ARTICLE

Synthesis of Enantiopure 1,2,3-Triazolylidene-Type Mesoionic Carbenes (MICs) Conjugate Acids Featuring a Rigid Bicyclic Scaffold

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Chiral NHCs have found numerous applications as ligands for transition metals and in their own rights for asymmetric catalysis. Here, we report a synthetic route from L-malic acid to enantiopure 1,2,3-triazoliums (mesoionic carbene conjugate acids) with the chiral center in a fused ring.

Introduction

Chirality, a fundamental property of nature, is vital in many fields including chemistry, biology, physic and material science. Reactions employing chiral transition metal catalysts or organocatalysts are the most efficient ways to obtain enantiomerically pure compounds from achiral feedstocks. Over the past decades, *N*-heterocyclic carbenes (NHCs) have been demonstrated to be both powerful ligands for transition metal catalysts[1] and organocatalysts in their own right,[2] and a series of chiral NHCs have been reported.[3] The stereocenter can be located in the sidechain of the NHCs (Figure 1a, type A) or the the saturated backbone (Figure 1a, type B). These two types of chiral NHCs have been shown to perform well as ligands for asymmetric metal catalysis.[4] However, a breakthrough for asymmetric induction in NHC-catalyzed reactions came from the work of Leeper,[5] Enders,[6] Rovis,[7] and Bode,[8] which introduced rigid bicyclic scaffolds (Figure 1a, type C, and Figure 1b). For example, excellent enantioselectivity was observed in NHC-Ir catalyzed transfer hydrogenation,[9] NHC-Cu catalyzed allylic silylation[10] and NHC-catalyzed organic transformations.[2]

Another type of stable carbene, namely mesoionic carbenes, and more specifically 1,2,3-triazol-5-ylidenes,[11] has more recently showed excellent potential as ligands for transition metals catalysts[12] and as organocatalysts both *via* two-electron[13] and single electron transfer processes.[14] Importantly, MICs are readily available in large quantities, and contrarily to other carbenes, they don't dimerize. So far, there are just a handful of examples of chiral MICs all of them featuring flexible sidechain chirality (Figure 1c).[15-21]

Considering the remarkable potential of MICs in catalysis, it is necessary to broaden the types of chiral MICs/conjugate acids. Inspired by the success of pyrrolidine-fused chiral NHCs (Figure 1b), herein we report the preparation of enantiopure pyrrolidine-fused 1,2,3-triazol-5-ylidene conjugate acids using a readily available starting material from the chiral pool (Figure 1d).

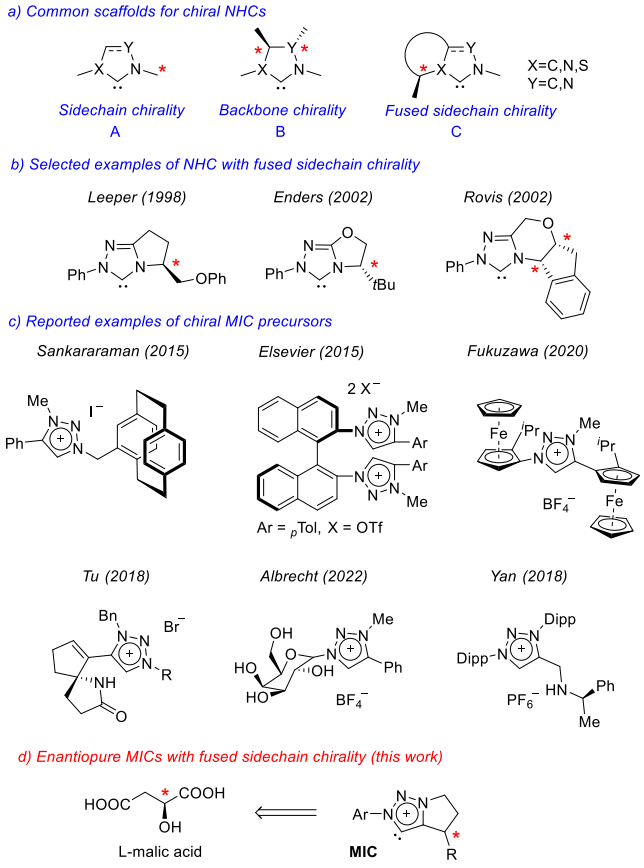

Figure 1. Chiral NHCs and MICs.

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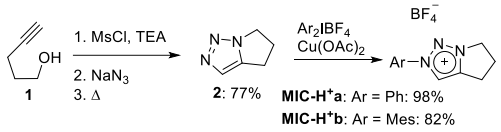
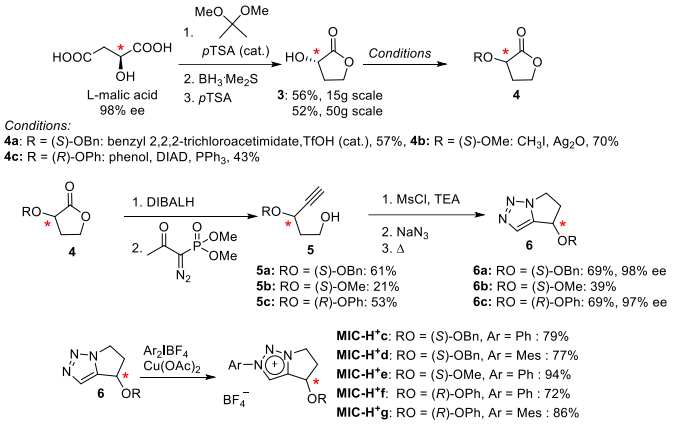
Results and discussion

To test the feasability of the key sequence of our synthetic strategy, we first prepared an achiral version of the fused triazole, using pent-4-yn-1-ol (**1**) as a precursor. Gratifyingly, we found that the desired heterocycle was readily accessible in three steps (Scheme 1).[22] The alcohol was treated with methanesulfonyl chloride, followed by a substitution reaction of the corresponding mesylate with sodium azide; then an intramolecular thermally-induced Huisgen cycloaddition reaction afforded the desired fused triazole **2**, which was isolated in 77% yield (over three steps). Lastly, quaternization by copper-catalyzed *N*-arylation[23] using diaryliodonium salts produced the corresponding achiral conjugate acids **MIC-H$^+$a, b** in excellent isolated yields.



Scheme 1. Synthesis of the achiral conjugate acid of pyrrolidine-fused 1,2,3-triazol-5-ylidenes. MsCl: methanesulfonyl chloride; Mes: 2,4,6-trimethylphenyl.

Then, we turned our attention to the chiral version. As a starting material, we chose enantiopure L-malic acid (Scheme 2). This chiral pool chemical was converted in three steps into hydroxylactone **3** using previously described conditions.[24] First, protection of the secondary alcohol and carboxy group with 2,2-dimethoxypropane, followed reduction of the second carboxylic moiety by borane and lastly an acid-catalyzed ring closing esterification afforded hydroxylactone **3** (56% yield, over three steps, 15 g scale). This sequence is easily scalable to 50 g scale of L-malic acid, with similar yields (52%). Then, **3** was *O*-alkylated and *O*-benzylated by reaction of **3** with benzyl-2,2,2-trichloroacetamidate and methyl iodide to yield **4a** and **4b**, respectively, with retention of configuration, whereas **4c** was prepared, with inversion of configuration, by successive reaction with DIAD and phenol. The corresponding lactones **4** were converted to alcohols **5** with a two-step procedure. First, lactones **4** were reduced with DIBALH giving the corresponding lactols, which was converted into **5** using the Bestmann-Ohira reagent (21-61% yield over two steps). From **5**, the formation of the 1,2,3-triazole ring was achieved in 39-77% yields, in three steps as described for the parent compound (Scheme 1). It is worth mentioning that the chiral HPLC of selected triazoles **6** confirmed that no significant drop in enantiopurity, occurred during the whole synthetic sequence from the malic acid (Scheme 2). Lastly, quaternization by copper-catalyzed *N*-arylation[23] using diaryliodonium salts provided a library of triazolium salts **MIC-H$^+$c-g** in good-to-excellent yields (72-94%).



Scheme 2. Synthesis of the chiral conjugate acid of pyrrolidine-fused 1,2,3-triazol-5-ylidenes. DIAD: diisopropyl azodicarboxylate.

The absolute configuration of the chiral center of **MIC-H$^+$f** was assigned as *R* using X-ray diffraction analysis (Figure 2, for more details refer to the Supporting Information file).

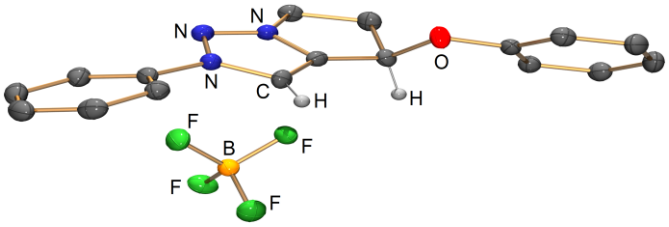
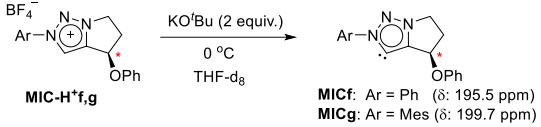


Figure 2. X-ray crystal structure of **MIC-H$^+$f**.

With precursors in hand, and as a proof of concept, we prepared free carbenes **MICf,g** by treatment of the corresponding triazolium **MIC-H$^+$f** and **MIC-H$^+$g** with an excess of KO*t*Bu at 0 °C (Scheme 3). The resulting carbenes were characterized by NMR spectroscopy, with the carbene carbon signals at 195.5 ppm (**MICf**) and 199.7 ppm (**MICg**) in THF-d_8. These chemical shifts are in accordance with those previously reported for MICs.[11] No significant decomposition was observed in solution at 0 °C after 48 hours. However, **MICg** is totally decomposed after 5 hrs at 40 °C (for more information, refer to the Supporting Information file). To check that no racemization occurred during the deprotonation of the triazolium salts, we prepared **MICf** at 0 °C following the procedure described above and added 3 equivalents of tetrafluorobic acid after 15 minutes. Measurement of the optical rotation of regenerated **MIC-H$^+$f** proved unchanged compared to the original sample.



Scheme 3. Generation of **MICf** and **MICg**.

Conclusions

This paper shows that enantiopure 1,2,3-triazolium salts, featuring a fused sidechain with a chirogenic center can be prepared in large quantities from a precursor belonging to the

chiral pool. Importantly, starting from cheap L-malic acid, both enantiomers of these chiral protonated MICs can be prepared, depending on the method used to transform the hydroxylactone **3** into **4**. Additionally, the ensuing free chiral MICs can be spectroscopically observed and are stable for a few days at low temperatures. Because of the success of their NHC cousins, featuring the same type of fused sidechain chirality, numerous applications of these MICs can be expected in asymmetric catalysis.

Author Contributions

V.D. performed and designed the synthesis of all compounds. G.B. and J.V. supervised the project. M.M. and S.P. performed the X-ray crystallographic analysis, and NMR experiments, respectively. V.D., X.Y. and G.B. wrote the manuscript. All authors have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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