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Syntheses of tetrahydroquinoline-based chiral carbene precursors and the related chiral NHC–Au(I) complex†

 Licheng Zhan, Gengtao Zhang, Jiwei Wang and Jun Zhang *

Four tetrahydroquinoline-based chiral carbene precursors were synthesized using unsymmetrical *N,N'*-diarylformamidines and chiral 2-allyloxiranes as starting materials. A representative NHC–gold complex has been prepared and fully characterized, the crystal structure of which reveals an intramolecular Au···H–C(sp³) interaction between Au(I) and the hydrogen atom of the isopropyl moiety in the *N*-aryl group.

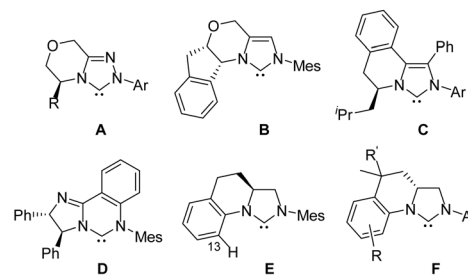
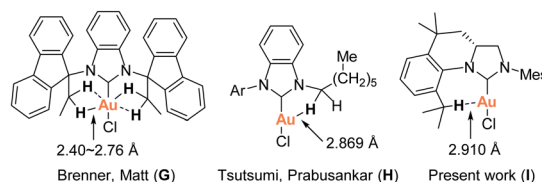
Imidazolidin-2-ylidene carbenes are among the most important N-heterocyclic carbenes (NHCs) due to their widespread and spectacular applications as organocatalysts and as ligands for organometallic catalysis.¹ Over the past twenty years, a great deal of effort has been made to employ chiral NHCs as organocatalysts and as ligands in asymmetric catalysis.² Despite the successful applications of a variety of chiral NHCs in asymmetric catalysis, the development of facile methodologies for structurally-specific chiral NHCs with structural diversity is highly desirable and a challenging issue in asymmetric catalysis. Several types of chiral backbone-unsaturated NHCs having a fused ring in their scaffolds, such as **A**,³ **B**,⁴ **C**,⁵ and **D**,⁶ have been successfully developed for organocatalysts and/or as ligands for organometallic catalysis (Scheme 1a). In their scaffolds, chiral moiety is directly linked to the N-atom and embedded in a fused ring. Due to the rigidity of the fused ring, the rotation of chiral moiety about the N–C bond is restricted, thereby enhancing the asymmetric induction of the NHCs in controlling the stereochemistry of the asymmetric catalytic reaction.

With different design strategy, Blechert *et al.* have developed chiral imidazolidin-2-ylidene **E** having a fused ring in the scaffold, which exhibited high efficiency in Ru-catalyzed asymmetric ring-opening cross-metathesis.⁷ The fused ring in **E** twists the framework, hampers rotation of the *N*-aryl substituent, and thus reaches the optimal transfer of chirality, while at the same time second *N*-mesityl substituent adopts a planar orientation. However, the approach for the synthesis of the

carbene precursors, imidazolium salts requires uncommon starting material and a kinetic enzymatic resolution, which limit modification of NHC ligands. Additionally, only the imidazolium salt of type **E** having no C13 substituent was prepared by the method.⁸ Varying the *N*-aryl substituents with different steric bulkiness in **E** might create a tunable chiral environment closer to the reactive site. Until very recently, a consecutive intermolecular reductive amination/asymmetric hydrogenation has been developed for the synthesis of the precursors of **E**.⁸

As part of our studies on the design and synthesis of various novel NHC ligands for carbene chemistry and catalysis,⁹ we herein wish to report a new synthetic strategy for the facile

a) Selected chiral NHCs having a fused ring in their scaffolds

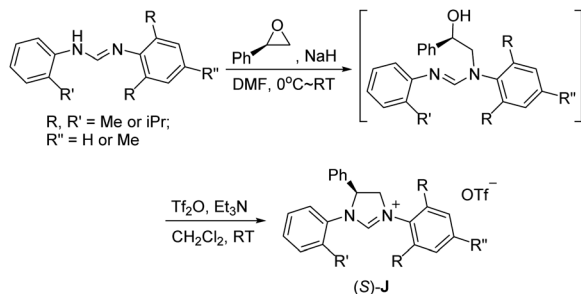

 b) Au(I)-NHC complexes with intramolecular Au···H–C(sp³) interactions


Key Laboratory for Advanced Materials, Joint International Research Laboratory of Precision Chemistry and Molecular Engineering, Feringa Nobel Prize Scientist Joint Research Center, School of Chemistry and Molecular Engineering, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China. E-mail: zhangj@ecust.edu.cn

† Electronic supplementary information (ESI) available: Characterization details of new compounds, crystallographic details, NMR spectra. CCDC 2011334 for (6). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ra07271k

Scheme 1 Chiral NHCs having a fused ring in their scaffolds and related NHC–Au(I) complexes with intramolecular Au···H–C(sp³) interaction.

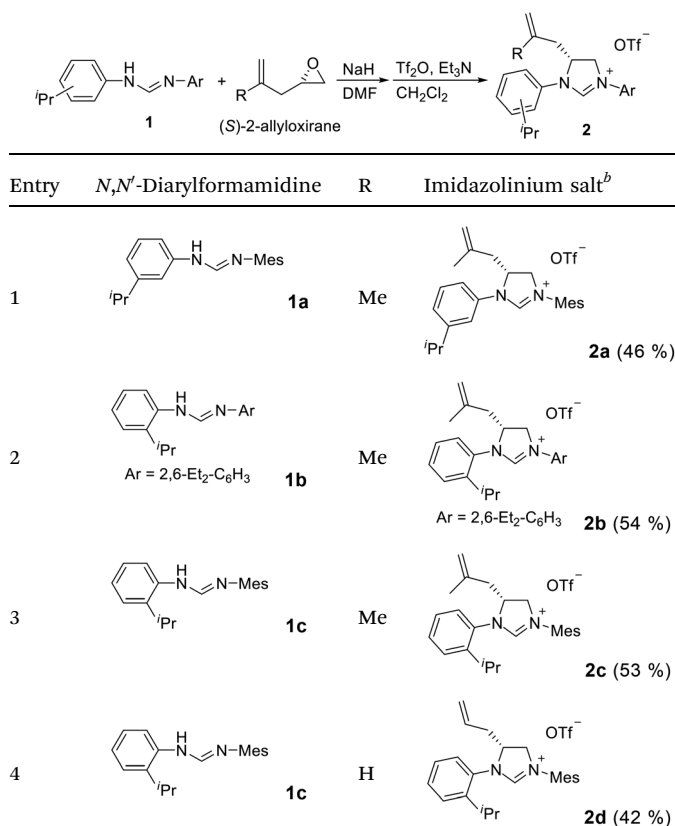




Scheme 2 Synthesis of chiral backbone-monosubstituted imidazolium salts from the reaction of formamidines with alkene oxide.^{9a}

preparation of various tetrahydroquinoline-based chiral carbene precursors of NHCs **F** using unsymmetrical *N,N'*-diarylfornamidines and chiral 2-allyloxiranes as starting materials. A representative NHC-gold complex **I** has been prepared and structurally characterized. The crystal structure of the NHC-gold reveals an intramolecular Au(i)⋯H-C(sp³) interaction between Au(i) and the hydrogen atom of isopropyl moiety

Table 1 Synthesis of chiral backbone-allyl-substituted imidazolium salts from the reaction of formamidines with chiral 2-allyloxiranes^a

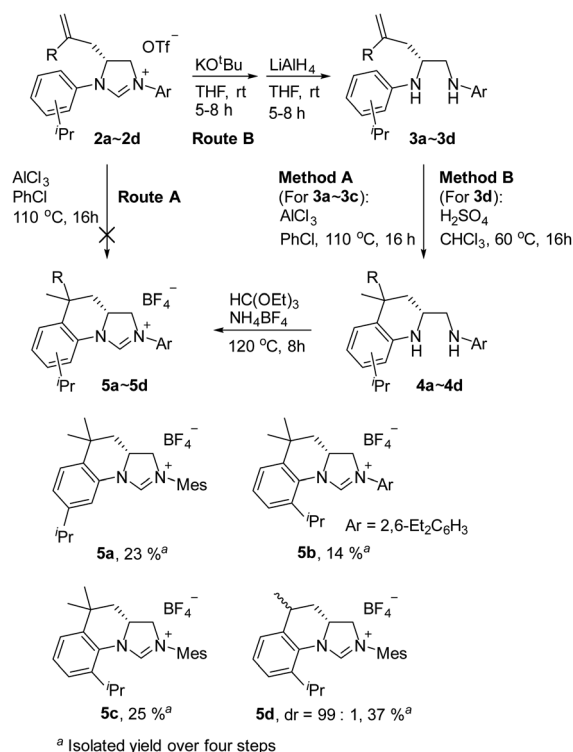


^a Reaction conditions. Step 1: **1** (1.0 equiv.), 2-allyloxirane (1.2 equiv.), NaH (1.5 mmol), DMF (10 mL), 0–70 °C, 6 h. Step 2: Tf₂O (1.1 equiv.), Et₃N (1.1 equiv.), DCM (5 mL), 25 °C, 5–8 h. ^b Isolated yield over two steps.

(Scheme 1b). Recently, the Au(i)⋯H-C(sp³) hydrogen-bonding interaction have been observed in NHC–Au(i) complexes **G** and **H**, which are believed to either stabilise the out-of-plane conformation (**G**)^{10a} or make partial contributions to the luminescence properties of the NHC–Au(i) complex (**H**)^{10b} (Scheme 1b). Additionally, Au⋯H–C hydrogen-bonding interactions in NHC–Au complexes have been proposed as key intermediates in the mechanistic studies of NHC–Au catalyzed C–H activation.¹¹

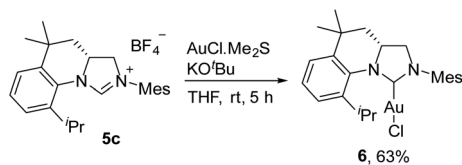
We have previously developed a versatile and modular method for the preparation of various backbone-substituted imidazolium salts from the reaction of formamidines with alkene oxides.^{9a} The methodology exhibits high regiochemistry. When reacting styrene oxide with the unsymmetrical *N,N'*-diarylfornamidines bearing a mono-*o*-substituted aryl group and a di-*o*-substituted aryl group, only one regioisomer in which the backbone-substituted phenyl group is on the carbon atom close to the mono-substituted aryl ring was formed. More importantly, chiral monosubstituted imidazolium salts, (*S*)-**J** could be obtained when using (*R*)-styrene oxide, indicating that inversion of the configuration of (*R*)-styrene oxide occurred in the two-step synthesis (Scheme 2).^{9a} Therefore, we decide to use (*S*)-2-allyloxirane and the unsymmetrical *N,N'*-diarylfornamidines to synthesize chiral backbone-allyl-substituted imidazolium salts, which is supposed to undergo intramolecular Friedel–Crafts alkylation¹² to afford chiral imidazolium salts as the precursors of the chiral NHCs of type **F**.

As expected, the ring opening reaction of unsymmetrical *N,N'*-diarylfornamidines **1a–1d** with (*S*)-2-allyloxiranes followed by cyclization afforded four backbone-allyl-substituted



Scheme 3 Synthesis of the desired chiral tetrahydroquinoline-based imidazolium salts **5a–5d**.





Scheme 4 Synthesis of a representative chiral NHC–gold complex 6.

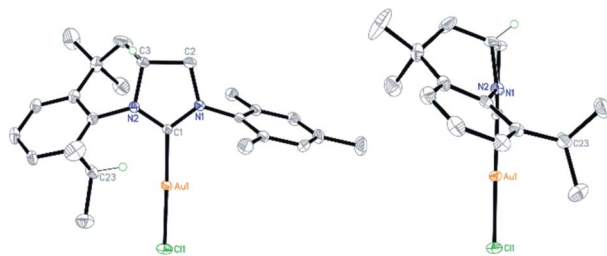
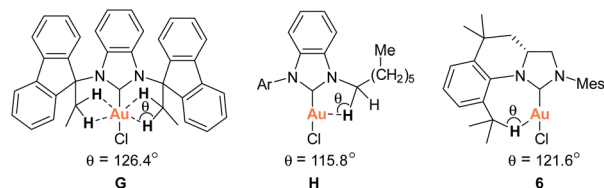


Fig. 1 Left: molecular structure of **6**. Right: side-view of **6** (mesityl group omitted for clarity). Selected bond distances (Å) and angles (deg): Au(1)–C(1) 1.972(6), Au(1)–Cl(1) 2.278(2), N(1)–C(1) 1.327(7), N(1)–C(2) 1.482(8), N(2)–C(1) 1.352(8), N(2)–C(3) 1.484(8), C(2)–C(3) 1.519(10), N(1)–C(1)–Au(1) 126.2(5), N(2)–C(1)–Au(1) 125.3(4).

imidazolium salts **2a–2d**, respectively (Table 1). However, attempts to direct Friedel–Crafts alkylation of **2a–2d** failed (Route A, Scheme 3). Therefore, an alternative route was investigated. In the presence of KOtBu as base, the ring opening of **2a–2d** followed by reduction using LiAlH₄ afforded diamines **3a–3d** (Route b, Scheme 3).¹³ Delightfully, in the presence of either AlCl₃ (for **3a–3c**) or H₂SO₄ (**3d**), the resulting amines could smoothly undergo intramolecular Friedel–Crafts alkylation to give diamines **4a–4d**. Finally, cyclization of the diamines **4a–4d** with HC(OEt)₃ in the presence of NH₄BF₄ generated the desired chiral imidazolium salts **5a–5d**. During the transformations, a partial racemization was detected. The ee value of **4a** was determined as 88% on the basis of chiral HPLC analysis (p. S8, see ESI†).

The ability of the novel tetrahydroquinoline-based chiral imidazolidin-2-ylidene carbene to ligate a transition metal fragment was also examined. Treatment of the *in situ* generated free carbene with AuCl·Me₂S gave the chiral NHC gold complex **6** in 63% yield (Scheme 4). The structure of **6** was determined by single-crystal X-ray diffraction, which exhibits the expected linear coordination geometry, and also shows that the chiral NHC in **6** has the R configuration (Fig. 1). In **6**, the Au–C bond length at the normal C2 position (1.972(6) Å) is typical of NHC–Au complexes.¹⁴ The crystal structure also reveals that the C2 bridge at the chirality center leads to a dihedral angle of 58° between the *N*-aryl group and the imidazoline plane and enforces a close approach of isopropyl group to the coordination sphere of the gold center. The Au···H–C distance found in **6** (2.910 Å) is comparable with that of a NHC–Au(I) complex ligated by *N*-(9-anthracenyl)-*N'*-(heptyl) benzimidazol-2-ylidene (2.869 Å), and van der Waals radii (2.86 Å),¹⁰ suggesting the presence of a rare Au···H–C(sp³) interaction in gold complex **6** (Scheme 1b). The Au···H–C(sp³) angle in **6** (121.6°) is similar to those observed in **G** (126.4°) and **H** (115.8°) (Fig. 2). The ¹H NMR resonance for the hydrogen atom H23 in **6** appears

Fig. 2 Comparison of Au···H–C(sp³) angles in **G**, **H** and **6**.

at 4.10 ppm downfield relative to that for its precursor, imidazolium salt **5c**.

In conclusion, we present a method for the synthesis of tetrahydroquinoline-based chiral carbene precursors using unsymmetrical *N,N'*-diarylformamidines and 2-allyloxiranes as starting materials. Treatment of unsymmetrical *N,N'*-diarylformamidines with 2-allyloxirane followed by cyclization gave backbone-allyl-substituted imidazolium salts, which could be transformed into the desired tetrahydroquinoline-based chiral carbene precursors through a key intramolecular Friedel–Crafts alkylation. A representative chiral NHC–gold complex has been prepared by the reaction of the *in situ* generated free carbene with AuCl·Me₂S. The crystal structure of the NHC–gold complex reveals a rare intramolecular Au···H–C(sp³) interaction between Au(I) and the hydrogen atom of isopropyl moiety. We are currently exploring the application of the resulting chiral carbene metal complexes in transition metal-catalyzed asymmetric synthetic transformations.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

- (a) D. Enders, O. Niemeier and A. Henseler, *Chem. Rev.*, 2007, **107**, 5606–5655; (b) P. L. Arnold and I. J. Casely, *Chem. Rev.*, 2009, **109**, 3599–3611; (c) C. Samojłowicz, M. Bieniek and K. Grela, *Chem. Rev.*, 2009, **109**, 3708–3742; (d) J. C. Y. Lin, R. T. W. Huang, C. S. Lee, A. Bhattacharyya, W. S. Hwang and I. J. B. Lin, *Chem. Rev.*, 2009, **109**, 3561–3598; (e) G. C. Vougioukalakis and R. H. Grubbs, *Chem. Rev.*, 2010, **110**, 1746–1787; (f) T. Dröge and F. Glorius, *Angew. Chem., Int. Ed.*, 2010, **49**, 6940–6952; (g) Q. Zhao, G. Meng, S. P. Nolan and M. Szostak, *Chem. Rev.*, 2020, **120**, 1981–2048; (h) M. J. Benedikter, F. Ziegler, J. Groos, P. M. Hauser, R. Schowner and M. R. Buchmeiser, *Coord. Chem. Rev.*, 2020, **415**, 213315; (i) T. Ishii, K. Nagao and H. Ohmiya, *Chem. Sci.*, 2020, **11**, 5630–5636.
- (a) F. Wang, L. Liu, W. Wang, S. Li and M. Shi, *Coord. Chem. Rev.*, 2012, **256**, 804–853; (b) D. Janssen-Müller,



- C. Schleppehorst and F. Glorius, *Chem. Soc. Rev.*, 2017, **46**, 4845–4854; (c) L. Prieto, E. Sánchez-Diez, U. Uria, E. Reyes, L. Carrillo and J. L. Vicario, *Adv. Synth. Catal.*, 2017, **359**, 1678–1683; (d) J. Thongpaen, R. Manguin and O. Baslé, *Angew. Chem., Int. Ed.*, 2020, **59**, 10242–10251; (e) X. Chen, Z. Gao and S. Ye, *Acc. Chem. Res.*, 2020, **53**, 690–702.
- 3 L. Zhou, X. Wu, X. Yang, C. Mou, R. Song, S. Yu, H. Chai, L. Pan, Z. Jin and Y. R. Chi, *Angew. Chem., Int. Ed.*, 2020, **59**, 1557–1561.
- 4 (a) C. Guo, D. Janssen-Müller, M. Fleige, A. Lerchen, C. G. Daniliuc and F. Glorius, *J. Am. Chem. Soc.*, 2017, **139**, 4443–4451; (b) S. Singha, E. Serrano, S. Mondal, C. G. Daniliuc and F. Glorius, *Nat. Catal.*, 2020, **3**, 48–54.
- 5 D. Hirsch-Weil, K. A. Abboud and S. Hong, *Chem. Commun.*, 2010, **46**, 7525–7527.
- 6 (a) J. K. Park, H. H. Lackey, M. D. Rexford, K. Kovnir, M. Shatruk and D. T. McQuade, *Org. Lett.*, 2010, **12**, 5008–5011; (b) S. Budagumpi, R. S. Keri, G. Achar and K. N. Brinda, *Adv. Synth. Catal.*, 2020, **362**, 970–997.
- 7 A. Kannenberg, D. Rost, S. Eibauer, S. Tiede and S. Blechert, *Angew. Chem., Int. Ed.*, 2011, **50**, 3299–3302.
- 8 Y. Chen, Y. Pan, Y. He and Q. Fan, *Angew. Chem., Int. Ed.*, 2019, **58**, 16831–16834.
- 9 (a) J. Zhang, X. Su, J. Fu and M. Shi, *Chem. Commun.*, 2011, **47**, 12541–12543; (b) J. Zhang, X. Su, J. Fu, X. Qin, M. Zhao and M. Shi, *Chem. Commun.*, 2012, **48**, 9192–9194; (c) J. Zhang, J. Fu, X. Su, X. Qin, M. Zhao and M. Shi, *Chem. Commun.*, 2012, **48**, 9625–9627; (d) J. Zhang, S. Song, X. Wang, J. Jiao and M. Shi, *Chem. Commun.*, 2013, **49**, 9491–9493; (e) S. Lv, J. Wang, C. Zhang, S. Xu, M. Shi and J. Zhang, *Angew. Chem., Int. Ed.*, 2015, **54**, 14941–14946; (f) J. Wang, X. Cao, S. Lv, C. Zhang, S. Xu, M. Shi and J. Zhang, *Nat. Commun.*, 2017, **8**, 14625; (g) H. Chen, J. Wang, Z. Hu, S. Xu, M. Shi and J. Zhang, *Chem. Commun.*, 2017, **53**, 10835–10838.
- 10 (a) M. Teci, E. Brenner, D. Matt, C. Gourlaouen and L. Toupet, *Chem.–Eur. J.*, 2015, **21**, 10997–11000; (b) M. Vaddamanu, A. Sathyanarayana, Y. Masaya, S. Sugiyama, O. Kazuhisa, K. Velappan, K. Subramaniam, K. Hisano, O. Tsutsumi and G. Prabusankar, *Organometallics*, 2020, **39**, 2202–2206.
- 11 (a) Q. Zhao, G. Meng, S. P. Nolan and M. Szostak, *Chem. Rev.*, 2020, **120**, 1981–2048; (b) W.-P. To, G. S.-M. Tong, W. Lu, C. Ma, J. Liu, A. L.-F. Chow and C.-M. Che, *Angew. Chem., Int. Ed.*, 2012, **51**, 2654–2657; (c) M. R. Fructos, T. R. Belderrain, P. de Frémont, N. M. Scott, S. P. Nolan, M. M. Díaz-Requejo and P. J. Pérez, *Angew. Chem., Int. Ed.*, 2005, **44**, 5284–5288; (d) M. R. Fructos, P. de Frémont, S. P. Nolan, M. M. Díaz-Requejo and P. J. Pérez, *Organometallics*, 2006, **25**, 2237–2241.
- 12 The intramolecular Friedel–Crafts alkylation approach was also previously used to construct chiral NHC ligands having a 2,2′-bisquinoline-based C₂ symmetric skeleton: L. Liu, N. Ishida, S. Ashida and M. Murakami, *Org. Lett.*, 2011, **13**, 1666–1669.
- 13 (a) S. Bulut and W. L. Queen, *J. Org. Chem.*, 2018, **83**, 3806–3818; (b) O. Hollóczki, P. Terleczy, D. Szieberth, G. Mourgas, D. Gudat and L. Nyulászi, *J. Am. Chem. Soc.*, 2011, **133**, 780–789; (c) B. J. van Lierop, A. M. Reckling, J. A. M. Lummiss and D. E. Fogg, *ChemCatChem*, 2012, **4**, 2020–2025; (d) M. K. Denk, J. M. Rodezno, S. Gupta and A. J. Lough, *J. Organomet. Chem.*, 2001, **617–618**, 242–253.
- 14 (a) P. de Frémont, N. M. Scott, E. D. Stevens and S. P. Nolan, *Organometallics*, 2005, **24**, 2411–2418; (b) P. Ai, M. Mauro, L. De Cola, A. A. Danopoulos and P. Braunstein, *Angew. Chem., Int. Ed.*, 2016, **55**, 3338–3341.

