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Synthesis and Isolation of a Stable, Axially-Chiral Seven-Membered *N*-Heterocyclic Carbene

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Abstract

A chiral seven-membered *N*-heterocyclic carbene (NHC) has been synthesized from its phenol adduct (NHC-HOPh) by a novel base-induced α -elimination method, and its donor strength has been determined from the IR stretching frequencies of the NHC-Rh(CO)₂Cl complex.

Stable *N*-heterocyclic carbenes (NHCs) have received considerable attention in recent years, and they have found widespread use in catalysis. NHCs are versatile ancillary ligands for transition-metal catalysts,¹ and they also serve as effective nucleophilic catalysts.² The development of new chiral NHCs for use in asymmetric catalysis remains an important challenge in this field.³ Recent efforts in our laboratory have targeted a new class of NHCs that feature an axially chiral seven-membered heterocyclic framework derived from 2,2'-diaminobiphenyl (**A**).^{4,5} These seven-membered NHCs are unique from other known 4-,⁶ 5-,¹ 6-,^{7,8} and 7-membered⁹ NHCs because of the significant torsional twist induced by the conformationally-constrained biaryl backbone. Here, we present a synthetic approach that provides access to the first stable free carbene of the type **A**, together with data describing the donor properties of this NHC.

We originally envisioned that the seven-membered NHCs **A** could be obtained directly from the corresponding amidinium salts **B**. Several Ag and Pd complexes were prepared by insitu deprotonation of the seven-membered amidinium salts in the presence of suitable metal precursors (e.g., eqn 1).⁴ These results have enabled preliminary investigation of these ligands in catalytic applications,¹⁰ but the scope of metal complexes accessible by this protocol has proven to be limited. Moreover, this route did not provide access to the free carbene. These limitations prompted us to explore alternative routes to the free carbene. The studies presented below reveal differences in chemical reactivity between the seven-membered rings **A** and **B** vis-à-vis the more traditional five-membered *N*-heterocycles.

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(1)

Free NHCs are generally synthesized by combining a strong base, usually KOtBu , with an amidinium salt,¹ resulting in direct formation of the free 5-membered NHC when imidazolium precursors are used. Reaction with the saturated imidazolidinium salts, however, often yields the alcohol adduct of the carbene, NHC-HOR , which may be thermolyzed to afford the free NHC and HOR.¹¹ Other bases or base combinations (e.g. KHMDs , NaH and catalytic KOtBu) have also been used.¹ The direct-deprotonation protocol recently was successfully applied to the synthesis of seven-membered NHCs that exhibit greater conformational flexibility relative to **A**.⁹ With our seven-membered amidinium salts (**B**), however, none of the known direct-deprotonation conditions resulted in formation of the free NHC, and the only bases that led a single product were alkoxides, which produced the NHC-HOR complexes **3OR** (eqn 2).⁴ Unlike 5-membered NHCs, the alcohol adducts **3OR** did not afford the free NHC upon thermolysis.¹¹ The origin of the different reactivity is not clear, but the torsional twist of the seven-membered heterocyclic framework may destabilize the free carbene relative to the alcohol adduct. The synthetic inaccessibility of free NHCs of the type **A** using traditional routes indicated that a new strategy was needed for preparation of the free NHC.

(2)

The base-induced elimination of HCl from chloroform to yield dichlorocarbene has been known for many years.¹² To our knowledge, a similar approach has never been employed for the synthesis of free NHCs. We speculated that the free carbenes might be accessible from the alcohol adducts **3OR** via such a base-induced α -elimination pathway. We investigated the use of bases anticipated to be strong enough to deprotonate the alcohol adduct and induce the expulsion of alkoxide. Initial studies were promising, but only partially successful. For example, reaction of amidinium salt **2** with a slight excess of NaOMe (1.35 equiv) in dry Et_2O afforded **3OMe** in quantitative yield. Addition of $n\text{-BuLi}$ to the crude reaction product (i.e., with some unreacted NaOMe remaining in solution) led to partial formation of the free NHC **4**, evident by ^1H NMR spectroscopy (eqn 3). The yields obtained with this protocol were highly variable, however, ranging from <10 –71 %. When $n\text{-BuLi}$ was added to a purified

sample of **3^{OMe}** in Et₂O (i.e., with no NaOMe present in solution), no reaction was observed. These results suggested that use of a “superbase”, consisting of a mixture of alkyl lithium reagent and alkali metal alkoxide,¹³ might be needed to induce the elimination of methoxide. Use of more traditional superbase conditions,¹³ however, did not afford the free NHC. As an alternative strategy, we decided to test the reactivity of **3^{O^{Ph}}** because phenoxide should be a better leaving group than methoxide in the elimination reaction. The phenol adduct **3^{O^{Ph}}** was prepared by addition of NaOPh to **2** in Et₂O. Subsequent addition of *n*-BuLi to a purified sample of **3^{O^{Ph}}** in pentane afforded the free NHC **4** in 87% yield (eqn 4). This complex was crystallized from benzene, and its structure was established by X-ray crystallography (Figure 1).

(3)

(4)

The seven-membered carbene **4** features similar average N–C_{NHC} bond lengths to other common NHC ligands (1.362 Å in **4**, 1.374 Å in IMes,[‡] and 1.359 Å in Richeson’s 6-membered NHC (Table 1, entry 4)). However, the average N–C_{NHC}–N angle changes significantly from IMes to **4** to the 6-membered NHC (Table 1, entry 4): 101.4°, 112.8°, and 115.3°, respectively.

Access to free carbenes of this type should significantly expand the utility of these molecules as ligands. For example, previous efforts to prepare the NHC–Rh complexes via in situ deprotonation of the amidinium salt **2** were unsuccessful; however, addition of **4** to [(Rh(COD)(μ-Cl))₂ (COD = 1,5- cyclooctadiene) in THF afforded the air- and moisture-stable (NHC)Rh(COD)Cl **5** (Scheme 1). The latter complex was readily converted to the corresponding Rh-dicarbonyl complex **6** in the presence of 4 atm of CO.

Synthesis of *cis*-(NHC)Rh(CO)₂Cl **6** provides the opportunity to evaluate the electronic properties of seven-membered NHC ligands relative to those of other NHC ligands. The relative donor strength of NHCs is commonly determined by comparison of the infrared stretching frequencies of the carbonyl ligands in the corresponding (NHC)Rh(CO)₂Cl complexes.^{7,8, 14–21} The IR stretching frequencies of **6** (2078 cm^{–1} and 1988 cm^{–1}, ν_{ave} = 2033 cm^{–1}) indicate

[‡]IMes = 1,3-bis(2,4,6-trimethylphenyl)-2,3-dihydro-1*H*-imidazol-2-ylidene.

that this 7-membered NHC is a stronger donor than traditional (saturated and unsaturated) 5-membered NHCs for which such CO stretching frequencies have been measured (Table 1), but not as strong as the acyclic and 6-membered derivatives.

The studies described here provide an important foundation for future investigations of axially-chiral seven-membered NHCs. The non-traditional synthetic route consisting of base-induced α -elimination from the alcohol adduct provides access to the free seven-membered carbene, thereby expanding the scope of the NHC-metal complexes and catalytic applications that can be explored with these structures. Prominent targets of our ongoing studies include the preparation of enantiomerically resolved NHCs and investigation of their application to asymmetric catalysis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Solid-state molecular structure of **4** (one of two independent molecules of **4** in the unit cell). Hydrogen atoms and a solvent molecule (benzene) are omitted for clarity. Selected bond lengths (Å) and angles (°): N(1)–C(1) 1.377(3), N(2)–C(1) 1.342(3), N(1)–C(1)–N(2) 113.4(2), biphenyl torsion angle 45.2(3).

Scheme 1. Preparation of NHC-Rh complexes from free NHC **4**.

Table 1Average CO stretching frequencies (ν_{ave}) of various (carbene)Rh(CO)₂Cl complexes.

entry	Carbene	$\nu_{\text{ave}}/\text{cm}^{-1}$
1		2012
2		2014

entry	Carbene	$\nu_{\text{ave}}/\text{cm}^{-1}$
3		2020
4		2029
5		2032

entry	Carbene	$\nu_{\text{ave}}/\text{cm}^{-1}$
6		2033
7		2036
8		2038
9		2041
10		2042
11		2049