ORGANIC LETTERS

2010
Vol. 12, No. 8
1764−1767

Bicyclic Imidazoles for Modular Synthesis of Chiral Imidazolium Salts

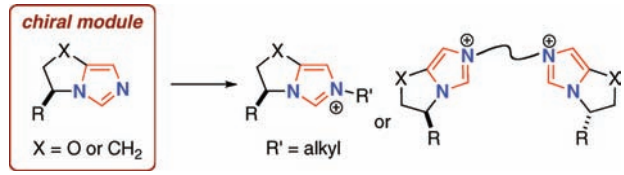
Kazuhiro Yoshida,* Shingo Horiuchi, Tomoko Takeichi, Hiroaki Shida, Tsuneo Imamoto, and Akira Yanagisawa*

Department of Chemistry, Graduate School of Science, Chiba University, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

kyoshida@faculty.chiba-u.jp

Received February 12, 2010

ABSTRACT



The preparation of new chiral bicyclic imidazoles 5 and their transformation into imidazolium salts 6 and 7 are reported. The utility of the salts as precursors for chiral *N*-heterocyclic carbenes was demonstrated by the synthesis of C−N−C pincer Ni-complex 13h, the structure of which was characterized by single-crystal X-ray analysis.

Chiral *N*-heterocyclic carbenes (NHCs) have recently received growing attention in the fields of coordination chemistry and asymmetric catalysis.[1] Among the chiral NHCs reported so far, those generated from bicyclic azolium salts, such as triazolium salts **1**−**3** or imidazolium salt **4**, are one of the successful classes of compounds used for various asymmetric reactions (Figure 1).[2] These NHCs, which are classified as NHCs that possess a chiral component on the nitrogen atom, present an advantage for asymmetric induction, which arises from the restriction of unfavorable internal rotation around the N−C (substituent) axis due to the fused bicyclic molecular structure. The common features of azolium salts **1**−**4** are their possession of aryl groups on the nitrogen atom,[3] which likely affects both reactivity and selectivity, and their method of preparation. Condensation using C_1-fragments to construct the azolium rings has been employed as the final transformation step to access these salts.

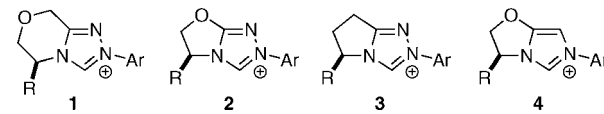


Figure 1. Known chiral bicyclic azolium salts.

In 2008, Ishida and Saigo reported an efficient method for the preparation of chiral *N*-alkyl bicyclic imidazolium salts, which involved the alkylation of morpholine-fused

(1) For recent reviews, see: (a) *N-Heterocyclic Carbenes in Synthesis*; Nolan, S. P., Ed.; Wiley-VCH; Weinheim, Germany, 2006. (b) *N-Heterocyclic Carbenes in Transition Metal Catalysis*; Glorius, F., Ed.; Springer; Berlin, Germany, 2007. (c) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655. (d) Díez-González, S.; Marion, N.; Nolan, S. P. *Chem. Rev.* **2009**, *109*, 3612–3676.

(2) For examples, see: (a) Knight, R. L.; Leeper, F. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1891–1894. (b) Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743–1745. (c) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298–10299. (d) Glorius, F.; Altenhoff, G.; Goddard, R.; Lehmann, C. *Chem. Commun.* **2002**, 2704–2705. (e) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725–5728. (f) Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1463–1467. (g) Takikawa, H.; Hachisu, Y.; Bode, J. W.; Suzuki, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 3492–3494. (h) Seayad, J.; Patra, P. K.; Zhang, Y.; Ying, J. Y. *Org. Lett.* **2008**, *10*, 953–956. (i) Ma, Y.; Wei, S.; Wu, J.; Yang, F.; Liu, B.; Lan, J.; Yang, S.; You, J. *Adv. Synth. Catal.* **2008**, *350*, 2645–2651. (j) Wang, X.-N.; Shao, P.-L.; Lv, H.; Ye, S. *Org. Lett.* **2009**, *11*, 4029–4031. For a review, see: (k) Arduengo, A. J., III; Iconaru, L. I. *Dalton Trans.* **2009**, 6903–6914.

(3) For examples of related chiral *N*-alkyl azolium salts, see: (a) Struble, J. R.; Bode, J. W. *Tetrahedron* **2008**, *64*, 6961–6972. (b) Enders, D.; Han, J.; Henseler, A. *Chem. Commun.* **2008**, 3989–3991. (c) Metallinos, C.; Xu, S. *Org. Lett.* **2010**, *12*, 76–79.

10.1021/ol1003737 © 2010 American Chemical Society
Published on Web 03/16/2010

imidazoles.[4] Although the alkylation of existing imidazoles is a well-known strategy for the preparation of azolium salts, it is not common for chiral bicyclic azolium salts.

Herein we report the preparation of new chiral bicyclic imidazoles[5] **5** and the transformation of **5** into chiral imidazolium salts, including *N*-alkyl imidazolium salts **6** and bisimidazolium salts[6] **7** (Figure 2). As **7** are prepared with

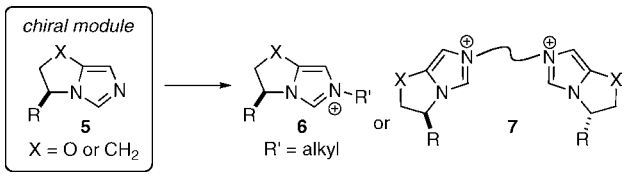
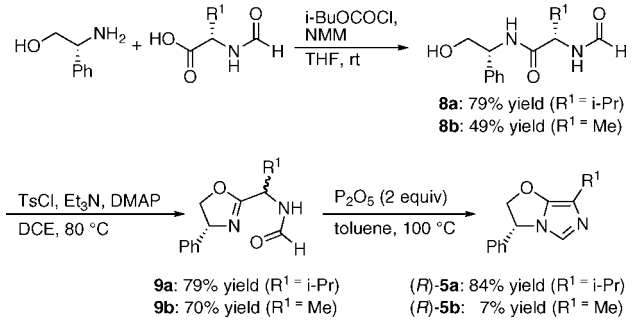


Figure 2. Modular synthesis of chiral bicyclic imidazolium salts **6** and **7**.

the intent of applying them to metal-catalyzed asymmetric reactions,[1a,b,d,7] the synthesis and the crystal structure of a new chiral Ni-complex are also presented.

First of all, we tried to prepare chiral oxazolidine-fused imidazole (*R*)-**5a** (Scheme 1). After many attempts, we found

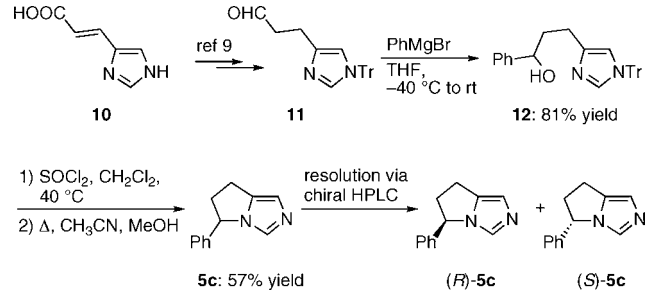
Scheme 1. Preparation of Chiral Oxazolidine-Fused Imidazoles **5a** and **5b**



that a stepwise construction of two rings from diamide **8a**, which contains all the components required for the bicyclic structure, is the appropriate approach to obtain (*R*)-**5a**. Compound **8a** was prepared by the condensation of readily available (*S*)-*N*-formylvaline with (*R*)-2-phenylglycinol and the resulting **8a** was treated with tosyl chloride under basic conditions to produce oxazoline **9a**. Bicyclic imidazole (*R*)-**5a** was obtained by dehydration of **9a** with phosphorus pentoxide. The introduction of a formyl group on the *N*-terminus[8] of **8a** was critical to the success of the reaction. Other synthetic routes in which the imidazole ring was constructed from imine oxazoline and electrophilic C_1-fragments were unsuccessful. As the dehydrating agent, phosphorus pentoxide showed the best result for the final step and low yields were observed with other reagents, such as $POCl_3$. When we tried to prepare (*R*)-**5b**, which has a methyl group at the R^1 position, by means of the same procedure using (*S*)-*N*-formylalanine instead of (*S*)-*N*-formylvaline as the starting material, the final dehydration step of the oxazole ring was unsuccessful.

We also prepared chiral pyrrolidine-fused imidazole **5c**, which has a simpler structure than **5a** and **5b** (Scheme 2). A

Scheme 2. Preparation of Chiral Pyrrolidine-Fused Imidazole **5c**



synthetic route that was based on Browne's procedure[9] starting from commercially available urocanic acid **10** was employed for this purpose and racemic **5c** was efficiently furnished. Enantiomerically pure (*R*)-**5c** and (*S*)-**5c** were obtained from the racemic product by separation, using preparative HPLC with a chiral column.

The results of the synthesis of *N*-alkyl imidazolium salts **6** and bisimidazolium salts **7** are summarized in Table 1. When the reaction of **5a** with iodomethane was performed at 70 °C in acetonitrile, the desired *N*-methyl imidazolium salt **6a**[10] was obtained in good yield, as expected (entry 1). On the other hand, when the reaction of **5a** with dibromomethane was performed, only decomposed products were formed instead of bisimidazolium salt **7a** (entry 2). The reaction with 1,2-dibromoethane was also unsuccessful and *N*-2-bromoethyl imidazolium salt was obtained as the major product with a trace amount of **7b** (entry 3). These results can be attributed to the steric interaction between the two imidazoles. In fact, for the synthesis of **7c** and **7d,** which

(4) Matsuoka, Y.; Ishida, Y.; Saigo, K. *Tetrahedron Lett.* **2008**, *49*, 2985–2989.

(5) For examples of known chiral bicyclic imidazoles, see: (a) Tschamber, T.; Siendt, H.; Tarnus, C.; Deredas, D.; Frankowski, A.; Kohler, S.; Streith, J. *Eur. J. Org. Chem.* **2002**, 702–712. (b) Weinberg, K.; Jankowski, S.; Le Nouen, D.; Frankowski, A. *Tetrahedron Lett.* **2002**, *43*, 1089–1092. (c) Frankowski, A.; Deredas, D.; Dubost, E.; Gessier, F.; Jankowski, S.; Neuburger, M.; Seliga, C.; Tschamber, T.; Weinberg, K. *Tetrahedron* **2003**, *59*, 6503–6520. (d) Deredas, D.; Skowron, M.; Salomon, E.; Tarnus, C.; Tschamber, T.; Wolf, W. M.; Frankowski, A. *Tetrahedron* **2007**, *63*, 2915–2922.

(6) You et al. reported chiral bistriazolium salts and their applications to asymmetric intermolecular benzoin condensation. See ref 2i.

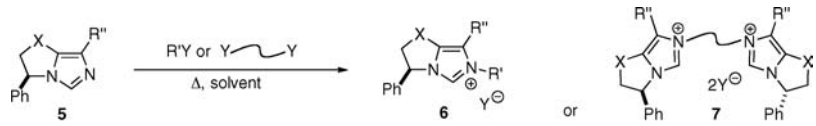
(7) (a) Lowry, R. J.; Veige, M. K.; Clément, O.; Abboud, K. A.; Ghiviriga, I.; Veige, A. S. *Organometallics* **2008**, *27*, 5184–5195, and references cited therein. (b) Ma, G.-N.; Zhang, T.; Shi, M. *Org. Lett.* **2009**, *11*, 875–878.

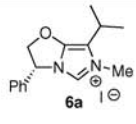
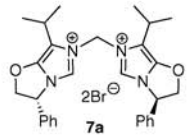
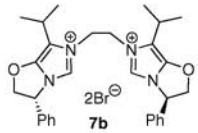
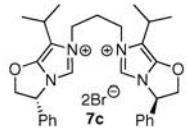
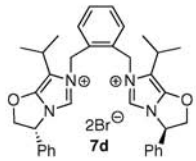
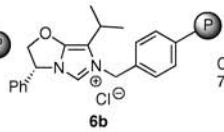
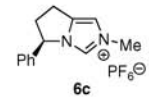
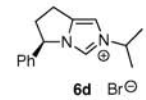
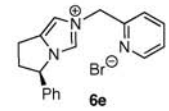
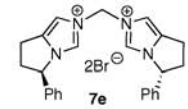
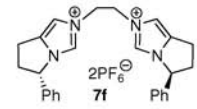
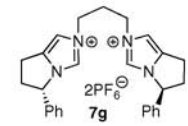
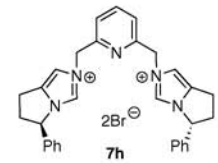
(8) Fürstner and co-workers reported a powerful method for the synthesis of imidazolium salts from *N*-formylamines, see: Fürstner, A.; Alcarazo, M.; César, V.; Lehmann, C. W. *Chem. Commun.* **2006**, 2176–2178.

(9) (a) Browne, L. J.; Gude, C.; Rodriguez, H.; Steele, R. E.; Bhatnager, A. *J. Med. Chem.* **1991**, *34*, 725–736. (b) Pirrung, M. C.; Pei, T. *J. Org. Chem.* **2000**, *65*, 2229–2230.

(10) See the Supporting Information for the crystal structure of **6a**.

Table 1. Synthesis of Chiral Imidazolium Salts **6** and **7** from Imidazoles **5**[a]



entry	reagents	product	conditions	yield (%)[b]
1	(*R*)-**5a** CH_3I (1:20)	 **6a**	CH_3CN, 70 °C, 12 h	80
2	(*R*)-**5a** CH_2Br_2 (2.2:1)	 **7a**	CH_3CN, 70 °C, 6 days	0
3	(*R*)-**5a** Br—Br (2:1)	 **7b**	CH_3CN, 80 °C, 4 days	trace
4	(*R*)-**5a** Br—Br (2.2:1)	 **7c**	CH_3CN, 70 °C, 5 days	82
5	(*R*)-**5a** Br—Br (2.2:1)	 **7d**	CH_3CN, 70 °C, 40 h	99
6	(*R*)-**5a** Cl (10:1)	 **6b**	CH_3CN, 70 °C, 5 days	97
7	(*R*)-**5c** CH_3I (1:20)	 **6c**	1) CH_3CN, 70 °C, 3 days 2) KPF_6	92
8	(*R*)-**5c** i-PrBr (1:20)	 **6d**	CH_3CN, 70 °C, 5 days	99
9	(*R*)-**5c** Br (1:1.2)	 **6e**	MeOH, 75 °C, 48 h	>99
10	(*R*)-**5c** CH_2Br_2 (1:5)	 **7e**	CH_3CN, 70 °C, 5 days	93
11	(*S*)-**5c** Br—Br (2.1:1)	 **7f**	1) CH_3CN, 70 °C, 2 days 80 °C, 3 days 2) KPF_6	>99
12	(*S*)-**5c** Br—Br (2.1:1)	 **7g**	1) CH_3CN, 70 °C, 2 days 80 °C, 3 days 2) KPF_6	>99
13	(*R*)-**5c** Br Br (2.4:1)	 **7h**	1) MeOH, 75 °C, 48 h	97

[a] All reactions were carried out in CH_3CN or MeOH at 70−80 °C. [b] Isolated yields.

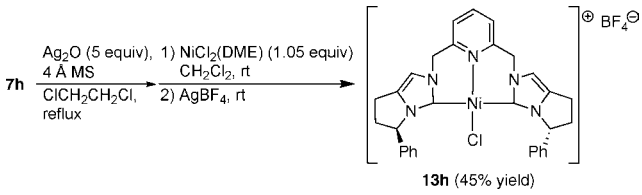
have long cross-linkers, the reaction proceeded without any problems (entries 4 and 5). Moreover, the reaction of **5a** with Merrifield resin[11] gave corresponding imidazolium salt **6b** (entry 6). Pyrrolidine-fused imidazolium salts were likewise prepared. The reaction of **5c** with iodomethane, isopropyl bromide, and 2-bromomethylpyridine gave *N*-alkylated salts **6c**−**e**, respectively (entries 7−9). In contrast to **5a**, the reaction of more compact **5c** produced methylene, ethylene, and propylene bridged bisimidazolium salts **7e**−**g** regardless of the lengths of the cross-linkers (entries 10−12). These results suggest that the steric bulkiness of the isopropyl group of **5a** is responsible for the failure of the formation of **7a** and **7b** (entries 2 and 3). The last example is the formation of bisimidazolium salt **7h** that has a pyridyl moiety in the cross-linker (entry 13). The reaction of **5c** with 2,6-bis(bromomethyl)pyridine[12] proceeded well to give desired product **7h** in 97% yield.

The synthesized imidazolium salts can be utilized as precursors for chiral NHCs. For example, we tried to synthesize C−N−C pincer Ni-complex[1a,13] **13h** from **7h** (Scheme 3). The transformation was performed by reacting

(11) Wang, Z.; Yan, J.; Zhang, X.; Wang, L. *Synlett* **2009**, 3744–3750.

(12) Danopoulos, A. A.; Tulloch, A. A. D.; Winston, S.; Eastham, G.; Hursthouse, M. B. *Dalton Trans.* **2003**, 1009–1015.

Scheme 3. Synthesis of C−N−C Pincer Ni-Complex **13h** from **7h**



$NiCl_2$(DME) with a silver complex that was prepared from **7h** and Ag_2O, followed by counteranion exchange with $AgBF_4$.[14] As a result, chiral complex **13h** was obtained in 45% yield. Similar to the general agreement for NHC complexes, **13h** was found to be quite stable in air. Its purification was possible even by open silica gel column chromatography.

A single crystal suitable for X-ray single-crystal structure determination was obtained by slow diffusion of pentane into a solution of **13h** in CH_2Cl_2. The structure of **13h** displays an expected C_2-symmetric chiral environment with square-planar coordination geometry (Figure 3).[15]

In conclusion, we have prepared new chiral bicyclic imidazoles **5** and applied them to the modular synthesis of imidazolium salts **6** and **7**. Obviously, this approach can provide a wide variety of imidazolium salts beyond the range we have demonstrated here. Our ongoing study is focusing on various asymmetric reactions using these salts, and the results will be reported in due course.

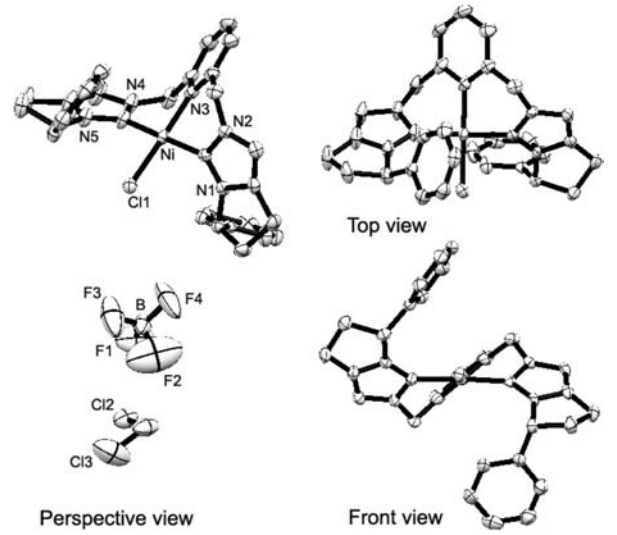


Figure 3. Crystal structure of **13h**: Hydrogen atoms are omitted for clarity (perspective view). Hydrogen atoms, CH_2Cl_2, and BF_4^- anion are omitted for clarity (top and front views).

Acknowledgment. We appreciate the financial support from the Uehara Memorial Foundation and NOVARTIS Foundation (Japan) for the Promotion of Science. We also thank Nippon Chemical Industrial Co., Ltd. for lending Daicel Chiralcel OD-H (2 cm × 25 cm).

Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra of new compounds and X-ray crystal structure files (CIF) for **6a** and **13h**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1003737

(13) (a) Pugh, D.; Danopoulos, A. A. *Coord. Chem. Rev.* **2007**, *251*, 610–641. (b) Poyatos, M.; Mata, J. A.; Peris, E. *Chem. Rev.* **2009**, *109*, 3677–3707.

(14) Inamoto, K.; Kuroda, J.; Kwon, E.; Hiroya, K.; Doi, T. *J. Organomet. Chem.* **2009**, *694*, 389–396.

(15) The crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre; deposition no. 761554. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 IEZ, UK; fax (+44) 1223−336−033; e-mail deposit@ccdc.cam.ac.uk).