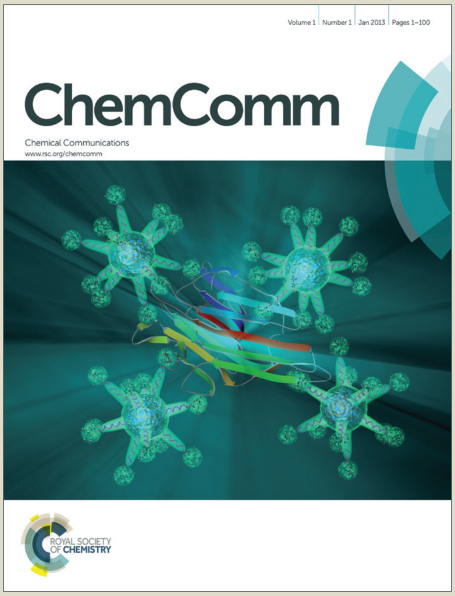

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Spiro-Fused Six-Membered N-Heterocyclic Carbene: New Scaffold toward Unique Properties and Activities

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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. The properties lead to interesting reactivities of this spiro-fused six-memebered NHC. For example, 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.

The 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 these NHCs reported, those with 5-membered 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 attentions.[5] Both synthesis and application of these 6-memebered NHCs are much less developed. The relatively scarce studies on 6-memebered NHCs are in part caused by the challenges associated with the less rigid 6-memebered rings, in comparison with their 5-memebered analogues. On the other hand, the strong σ-donating property[6] of 6-memebered NHCs makes them as 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 structure characteristics, have proved to be of the excellent stereochemical control in a lot of asymmetric reactions.[7] In connection with our long-term synthesis interesting in these spirocyclic units,[8] we decide to employ spiro-cyclic scaffolds to control the structural rigidity of 6-membered NHCs with the aim to develop a class of catalysts and ligands with new activities (Figure 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 an evaluation of its interesting properties and reactivities.

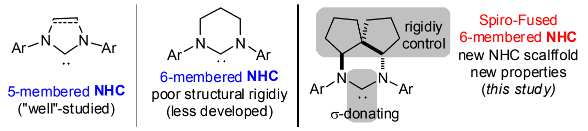
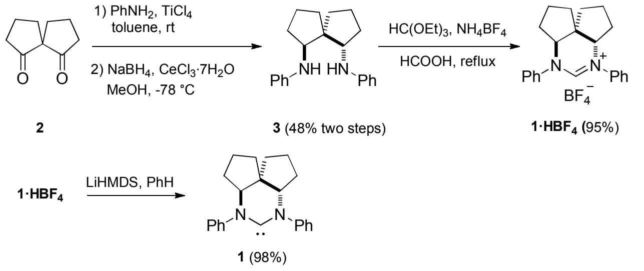


Figure 1 Design of Spiro-Fused 6-Membered NHC **1**



Scheme 1 Synthesis of NHC **1**

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·HBF₄**. Treatment of the salt **1·HBF₄** with LiHMDS (lithium hexamethyldisilazide) at room temperature afforded the desired NHC **1**, which could be purified through re-crystallization from petroleum ether/toluene in glove box at -40 ℃. Its structure was determined by NMR and X-ray diffraction. The ^1H 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 (Figure 2).[10] Comparing the X-ray diffraction data (see Supporting Information) of **1** with those of the corresponding spirocyclodiol **2′**[9] and the non-fused NHC **6-Mes**[5h] revealed obvious difference in bond lengths (the largest Δ = 0.060Å) and angles (the largest Δ = 6.900°) around the fused C2-C4. Details of this comparison are included in the

Supplementary Information. Furthermore, as we expected, NHC **1** was quite stable at room temperature for at least two months either in solution or in solid state in glove box.

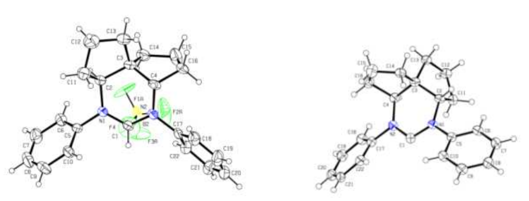
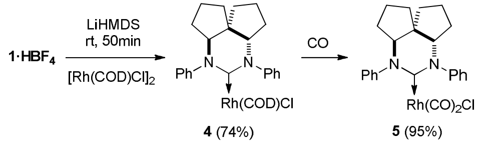


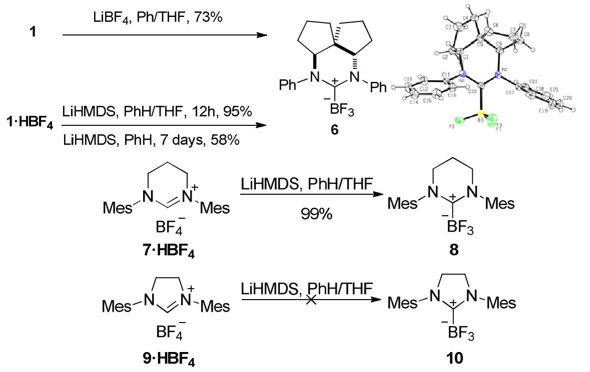
Figure 2 X-ray Structures of **1·HBF$_4$** and NHC **1**

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 **1·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 spectroscopy of **5** showed the CO stretching vibrations of similar intensity at 1990.6 cm^{-1} and 2070.8 cm^{-1}. From the values, we inferred a Tolman electronic parameter (TEP)[6a, 11] value of 2043.9 cm^{-1}. This value indicated **1** would have stronger σ-donation nature than most of normal 5-membered NHCs,[6] which thus prompted us to further evaluate its possible unusual nucleophilic property.



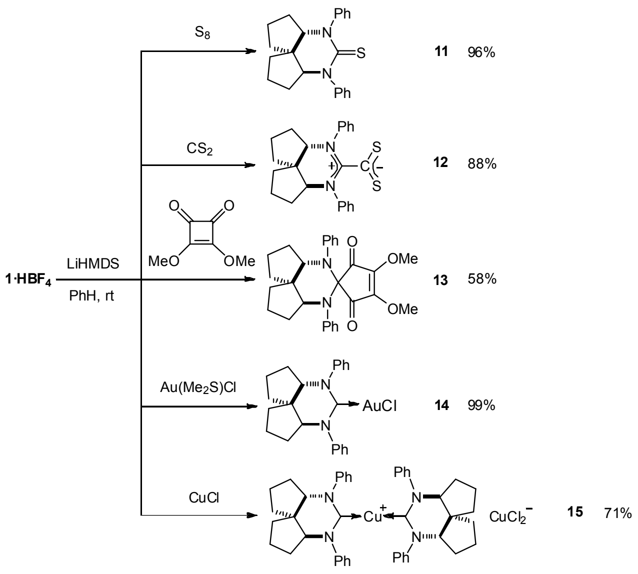
Scheme 2 Synthesis of $RhCl(COD)(NHC)$ **4** and $RhCl(CO)_2(NHC)$ **5**

Following above deduction, we tested the trifluorboranation 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·BF_3 or Et_2O·BF_3.[13] With careful studies (Scheme 3), we found that 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 **1·HBF$_4$** could directly undergo effective transformation to give complex **6**. In the case of using **1·HBF$_4$** directly, the choice of solvent and base was critical. When PhH/THF (20/1) was used, reaction of **1·HBF$_4$** with LiHMDS could be readily completed within 13 hours at ambient temperature to give the complex **6** in 95% yield. If PhH was used as the solvent, 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^{t}Bu. 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 **7·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 (2057.0 cm^{-1})[10d] than that of NHC **1**. The tetrafluoroborate salt **9·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 stronger nuclophilic reactivity than its 5-membered analog toward trifluoroboratation.



Scheme 3 Direct Reaction of Tetrafluroborate Salt or NHC with $LiBF_4$ for Convenient Preparation of NHC-BF_3 Complex[15]

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 **1·HBF$_4$** with LiHMDS could be trapped with S_8 at room temperature afforded thiourea **11** as light yellow solid in excellent yield of 96%. When carbon disulfide was added to the reaction system at ambient temperature of **1·HBF$_4$** and LiHMDS, the dipolar cross-coupling product **12** was formed smoothly as 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



Scheme 4 Additional Reactivities of NHC **1** with Metal and Non-Metal Substrates

as an excellent ligand for transition metals. For example, **1** could react easily with Au(Me$_2$S)Cl in 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 Supporting Information).

In summary, we have designed, synthesized, and characterized a new spirocarbocyclo-fused N-heterocyclic carbene **1**, which has *C2* symmetry axis. For the first time, we observed stronger nucleophilic property of 6-membered NHC (e.g., **1)** than typical 5-membered NHC (e.g. **9)** toward the trifluroboration. This carbene trifluroboration reaction might be used as a general method to estimate the nucleophilic reactivity of NHCs. In addition, our study provides a very convenient and practical method for the preparation of NHC-BF$_3$ complex directly from 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 class of new NHC scaffold and/or its transition metal complexes are now under investigation.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

1 (a) K. Öfele, *J. Organomet. Chem.* 1968, **12**, P42; (b) H.-W. Wanzlick, *Angew. Chem. Int. Ed. Engl.* 1962, **1**, 75; (c) H.-W. Wanzlick and H. J. Schönherr, *Angew. Chem. Int. Ed. Engl.* 1968, **7**, 141; (d) A. J. Arduengo III, R. L. Harlow and M. Kline, *J. Am. Chem. Soc*. 1991, **113**, 361; (e) A. J. Arduengo III, H. V. Rasika Dias, R. L. Harlow and M. Kline, *J. Am. Chem. Soc*. 1992, **114**, 5530.

2 (a) V. Nair, S. Bindu and V. Sreekumar, *Angew. Chem. Int. Ed.* 2004, **43**, 5130; (b) L. Delaude, *Eur. J. Inorg. Chem.* 2009, 1681; (c) T. W. Hudnall, E. J. Moorhead D. G. Gusev and C. W. Bielawski, *J. Org. Chem.* 2010, **75**, 2763; (d) J. P. Moerdyk and C. W. Bielawski, *Nat. Chem.* 2011, **4**, 275.

3 For comprehensive reviews see for example: (a) W. A. Herrmann and C. Köcher, *Angew. Chem. Int. Ed. Engl.* 1997, **36**, 2162; (b) W. A. Herrmann, *Angew. Chem. Int. Ed*. 2002, **41**, 1290; (c) F. E. Hahn and M. C. Jahnke, *Angew. Chem. Int. Ed*. 2008, **47**, 3122; (d) S. Díez-González, N. Marion and S. P. Nolan, *Chem. Rev.* 2009**, 109**, 3612; (e) G. C. Vougioukalakis and R. H. Grubbs, *Chem. Rev*. 2010, **110**, 1746; (f) D. Martin, M. Soleilhavoup and G. Bertrand, *Chem. Sci.* 2011, **2**, 389; (g) W. Liu and R. Gust, *Chem. Soc. Rev.* 2013, **42**, 755.

4 For comprehensive reviews see for example: (a) D. Enders and T. Balensiefer, *Acc. Chem. Res*. 2004, **37**, 534; (b) N. Marion, S. Díez-González and S. P. Nolan, *Angew. Chem. Int. Ed.* 2007, **46**, 2988; (c) D. Enders, O. Niemeier and A. Henseler, *Chem. Rev*. 2007, **107**, 5606; (d) M. Melaimi, M. Soleilhavoup and G. Bertrand, *Angew. Chem. Int. Ed*. 2010, **49**, 8810; (e) M. Fèvre, J. Pinaud, Y. Gnanou, J. Vignolle and D. Taton, *Chem. Soc. Rev.* 2013, **42**, 2142. (f) J. Mahatthananchai and J. W. Bode. *Acc. Chem. Res*. 2014, **47**, 696..

5 (a) R. W. Alder, M. E. Blake, C. Bortolotti, S. Bufali, C. P. Butts, E. Linehan, J. M. Oliva, A. G. Orpen and M. J. Quayle, *Chem. Commun.* 1999, 241; (b) P. Bazinet, G. P. A. Yap and D. S. Richeson, *J. Am. Chem. Soc.* 2003, **125**, 13314; (c) M. Mayr, K. Wurst, K.-H. Ongania and M. R. Buchmeiser, *Chem. Eur. J.* 2004, **10**, 1256; (d) M. Mayr and M. R. Buchmeiser, *Macromol. Rapid Commun.* 2004, **25**, 231; (e) C. Präsang, B. Donnadieu and G. Bertrand, *J. Am. Chem. Soc.* 2005, **127**, 10182; (f) P. Bazinet, T.-G. Ong, J. S. O’Brien, N. Lavoie, E. Bell, G. P. A. Yap, I. Korobkov and D. S. Richeson, *Organometallics* 2007, **26**, 2885; (g) M. Iglesias, D. J. Beetstra, A. Stasch, P. N. Horton, M. B. Hursthouse, S. J. Coles, K. J. Cavell, A. Dervisi and I. A. Fallis, *Organometallics* 2007, **26,** 4800; (h) M. Iglesias, D. J. Beetstra, J. C. Knight, L.-L. Ooi, A. Stasch, S. Coles, L. Male, M. B. Hursthouse, K. J. Cavell, A. Dervisi and I. A. Fallis, *Organometallics* 2008, **27**, 3279; (i) V. César, N. Lugan and G. Lavigne, *J. Am. Chem. Soc.* 2008, **130**, 11286; (j) T. W. Hudnall and C. W. Bielawski, *J. Am. Chem. Soc.* 2009, **131**, 16039; (k) E. L. Kolychev, I. A. Portnyagin, V. V. Shuntikov, V. N. Khrustalev and M. S. Nechaev, *J. Organomet. Chem.* 2009, **694**, 2454; (l) M. Iglesias, D. J. Beetstra, B. Kariuki, K. J. Cavell, A. Dervisi and I. A. Fallis, *Eur. J. Inorg. Chem.* 2009, 1913; (m) A. Binobaid, M. Iglesias, D. J. Beetstra, B. Kariuki, A. Dervisi, I. A. Fallis and K. J. Cavell, *Dalton Trans.* 2009, 7099; (n) J. K. Park, H. H. Lackey, M. D. Rexford, K. Kovnir, M. Shatruk and D. T. McQuade, *Org. Lett.* 2010, **12**, 5008; (o) D. Martin, N. Lassauque, B. Donnadieu and G. Bertrand, *Angew. Chem. Int. Ed.* 2012, **51**, 6172; (p) J. K. Park and D. T. McQuade, *Synthesis* 2012, **44**, 1485; (q) J. Zhang, X. Qin, J. Fu, X. Wang, X. Su, F. Hu, J. Jiao and M. Shi, *Organometallics* 2012, **31**, 8275; (r) A. Makhloufi, M. Wahl, W. Frank and C. Ganter, *Organometallics* 2013, **32**, 854.

6 (a) T. Dröge and F. Glorius, *Angew. Chem. Int. Ed.* 2010, **49**, 6940; (b) D. J. Nelson and S. P. Nolan, *Chem. Soc. Rev.* 2013, **42**, 6723.

7 (a) N. Srivastava and A. Mital, A. Kumar, *J. Chem. Soc. Chem. Commun.* 1992, 493; (b) A. S. C. Chan, W. Hu, C.-C. Pai, C.-P. Lau, Y. Jiang, A. Mi, M. Yan, J. Sun, R. Lou and J. Deng, *J. Am. Chem. Soc.* 1997, **119**, 9570; (c) W. Hu, M. Yan, C.-P. Lau, S. M. Yang, A. S. C. Chan, Y. Jiang and A. Mi, *Tetrahedron Lett.* 1999, **40**, 973; (d) Y. Jiang, S. Xue, Z. Li, J. Deng, A. Mi and A. S. C. Chan, *Tetrahedron: Asymmetry* 1998, **9**, 3185; (e) M. A. Arai, T. Arai and H. Sasai, *Org. Lett.* 1999, **1**, 1795; (f) Y. Jiang, S. Xue , K. Yu , Z. Li , J. Deng, A. Mi and A. S. C. Chan, *J. Organomet. Chem.* 1999, **586**, 159; (g) M. A. Arai, M. Kuraishi, T. Arai and H. Sasai, *Chirality* 2003, **15**, 101; (h) S. M. Lait, M. Parvez and B. A. Keay, *Tetrahedron: Asymmetry* 2004, **15***,* 155; (i) C. W. Lin, C.-C. Lin, L. F.-L. Lam, T. T.-L. Au-Yeung and A. S. C. Chan, *Tetrahedron Lett.* 2004, **45***,* 7379; (j) Z. Guo, X. Guan and Z. Chen, *Tetrahedron: Asymmetry* 2006, **17***,* 468; (k) S.-F. Zhu, J.-B. Xie, Y.-Z. Zhang, S. Li and Q.-L. Zhou, *J. Am. Chem. Soc.* 2006, **128**, 12886; (l) J.-H. Xie and Q.-L. Zhou, *Acc. Chem. Res*. 2008**, 41**,581; (m) K. Ding, Z. Han and Z. Wang, *Chem. Asian J.* 2009, **4**, 32; (n) G. B. Bajracharya, M. A. Arai, P. S. Koranne, T. Suzuki, S. Takizawa and H. Sasai, *Bull. Chem. Soc. Jpn.* 2009, **82**, 285; (o) Z. Han, Z. Wang, X. Zhang and K. Ding, *Angew. Chem. Int. Ed.* 2009, **48**, 5345.

8 (a) Y. Q. Tu, L. M. Yang and Y. Z. Chen, *Chem. Lett*. 1998, **27**, 285; (b) Y. Q. Tu, L. D. Su and P. Z. Wang, *J. Org. Chem.* 1999, **64**, 629; (c) B. Wang and Y. Q. Tu, *Acc. Chem. Res*. 2011**, 44**, 1207.

9 J. A. Nieman, M. Parvez and B. A. Keay, *Tetrahedron: Asymmetry* 1993, **4**, 1973.

10 The crystal structure of **1·HBF$_4$** and **1** have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number: 973597 (**1·HBF$_4$**) and 973601 (**1**).

11 (a) C. A. Tolman, *Chem. Rev*. 1977, **77**, 313; (b) W. Strohmeier and F.-J. Müller, *Chem. Ber.* 1967, **100**, 2812; (c) G. Bouquet, A. Loutellier and M. Bigorgne, *J. Mol. Struct.* 1968, **1**, 211; (d) R. A. Kelly III, H. Clavier, S. Giudice, N. M. Scott, E. D. Stevens, J. Bordner, I. Samardjiev, C. D. Hoff, L. Cavallo and S. P. Nolan, *Organometallic* 2008, **27**, 202; (e) S. Wolf and H. Plenio, *J. Organomet. Chem.* 2009, **694**,1487.

12 D. P. Curran, A. Solovyev, M. M. Brahmi, L. Fensterbank, M. Malacria and E. Lacôte, *Angew. Chem. Int. Ed.* 2011, **50**, 10294.

13 (a) N. Kuhn, G. Henkel, T. Kratz, J. Kreutzberg, R. Boese and A. H. Maulitz, *Chern. Ber.* 1993, **126**, 2041; (b) A. J. Arduengo, F.

Davidson, R. Krafczyk, W. J. Marshall and R. Schmutzler, *Monatsh. Chem*. 2000, **131**, 251; (c) W. Kirmse, *Eur. J. Org. Chem.* 2005, 237.

14 M. Iglesias, D. J. Beetstra, B. Kariuki, K. J. Cavell, A. Dervisi and I. A. Fallis, *Eur. J. Inorg. Chem.* 2009, 1913.

15 The crystal structure of **6** has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number: 973599.