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A Benzimidazole-Based *N*-Heterocyclic Carbene Derived from 1,10-Phenanthroline

Costa Metallinos,* Fred B. Barrett, Jennifer L. Chaytor, and Mary E. A. Heska

Department of Chemistry, Brock University, 500 Glenridge Avenue,
St. Catharines, Ontario L2S 3A1, Canada

metallic@brocku.ca

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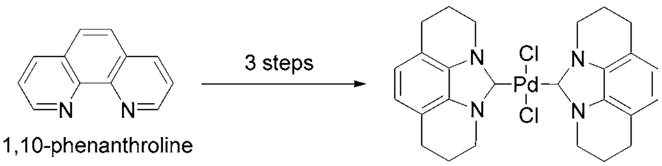
ABSTRACT



A catalytically active palladium-complexed tetracyclic *N*-heterocyclic carbene (NHC) was prepared in three steps from commercially available 1,10-phenanthroline by using a reduction–cyclization–deprotonation sequence. The new carbene framework is a prototype for the development of a series of chiral *N*-heterocyclic carbenes.

Substituted 1,10-phenanthrolines have a rich history as ligands for transition-metal catalysis.[1,2] The majority of such compounds reported to date retain the full aromatic backbone of 1,10-phenanthroline (**1**) (Figure 1). Much less attention has been directed toward the use of the partially reduced 1,2,3,4-tetrahydro-[3] (**2**) or 1,2,3,4,7,8,9,10-octahydro-1,10-phenanthrolines (**3** and **4**) as precursors for new ligands[4] such as benzimidazole-based *N*-heterocyclic carbenes (NHCs).[5] Previous NHCs with benzimidazole backbones, or their derived metal complexes,[6] have contained pendant acyclic substituents such as achiral[7] and chiral[8−10] alkyl groups (**5** and **6**) or the ferrocene moiety[11] (**7**) adjacent to the nitrogen

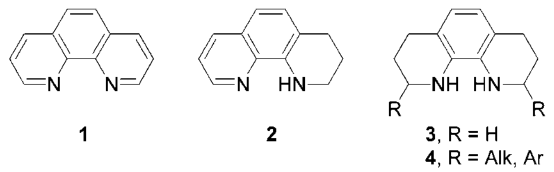


Figure 1. 1,2,3,4,7,8,9,10-Octahydro-1,10-phenanthrolines (**3** and **4**) as a framework for chiral and achiral ligands.

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* To whom correspondence should be addressed.

[1] Review: Schoffers, E. *Eur. J. Org. Chem.* **2003**, 1145.

[2] For a recent example, see: Zhou, J.; Fu, G. C. *J. Am. Chem. Soc.* **2004**, *126*, 1340.

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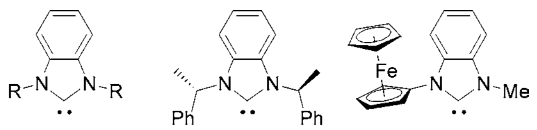


5a, R = Me
5b, R = CH_2t-Bu
6
7

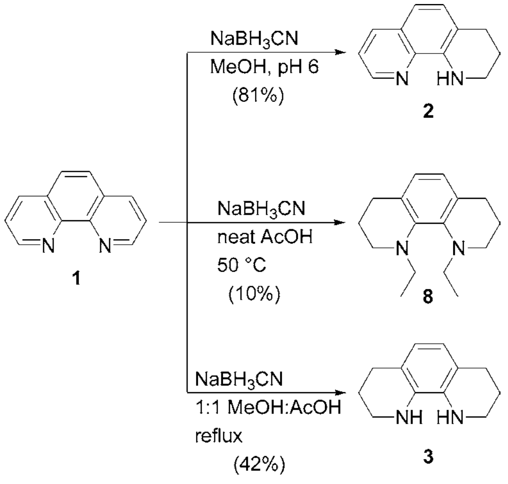
Figure 2. Examples of benzimidazole-based *N*-heterocyclic carbenes.

atoms (Figure 2). These substituents have typically been installed via aryl amination[8] or amidation chemistry[11] (**6** and **7**) or by direct *N*-alkylation[7,9] of benzimidazoles (**5**).

As part of a program aimed at ligand synthesis in our laboratory, we envisioned that 1,2,3,4,7,8,9,10-octahydro-1,10-phenanthroline (**3**, R = H), prepared by reduction of the pyridyl rings of 1,10-phenanthroline, could serve as a versatile precursor for a new class of benzimidazole-based NHCs (Figure 1). The successful preparation of such a compound would stimulate the development of chiral analogues with stereogenic centers α to the nitrogen atoms of reduced 2-substituted and 2,9-disubstituted phenanthrolines (**4**).[12] It is anticipated that the greater rigidity afforded by the structural motif exemplified by **3** will lead to useful reagents for asymmetric transformations for subsequent chiral derivatives.

Our proposed *N*-heterocyclic carbene synthesis required a reasonable quantity (0.5−2 g) of 1,2,3,4,7,8,9,10-octahydro-1,10-phenanthroline **3** being prepared (Scheme 1).

Scheme 1. Alternate Preparation of 1,2,3,4,7,8,9,10-Octahydrophenanthroline



Although several methods are known for the preparation of 1,2,3,4-tetrahydro-1,10-phenantholine (**2**) in moderate to good yields,[3] to the best of our knowledge, only two reports have appeared regarding the preparation of the octahydro derivative (**3**). The first of these used borane reduction of 1,10-phenanthroline, giving a mixture of **2** and **3** in low (<10%) combined yield.[13] The second method employed high pressure and high-temperature hydrogenation of **1** with Raney nickel[14] [27.6 bar (400 psi), 100 °C for 36 h], providing **3** in 92% yield. We wished to explore a milder set of conditions with which to prepare **3**. Previous reductions of 1,10-phenanthroline to the tetrahydro derivative (**2**) have used borohydrides such as $Zn(BH_4)_2$ under sonication[15] or $NaBH_3CN/BF_3{\cdot}OEt_2$ under anhydrous conditions,[16] which gave **2** in 80% and 70% yields, respectively. We thought it should be possible, with appropriate modification of these procedures, to elicit more complete reduction of **1**−**3**.

Initial experiments ($NaBH_3CN$, MeOH, pH 6) led only to isolation of **2** (Scheme 1). Addition of more $NaBH_3CN$ failed to advance the reduction to the desired octahydro product (**3**). Further reduction of **2** was likely hampered by the generation of the more basic piperidine-like nitrogen atom, and the acidity of the medium was insufficient to protonate the remaining aromatic nitrogen, a requirement in reductions of π-deficient pyridyl rings.[17−19] Performing the reaction in glacial acetic acid[20] as solvent would ensure the double protonation of nitrogens in tetrahydro intermediate **2**, allowing the reduction to continue. Although this set of conditions did initially form octahydro **3**, the product surprisingly reacted further, undergoing diethylation with concomitant decomposition to give the undesired *N1,N10*-diethyl-2,3,4,7,8,9-hexahydrophenanthroline (**8**) as the only isolable product in low 10% yield.[21] In an effort to disfavor the side reaction of **3** with acetic acid, we diluted the reaction mixture with methanol. Thus, subjection of 1,10-phenanthroline to $NaBH_3CN$ reduction in 1:1 MeOH and glacial acetic acid[22] at reflux provided the desired product **3** in a modest, but useable, 42% yield after purification.[23] This reduction process is operationally simple in that it can be

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(19) For reductions of *N*-alkylpyridinium salts, see: (a) Wenkert, E. *Acc. Chem. Res.* **1968**, *1*, 78. (b) Liberatore, F.; Carelli, V.; Cardellini, M. *Tetrahedron Lett.* **1968**, *9*, 4735. (c) Hutchins, R. O.; Natale, N. R. *Synthesis* **1979**, 281. (d) Lavilla, R.; Gotsens, T.; Gullón, F.; Bosch, J. *Tetrahedron* **1994**, *50*, 5233. (e) McCullough, K. J.; MacTavish, J.; Proctor, G. R.; Redpath, J. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2553.

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(21) For a similar reductive ethylation with $NaBH_4$ in AcOH, see: Gribble, G. W.; Lord, P. D.; Skotnicki, J.; Dietz, S. E.; Eaton, J. T.; Johnson, J. *J. Am. Chem. Soc.* **1974**, *96*, 7812.

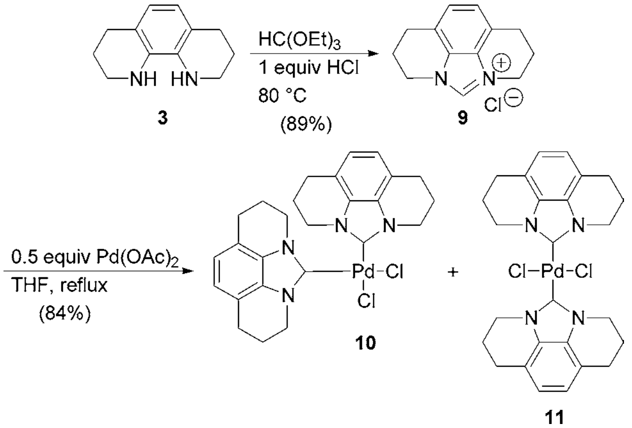
(22) The use of proportionately less acetic acid (e.g., 5:2 MeOH/AcOH) gave the undesired tetrahydro product **2**.

(23) With regards to the use of $NaBH_4$ or $NaBH(OAc)_3$ for the preparation of **3**, results indicate that $NaBH_4$ is an inferior reducing agent to $NaBH_3CN$ in this reaction. The reaction stops at the stage of tetrahydro product **2**, even under prolonged heating and with excess reagent. Since it is reasonable to assume that $NaBH(OAc)_3$ is produced in situ under the reaction conditions, this reagent can also be ruled out as an effective alternative to $NaBH_3CN$ for this process. Reactions performed in neat acetic acid were found to be difficult to control and stop at product **3**. Oftentimes, **3** completely vanished from the reaction mixture (NMR monitoring) to give a large number of unidentifiable products, of which only **8** could be identified concretely after purification.

performed in air, requires no hydrogenation equipment, and can be scaled up without difficulty.

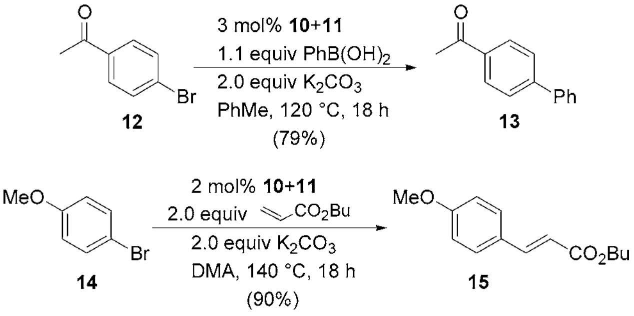
With diamine **3** in hand, we turned our attention to cyclization and NHC preparation. Treatment of **3** with neat triethyl orthoformate[8] containing 1 equiv of HCl provided the key tetracyclic benzimidazolium chloride **9** in 89% yield (Scheme 2). To test the propensity of **9** to act as a carbene ligand precursor, it was heated with 0.5 equiv of Pd(OAc)$_2$[11] (THF, reflux, 1 h). The reaction mixture underwent a distinct color change from orange to light gray, from which a pale gray precipitate was collected. NMR and mass spectral analysis confirmed the formation of palladium complexes **10** and **11** as a 1:1 mixture of cis and trans coordination isomers,[24] isolated in 84% yield.[25]

Scheme 2. Synthesis of Tetracyclic Benzimidazolium Chloride **9** and NHC Palladium Complexes **10** and **11**



Preliminary experiments have revealed that **10** + **11** is an active catalyst for C−C bond-forming reactions such as Suzuki−Miyaura and Heck couplings.[26] Subjection of 4-bromoacetophenone **12** to Suzuki−Miyaura coupling with phenylboronic acid in the presence of 3 mol % of **10** + **11** (K$_2$CO$_3$, PhMe, 120 °C, 18 h) gave biphenyl **13** in good 79% yield (Scheme 3). Alternatively, the more electron-rich 4-bromoanisole **14** reacts smoothly with butyl acrylate (2 mol % **10** + **11**, K$_2$CO$_3$, DMA, 140 °C, 18 h) to provide cinnamate **15** in excellent 90% isolated yield.

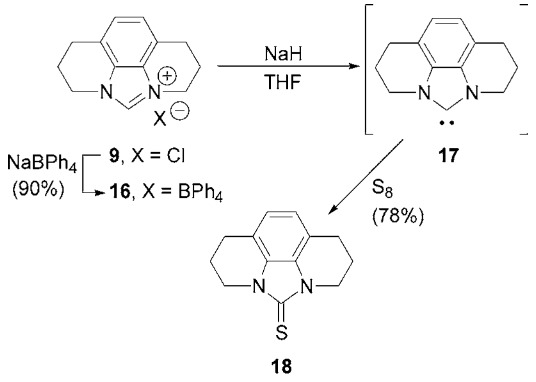
Scheme 3. Carbon−Carbon Bond-Forming Reactions Catalyzed by **10** + **11**



Previous benzimidazolium salts have been shown to serve as precursors to stable free carbenes via deprotonation when sufficiently bulky substituents are present on the nitrogens[7,8] (**5b**, **6**, Figure 2). Such NHCs are persistent under anhydrous conditions and typically display ^{13}C NMR chemical shifts near δ 224−231[7,8] for the carbenoid carbon. In contrast, benzimidazolium salts with smaller *N*-methyl substituents (**5a**) have a propensity to dimerize[7,27,28] to the corresponding alkenes upon deprotonation. An exception to this is the *N*-methyl-*N*-ferrocenyl NHC **7** which, although it could not be characterized as the "free" carbene and did not show a tendency to dimerize, could be trapped with elemental sulfur to give the corresponding thiourea in a reaction typical of NHCs.[11]

To prepare a stable free carbene from **9**, the Cl$^-$counterion was exchanged for BPh$_4^-$ (**16**) to improve solubility. Given the range of stabilities of previous benzimidazolium-derived NHCs, it was difficult to predict on the basis of steric or electronic factors which of the three preceding types of NHC (**5a**, **6**, or **7**) that compound **16** would behave like. Subsequent experiments revealed that the "free" NHC **17**, generated by treatment of **16** with KO-*t*-Bu or NaH in THF (Scheme 4), was too unstable to characterize by ^{1}H and ^{13}C NMR in THF-d_8. However, sequential deprotonation of **16** (NaH, THF, 1 h) followed by addition of elemental sulfur delivered the thiourea **18** in 78% yield. These results indicate that the tetracyclic NHC **17** closely resembles the behavior of *N*-ferrocenyl NHC **7**, both in the instability of its "free" carbene and in its lack of tendency to dimerize.

Scheme 4. Trapping of NHC **17** with Sulfur To Give Thiourea **18**



Current studies are underway to crystallographically characterize complexes **10** and **11**, as is the preparation of chiral

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(25) Compounds **10** and **11** are not separable by chromatography. *cis*-**10** is configurationally stable and does not isomerize to **11** even after prolonged heating (130 °C, 4 days) in DMSO-d_6, as determined by periodic ^{1}H NMR monitoring. No change in the ratio of **10**/**11** was observed over this period.

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versions of **9**, including those derived from C_2-symmetric reduction products of 2,9-disubstituted phenanthrolines (**4**, e.g., neocuproine, R = Me). The greater rigidity of these NHCs afforded by the tetracyclic benzimidazole framework exemplified by **9** is anticipated to provide useful ligands and reagents for asymmetric synthesis. The results of these studies will be reported in due course.

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Supporting Information Available: Experimental procedures for **3**, **9**−**11**, **13**, **15**, **16**, and **18** and characterization data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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