenation reactions. Future work will assess the importance of the carbene electronic tunability on this and other homogeneous catalytic reactions.

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Supporting Information Available: Synthetic details, NMR spectra, and X-ray structural data (CIF files) for **3d**, **4a**, **4c**, **4e**, **4f**, and **4h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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