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Spiro-fused six-membered N-heterocyclic carbene: a new scaffold toward unique properties and activities†

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A six-membered N-heterocyclic carbene fused with a spiro-scaffold is designed. The new NHC shows stronger σ-donation ability than typical 5-membered NHCs. This property leads to interesting reactivities of this spiro-fused six-membered NHC. For example, the NHC–BF_3 Lewis pair complex can be readily prepared by using $LiBF_4$ as the BF_3 source, or through a direct bond-reconstruction of the tetrafluoroborate salt NHC·HBF_4.

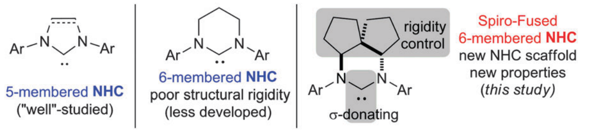
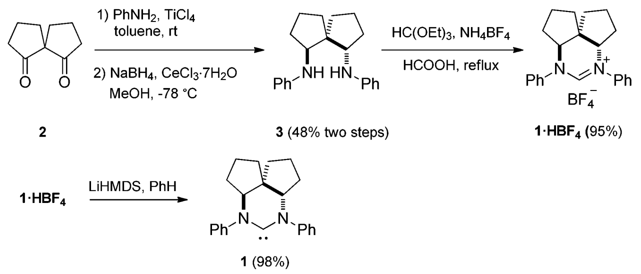


Fig. 1 Design of spiro-fused 6-membered NHC **1**.

N-heterocyclic carbenes (NHCs)[1] are important molecules. They are widely explored as reaction reagents,[2] ligands for metals,[3] and small molecule organocatalysts.[4] Over the past two decades, several types of NHCs, which vary in the sizes of cyclic frameworks (from 4 to 8 members) and/or hetero-atom species (N, O, S, and P), have been explored and examined. Among the NHCs reported, 5-membered NHCs derived from imidazolylidenes, imidazolidinylidenes, triazolylidenes, and thiazolylidenes have been extensively studied. In contrast, the related expanded 6-membered NHCs received impressive yet still much less attention.[5] Both synthesis and application of these 6-membered NHCs are much less developed. The relatively scarce studies on 6-membered NHCs are in part caused by the challenges associated with the less rigid 6-membered rings, in comparison with their 5-membered analogues. On the other hand, the strong σ-donating property[6] of 6-membered NHCs makes them attractive catalyst/ligand candidates especially for the discovery of new catalytic modes and reactions. In addition, the enormous practices in using NHCs as either ligands or organocatalysts have clearly shown that the catalytic activation modes, reaction efficiencies and selectivities are all heavily controlled by the structure of the NHCs. Therefore, it is undoubtedly that some of the future breakthroughs in reaction development should come from the employment of NHCs with unique scaffolds. Additionally, the spirocyclo[4,4]nonane-derived auxiliaries or ligands, due to their rigid structural characteristics, have proved to show excellent stereochemical control in a lot of asymmetric reactions.[7] In connection with our long-term interest in these spirocyclic units,[8] we decided to employ spiro-cyclic scaffolds to control the structural rigidity of 6-membered NHCs with the aim of developing a class of catalysts and ligands with new activities (Fig. 1). Here we present our preliminary results under this topic concerning the synthesis of the first 6-membered NHC (**1**) fused with a spirocyclic frame and the evaluation of its interesting properties and reactivities.

Our synthesis started with the spiro[4,4]nonane-1,6-dione **2** (Scheme 1), which was readily prepared from ethyl 2-oxocyclopentanecarboxylate according to literature procedures.[9] Thus **2** was subjected to condensation with aniline, followed by reduction of the formed imine with $NaBH_4$ to give the major *cis*,*cis*-diamine **3**. Cyclization of **3** with $HC(OEt)_3/NH_4BF_4$ in acidic medium at reflux furnished the tetrafluoroborate salt **1**·$\mathbf{HBF_4}$. Treatment of the salt **1**·$\mathbf{HBF_4}$ with LiHMDS (lithium hexamethyldisilazide) at room temperature afforded the desired NHC **1**, which could be purified through re-crystallization from petroleum ether/toluene in a glove



Scheme 1 Synthesis of NHC **1**.

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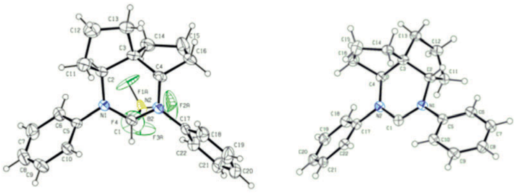
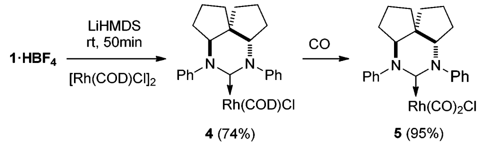


$1{\bullet}BF_4$ 1

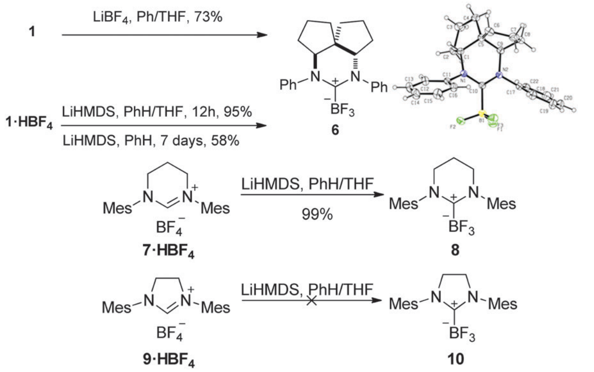
Fig. 2 X-ray structures of $\mathbf{1{\cdot}HBF_4}$ and NHC **1**.

box at −40 °C. Its structure was determined by NMR and X-ray diffraction. The ^{1}H and ^{13}C NMR signals of NHC **1** indicated that the two phenyl groups and two fused methynes have respectively the same chemical environment. The single-crystal X-ray diffraction analysis of the 6-membered ring structure showed that the five atoms (N1, C1, N2, C2, and C4) were almost in one plane, and the middle C3 was out of the plane (Fig. 2).[10] Comparing the X-ray diffraction data (see ESI†) of **1** with those of the corresponding spirocyclodiol **2′**[9] and the non-fused NHC **6-Mes**[5h] revealed an obvious difference in bond lengths (the largest Δ = 0.060 Å) and angles (the largest Δ = 6.900°) around the fused C2–C4. Details of this comparison are included in the ESI.† Furthermore, as we expected, NHC **1** was quite stable at room temperature for at least two months either in solution or in the solid state in a glove box.

Next, the reactivities and properties of the new NHC **1** were investigated. Firstly, its nucleophilic coordination with transition metal species (Scheme 2) was tested. Reaction of $\mathbf{1{\cdot}HBF_4}$ with $[Rh(COD)Cl]_2$ and then with CO under basic conditions afforded the corresponding Rh–NHC complex **4** and **5** in 74% and 95% yields, respectively. The IR spectrum of **5** showed the CO stretching vibrations of similar intensity at 1990.6 cm^{-1} and 2070.8 cm^{-1}. From these values, we inferred a Tolman electronic parameter (TEP)[6a,11] value of 2043.9 cm^{-1}. This value indicated that **1** would have a stronger σ-donation nature than most of the normal 5-membered NHCs,[6] which thus prompted us to further evaluate its possible unusual nucleophilic properties.



Scheme 2 Synthesis of $RhCl(COD)(NHC)$ **4** and $RhCl(CO)_2(NHC)$ **5**.

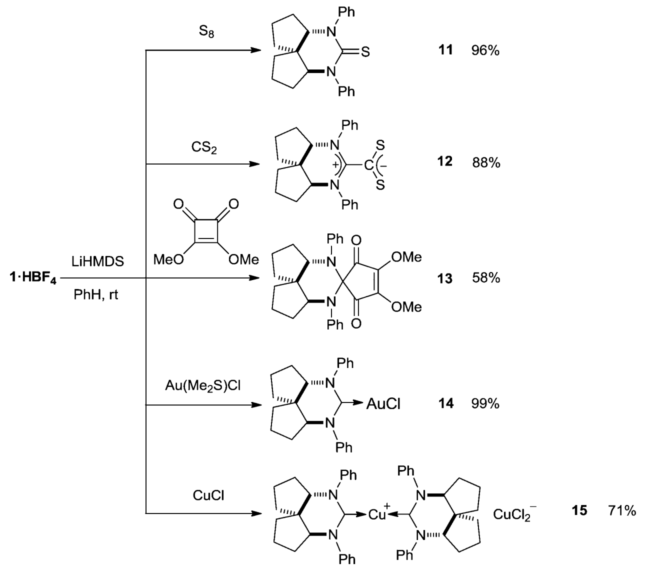


Scheme 3 Direct reaction of the tetrafluroborate salt or NHC with $LiBF_4$ for convenient preparation of the NHC–BF_3 complex.[15]

Following the above deduction, we tested the trifluoroboranation of NHC **1** toward preparation of the Lewis pair NHC–BF_3 **6**, because this kind of complex recently proved to possess some promising reactivity as non-metal catalysts, reactants, and reagents.[12] As reported, the previous preparation of NHC–BF_3 normally required the use of active reagents such as $THF{\cdot}BF_3$ or $Et_2O{\cdot}BF_3$.[13] With careful studies (Scheme 3), we found that a simple and normally inactive reagent, $LiBF_4$, could be used to react with NHC **1** in a mixture of PhH/THF (20/1) as the solvent at room temperature. The reaction smoothly afforded complex **6** in 73% yield. Our further studies showed that tetrafluoroborate salt $\mathbf{1{\cdot}HBF_4}$ could directly undergo effective transformation to give complex **6**. In the case of using $\mathbf{1{\cdot}HBF_4}$ directly, the choice of solvent and base was critical. When PhH/THF (20/1) was used, reaction of $\mathbf{1{\cdot}HBF_4}$ with LiHMDS could be readily completed within 13 hours at ambient temperature to give complex **6** in 95% yield. If PhH was used as the solvent, a much longer reaction time (over seven days) and lower yield (58%) were observed. No desired product **6** could be obtained in the presence of bases such as NaHMDS, KHMDS or KO^tBu. Encouraged by this interesting observation, we applied our method to a known non-fused 6-membered NHC **7** that has a TEP (2042.6 cm^{-1})[14] value similar to that of NHC **1**. To our delight, the tetrafluoroborate salt $\mathbf{7{\cdot}HBF_4}$ could react readily with LiHMDS in PhH/THF (20/1) at ambient temperature to produce the corresponding NHC–BF_3 complex **8** in 99% yield. In contrast, the typical 5-membered NHC **9** has a higher TEP value (2051.5 cm^{-1})[11d] than that of NHC **1**. The tetrafluoroborate salt $\mathbf{9{\cdot}HBF_4}$ could not be converted to the corresponding complex **10** under otherwise identical conditions. To the best of our knowledge, our result is the first observation that the 6-membered NHC displays a stronger nucleophilic reactivity than its 5-membered analog toward trifluoroboranation.

We also examined the reactivities of NHC **1** with other non-metal and metal species. As shown in Scheme 4, NHC **1** generated *in situ* from $\mathbf{1{\cdot}HBF_4}$ with LiHMDS could be trapped with S_8 at room temperature affording thiourea **11** as a light yellow solid in an excellent yield of 96%. When carbon disulfide was added to the reaction system at ambient temperature of $\mathbf{1{\cdot}HBF_4}$ and LiHMDS, the dipolar cross-coupling product **12** was formed smoothly as a deep red solid in 88% yield. NHC **1** could also react with 3,4-dimethoxycyclobut-3-ene-1,2-dione to afford the carbon-inserted product **13** in 58% yield. Our NHC also behaves as an excellent ligand for transition metals. For example, **1** could react easily with $Au(Me_2S)Cl$ in a glove box at ambient temperature, and a coordinate **14** was obtained in nearly quantitative yield as a white stable solid. Interestingly, a cationic Cu(I) bis-(NHC) compound **15** could also be obtained in 71% yield from the reaction between **1** and CuCl. The crystal structures of **11**, **14**, and **15** have been determined (see ESI†).

In summary, we have designed, synthesized, and characterized a new spirocarbocyclo-fused N-heterocyclic carbene **1**, which has C_2 symmetry axis. For the first time, we observed stronger nucleophilic properties of 6-membered NHC (*e.g.*, **1**) than typical 5-membered NHC (*e.g.* **9**) toward the trifluoroboranation. This carbene trifluoroboranation reaction might be used as a general method to estimate



Scheme 4 Additional reactions of NHC **1** with metal and non-metal substrates.

the nucleophilic reactivity of NHCs. In addition, our study provides a very convenient and practical method for the preparation of the NHC–BF_3 complex directly from the NHC·HBF_4 salt or by using $LiBF_4$ as the BF_3 source. New reaction development, including the search for new activation modes, and the design of asymmetric reactions using this new NHC scaffold and/or its transition metal complexes are now under investigation.

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