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Tetrahedron Letters 49 (2008) 2985–2989
Tetrahedron Letters

Chiral bicyclic imidazolium salts as a new class of N-heterocyclic carbene precursors

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Received 28 January 2008; revised 21 February 2008; accepted 28 February 2008
Available online 10 March 2008

Abstract

A N(1)–C(5) bridged chiral bicyclic imidazole with a morpholine framework was synthesized from an enantiopure 2-amino alcohol. The resultant imidazole reacted with various electrophiles, including primary and secondary alkyl halides, benzyne, and an electron-deficient aryl halide, to give the corresponding imidazolium salts. Some of the imidazolium salts were found to have potential as the precursor of a chiral N-heterocyclic carbene catalyst; by the direct annulation of an enal and a ketone through the intermediacy of a homoenolate and an activated carboxylate, the target lactone was obtained in an enantiomerically enriched form (up to 66% ee).

Keywords: Asymmetric catalyst; Imidazolium; Homoenolate; N-Heterocyclic carbene; Umpolung

Owing to the unique properties and potential utilities, N-heterocyclic carbenes (NHCs) have attracted increasing attention for the last two decades.[1] NHCs have been found to serve as universal ligands for transition metal-based catalysts,[2] of which the enhanced catalytic activities are originated from the strong σ-donating property of the NHC ligands.[3] In addition, NHCs are known to act as metal-free organocatalysts to promote several kinds of unique and uncommon organic transformations, which can hardly occur in other systems.[4] As an extension of these studies, the development of chiral NHCs and their application to enantioselective organic transformations are of special importance. In fact, a large number of chiral azolium salts (imidazolium, imidazolinium, triazolium, and thiazolium salts) have been developed as precursors of chiral NHCs, and some of them exhibited an excellent chiral induction ability.[4]

For the design of chiral NHC organocatalysts, those with a rigid bicyclic framework are known to be one of the most promising classes to realize high enantioselectivity; N(3)–C(4) bridged thiazolium salts (Fig. 1, **A**)[5] and C(3)–N(4) bridged triazolium salts (**B**)[6] have been proven to provide excellent NHC catalysts for various asymmetric reactions involving the umpolung of aldehydes, such as the benzoin condensation and the Stetter reaction. Considering

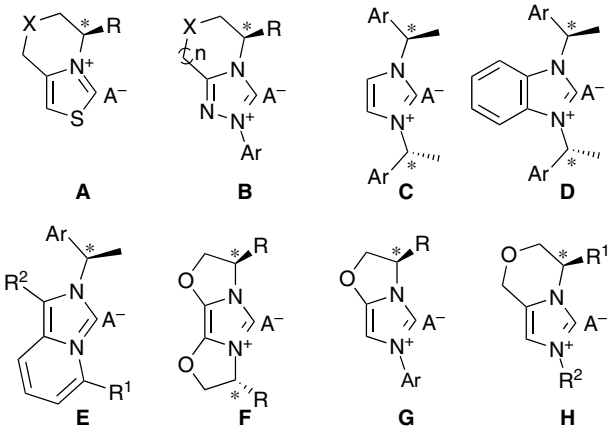

Fig. 1. Design of chiral azolium salts.

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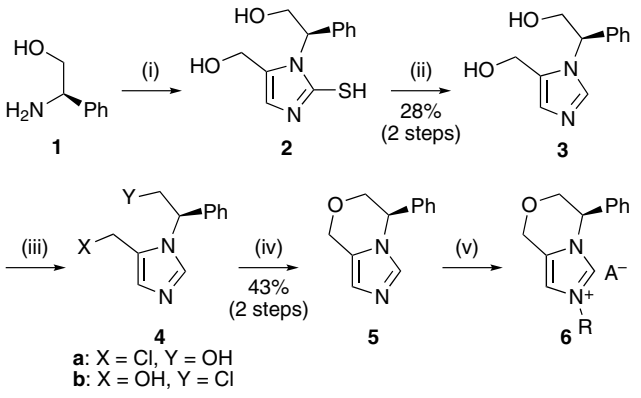
0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.02.175

the strong relationship between the properties of NHCs (nucleophilicity, basicity, catalytic activity, etc.) and the structure/species of their parent azolium salts, chiral imidazolylidenes, derived from the corresponding imidazolium salts with a fused-ring structure, should play a role complementary to traditional NHCs obtained from analogous thiazolium and triazolium salts (**A** and **B**). At the present time, however, the synthesis of chiral imidazolium salts with such a constrained structure has been limited compared with other azolium salts; relatively simple imidazolium salts having two 1-arylethyl substituents at the N(1) and N(3) positions (**C** and **D**) were most widely used as the precursors of chiral imidazolylidenes.[7] Rare and noteworthy exceptions are bicyclic/tricyclic imidazolium salts (**F** and **G**), of which the application to asymmetric induction in organic transformations is still at a developing stage.[8,9] These aspects prompted us to synthesize bicyclic imidazolium salts with a N(3)–C(4) bridged structure (**H**).[10]

In order to ensure the structural variation for NHCs, it would be advantageous to incorporate an easily accessible chiral building block into the skeleton of NHC precursors. On the basis of such consideration, we envisioned a synthetic route starting from an enantiopure 2-amino alcohol, as shown in Scheme 1. Imidazole **3** with two hydroxy groups was synthesized by applying well-established reactions for the preparation of N(3)-substituted and C(4)-hydroxymethylated imidazoles.[11] The cyclocondensation of (*R*)-2-amino-2-phenylethanol (**1**), 1,3-dihydroxypropan-2-one, and potassium thiocyanate in the presence of aqueous HCl and AcOH gave the corresponding mercaptoimidazole **2**, which was then desulfurized under oxidative conditions to give imidazole **3**.[11b] The high polarity of **2** and **3** made their purification difficult and lowered the yields to some extent. This problem might be solved by proper protection of the hydroxy group in **1**.

Then, we attempted the condensation of the two hydroxy groups in **3** to obtain the target imidazole **5** with a bicyclic framework. For this transformation, we envisaged the following reaction course: the conversion of either

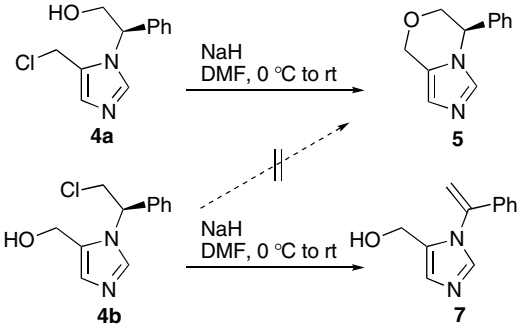


Scheme 1. Synthesis of the chiral bicyclic imidazolium salt **6**. Reagents and conditions: (i) 1,3-dihydroxypropan-2-one (dimer), KSCN, HClaq, AcOH/1-BuOH, 80 °C; (ii) H_2O_2, AcOH/water, rt; (iii) $(COCl)_2$/DMF, CH_3CN, 0 °C to rt; (iv) NaH, DMF, 0 °C to rt; (v) electrophile (see Fig. 2).

of the two hydroxy groups into a leaving group (chloro, *p*-toluenesulfonato, etc.), followed by the intramolecular condensation of this moiety with the other hydroxy group. For the first step, the treatment of **3** with thionyl chloride or with *p*-toluenesulfonyl chloride/pyridine gave a complex mixture. Therefore, we surveyed several reagents for the transformation of the hydroxy group into a chloro group and finally found that the Vilsmeier reagent, generated from oxalyl chloride/*N*,*N*-dimethylformamide, was effective.[11c] As a result, diol **3** was easily converted into a mixture of the monochlorinated products **4a** and **4b** in almost quantitative yield. Although only a slight chemoselection between the two hydroxy groups took place (**4a**:**4b** = 50:50–60:40), the dichlorinated byproduct was not generated at a detectable level; in this case, the second chlorinations would be a further slower process than the first chlorinations, probably because the electronic and/or steric effect of the introduced chlorine atom in the first place retards the second chlorination.

Concerned with the intramolecular ether formation, the two monochlorinated imidazoles **4a** and **4b** were expected to give the same product **5**. Contrary to our expectation, however, the treatment of the mixture with sodium hydride (2.0 equiv) gave not only the target compound **5**, but also the *N*-alkenylimidazole **7** in a considerable extent, which was undoubtedly generated by the base-promoted elimination of HCl from **4b**. Because the ratio of the two products in the resultant mixture (**5**:**7** = 50:50–60:40) was almost identical to that of the monochlorinated imidazoles **4a** and **4b** in the starting material, **4a** and **4b** were likely to be exclusively converted into **5** and **7**, respectively (Scheme 2). Thus, the chiral imidazole with a fused-ring structure **5** was obtained in an overall yield of 43% from the bis(hydroxy)imidazole **3**. The structure of **5** was unequivocally identified by an X-ray crystallographic analysis.[12]

In the next stage, various electrophiles were applied to the quaternization of **5**, which provided the N(3) substituent of the target imidazolium salts **6** (Fig. 2). In the synthesis of analogous triazolium/imidazolium salts established by several research groups (Fig. 1, **B** and **G**), only aromatic groups could be introduced at the N(3) position in convergent synthetic routes.[6,8] Compared with this, the synthesis of the present imidazolium salts has two notable characteristics: (i) imidazolium salts with various N-substituents can



Scheme 2. Transformation of **4a**,**b** by the treatment with a base.

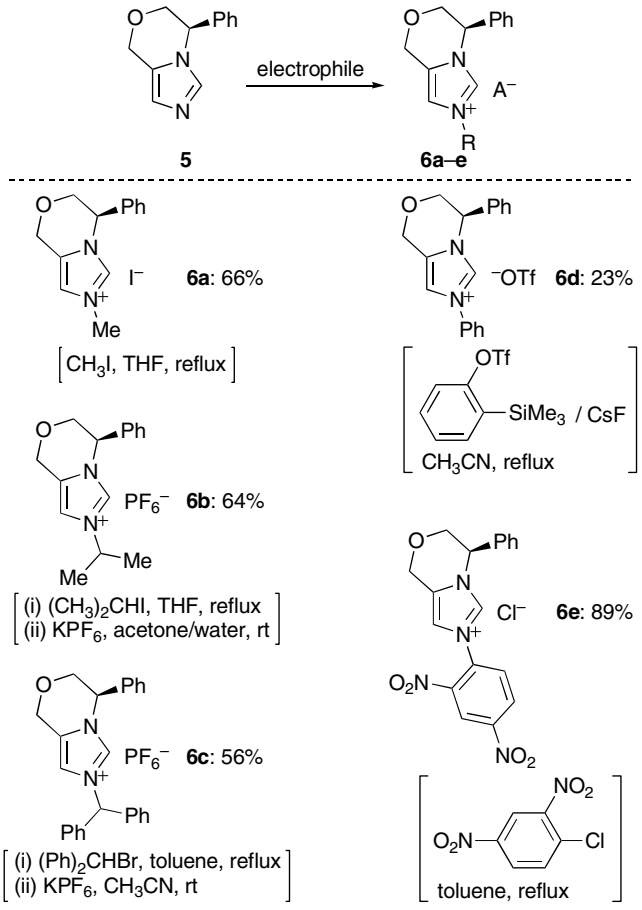


Fig. 2. Synthesis of imidazolium salts **6a**–**e** by the treatment of **5** with various electrophiles.

be derived from a common precursor imidazole in a divergent manner, just upon changing an electrophile for the quaternization, and (ii) both of aliphatic and aromatic substituents are potentially introduced at the N(3) of the parent imidazole by applying conventional methods for alkylation/arylation.[13] In fact, the reaction of primary and secondary alkyl halides with **5** proceeded very smoothly to afford the corresponding N(3)-alkylated imidazolium salts (**6a**–**c**) in acceptable yields. In addition to this, an aromatic ring could also be introduced at the same position, although there was room for the improvement in yield, variation of applicable aryl group, and convenience in isolation; the reaction of in situ generated benzyne[13a] and an electron-deficient aryl halide[13b] afforded the corresponding imidazolium salts (**6d** and **6e**) in 23% and 89% yields, respectively.

An analogue of **6a** with higher crystallinity (**6a′**) was prepared by the anion exchange from I^- to PF_6^-, and an X-ray crystallographic study was conducted for a single crystal of **6a′** (Fig. 3).[12] Noteworthy is the fact that the phenyl group is placed at the equatorial position of the six-membered ring taking a pseudo-chair conformation. As a result, the phenyl group efficiently shields a half space around the imidazolium C(2), which seems advantageous for efficient chiral induction.[14]

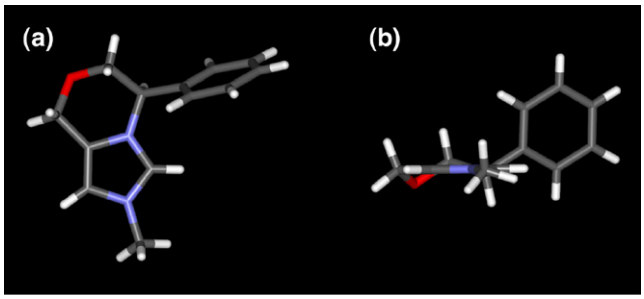
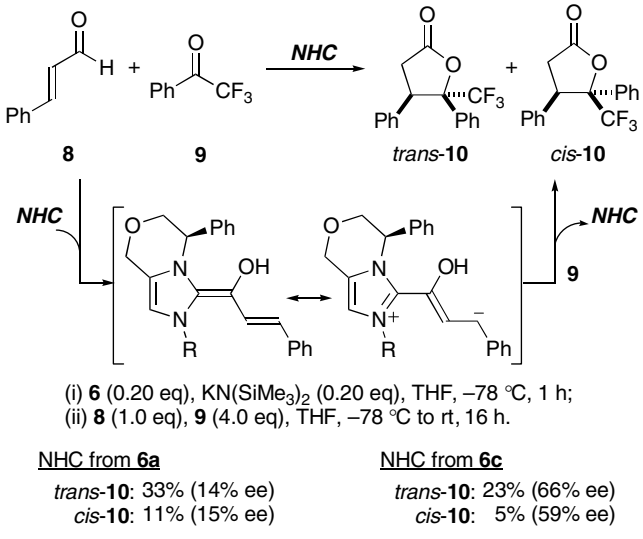


Fig. 3. X-ray crystal structure of a **6a′**; (a) top view and (b) side view. The counter anion (PF_6^-) is omitted for clarity.

In order to demonstrate the utility of imidazolylidene NHCs derived from these new imidazolium salts **6**, we attempted the NHC-catalyzed annulation of an enal and a ketone.[15] This reaction and relatives are expected to provide us a powerful tool for C–C bond formations in a novel mode, which involves the catalytic generation of a homoenolate from the enal unit, followed by the electrophilic trapping of the homoenolate (Scheme 3). Among NHCs derived from azolium salts, however, only imidazolylidenes are known to be able to catalyze this reaction efficiently, most likely because of the difference in their physical properties depending on the parent species.[10,15b,d] Moreover, in spite of no less than four years having past since the first report, there has been only one example of enantioselective version, where chiral induction with an unsatisfactory level was reported (up to 25% ee).[15b] Thus, the catalytic and asymmetric reaction of a homoenolate with an electrophile still remains as an unexplored realm in this field, which motivated us to apply the imidazolium precatalysts **6** for this reaction.[16]

At the beginning of this study, the condensations of cinnamaldehyde (**8**) with 2,2,2-trifluoroacetophenone (**9**) were conducted, by using imidazolylidene NHCs generated from



Scheme 3. NHC-catalyzed annulation of an enal with a ketone.

6a and **6c** with potassium hexamethyldisilazane (Scheme 3).[15b] In both these cases, the desired condensate **10** was obtained in acceptable yields (as mixtures of trans and cis isomers; 44% and 28% yields, respectively).[17] As for the stereochemical outcome of the condensations, however, there was a significant difference between the two catalytic systems; the NHC from **6c** achieved diastereo- and enantioselectivities much higher than did that from **6a**, which suggests that the NHC catalyst with a bulky N-substituent is advantageous for the control of the relative orientation of the homoenolate intermediate and the electrophile **9** (Scheme 3). Worth noting is the fact that diastereo- and enantio-controls achieved by the NHC from **6c** were the most excellent for the present condensation, as far as we know (dr = 84:16, $ee_{major} = 66\%$, $ee_{minor} = 59\%$). In addition, the dramatic change in stereochemical outcome between the two precatalysts **6a** and **6c** implies that we can further optimize the N-substituent, taking advantage of the divergent synthetic route from **5** to **6**.

In conclusion, we developed precursors (**6a**–**e**) for novel chiral imidazolylidenes, which have a bicyclic structure with a morpholine framework. The NHC derived from **6c** catalyzed the annulation of enal **8** and ketone **9** to give the lactone **10** with good diastereo- and enantioselectivities. Considering the peculiar reactivity of imidazolylidenes compared with those of thiazolylidenes and triazolylidenes, as well as the conformationally fixed structure advantageous for efficient chiral induction, we believe that the imidazolium salts **6a**–**e** would be widely useful as the precursors of chiral organocatalysts for various organic transformations.

Further optimization of the N-substituent in **6** and detailed studies on the physical properties, such as nucleophilicity, basicity, σ-donating property, and dimerization propensity, are under investigation.

Acknowledgments

We acknowledge Dr. M. Yamazaki (Rigaku Corporation) for the X-ray crystallography of **6a′**. We would also like to thank Professor Y. Nishibayashi and Dr. Y. Miyake (The University of Tokyo) for MS spectroscopy.

Supplementary data

Experimental details for the synthesis and characterization of **2**–**6** and for the enantioselective annulation of **8** and **9** to form **10** are available. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.02.175.

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10. During the reviewing process of this Letter, the development of a chiral bicyclic imidazolium salt with a framework quite similar to that of our imidazolium salts has been reported (type **H** in Figure 1, R^2 = mesityl). See: Struble, J. R.; Kaeobamrung, J.; Bode, J. W. *Org. Lett.* **2008**, *10*. doi:10.1021/ol800006m.
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12. Crystallographic data for **5** and **6a′** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Numbers CCDC 672454 and CCDC 672455, respectively. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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14. The imidazolium ring of **6a** takes a slightly distorted shape most likely because of the constrained bicyclic structure. The bond angle of N(1)–C(2)–N(3) in an imidazolium ring: **6a′**, 107.8°; usual N(1),N(3),C(5)-trialkylimidazoliums, 109°.
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16. During the reviewing process of this Letter, four reports (Ref. 10 and the following three papers) for enantioselective reactions involving NHC-catalyzed homoenolate formation have been published. See: (a) Phillips, E. M.; Reynolds, T. E.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**. doi:10.1021/ja710521m; (b) Seayad, J.; Patra, P. K.; Zhang, Y.; Ying, J. Y. *Org. Lett.* **2008**, *10*. doi:10.1021/ol800003n; (c) Chan, A.; Scheidt, K. A. *J. Am. Chem. Soc.* **2008**, *130*. doi:10.1021/ja711130p. In some of these examples, enantioselectivity much better than that in Ref. 15b was achieved (up to 93% ee) by using special electrophiles. However, it seems still difficult to realize satisfactory selectivity by using a simple aldehyde or ketone as an electrophile unit (up to 34% ee).
17. In both the cases, enal **8** was consumed almost completely, but the formation of another γ-lactone via the homo-annulation of **8** took place to reduce the yield of **10**. This problematic side reaction was commonly observed in the case of other imidazolylidene catalysts (see Ref. 15a).