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Synthesis of enantiopure 1,2,3-triazolylidene-type mesoionic carbene (MIC) conjugate acids featuring a rigid bicyclic scaffold†

 Vojtěch Dočekal, ^{a,b} Mohand Melaimi, ^b Simona Petrželová,^c Jan Veselý,^a Xiaoyu Yan ^d and Guy Bertrand ^{*b}
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Chiral NHCs have found numerous applications as ligands for transition metals and in their own right for asymmetric catalysis. Here, we report a synthetic route from L-malic acid to enantiopure 1,2,3-triazoliums (mesoionic carbene conjugate acids) with a chiral center in a fused ring.

Introduction

Chirality, a fundamental property of nature, is vital in many fields including chemistry, biology, physics and materials science. Reactions employing chiral transition metal catalysts or organocatalysts have been 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 catalysts¹ and organocatalysts in their own right,² and a series of chiral NHCs have been reported.³ The stereocenter can be located in the side chain of NHCs (Fig. 1a, type A) or the saturated backbone (Fig. 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 (Fig. 1a, type C, and Fig. 1b). For example, excellent enantioselectivity was observed in NHC-Ir catalyzed transfer hydrogenation,⁹ NHC-Cu catalyzed allylic silylation¹⁰ 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 shown excellent potential as ligands for transition metal catalysts¹² and organocatalysts both *via* two-electron¹³ and single-electron transfer processes.¹⁴ Importantly, MICs are readily available in large quantities, and contrary to other carbenes, they do not dimerize. So far, there are just a handful

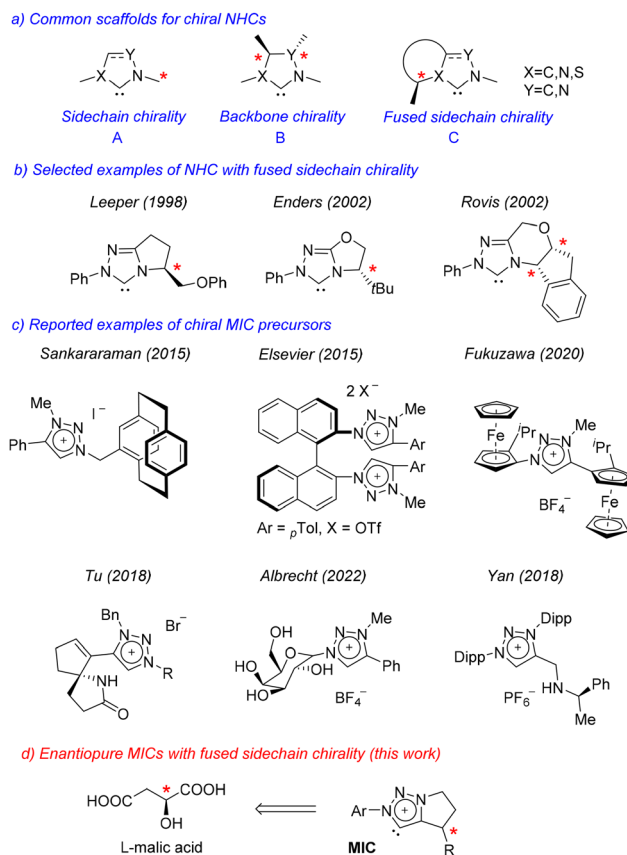


Fig. 1 Chiral NHCs and MICs.

^aDepartment of Organic Chemistry, Faculty of Science, Charles University, Hlavova 2030/8, 128 43 Prague 2, Czech Republic

^bUCSD-CNRS Joint Research Laboratory (IRL3555), Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, CA-92093-0343, USA. E-mail: gbertrand@ucsd.edu

^cDepartment of Chemistry Education, Faculty of Science, Charles University, Hlavova 2030/8, 128 43 Prague 2, Czech Republic

^dKey Laboratory of Advanced Light Conversion Materials and Biophotonics, Department of Chemistry, Renmin University of China, Beijing, 100872, China

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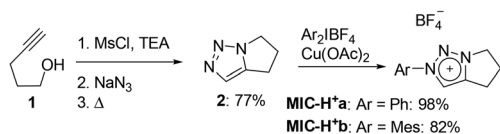
examples of chiral MICs, all of them featuring flexible side chain chirality (Fig. 1c).^{15–21}

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 (Fig. 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 (Fig. 1d).

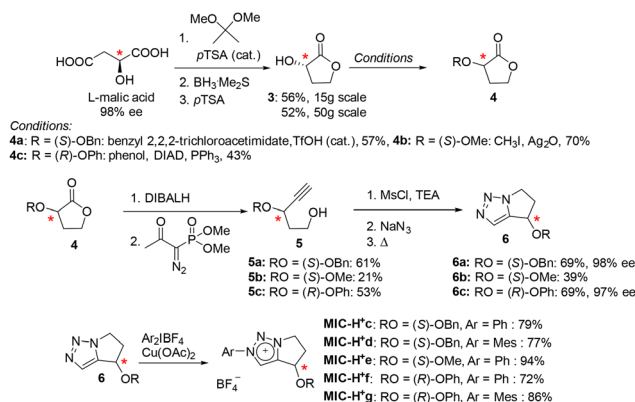
Results and discussion

To test the feasibility 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*-arylation²³ using diaryliodonium salts produced the corresponding achiral conjugate acids **MIC-H⁺a,b** in excellent isolated yields.

Then, we turned our attention to the chiral version. As starting material, we chose enantiopure *L*-malic acid (Scheme 2). This chiral pool chemical was converted in three steps into hydroxylactone **3** using the previously described conditions.²⁴ First, protection of the secondary alcohol and carboxyl group with 2,2-dimethoxypropane, followed by 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 a reaction of **3** with benzyl-2,2,2-trichloroacetamide and methyl iodide to yield **4a** and **4b**, respectively, with the retention of the configuration, whereas **4c** was prepared, with the inversion of the configuration, by a successive reaction with DIAD and phenol. The corresponding lactones **4** were converted to alcohols **5** by a two-step procedure. First, lactones **4** were reduced with DIBALH, giving the corresponding lactols, which were converted into **5** using the Bestmann–Ohira reagent (21–61% yield over two steps). From **5**, the 1,2,3-triazole ring was achieved in



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.



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

39–77% yields, in three steps as described for the parent compound (Scheme 1). It is worth mentioning that the chiral HPLC of the selected triazoles **6** confirmed that no significant decrease in enantiopurity occurred during the whole synthetic sequence from the malic acid (Scheme 2). Lastly, quaternization by copper-catalyzed *N*-arylation²³ using diaryliodonium salts provided a library of triazolium salts **MIC-H⁺c-g** in good to excellent yields (72–94%).

The absolute configuration of the chiral center of **MIC-H⁺f** was assigned *R* using X-ray diffraction analysis (Fig. 2; for more details, refer to the ESI[†]).

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^tBu 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 were in accordance with those previously reported for MICs.¹¹ No significant decomposition was observed in solution at 0 °C after 48 hours. However, **MICg** was totally decomposed after 5 h at 40 °C (for more infor-

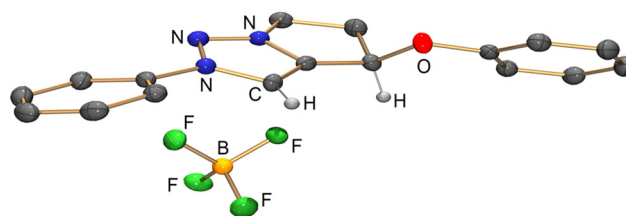
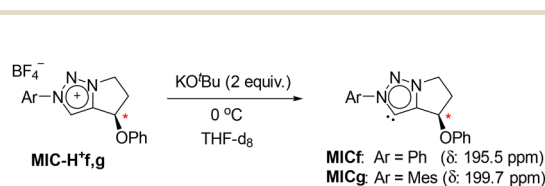


Fig. 2 X-ray crystal structure of **MIC-H⁺f**.



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

mation, refer to the ESI[†]). 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 tetrafluoroboric acid after 15 minutes. Measurement of the optical rotation of the regenerated MIC-H⁺f remained unchanged compared to the original sample.

Conclusions

This study shows that enantiopure 1,2,3-triazolium salts featuring a fused side chain 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 hydroxylactone **3** into **4**. Additionally, the ensuing free chiral MICs can be spectroscopically observed and were stable for a few days at low temperatures. Due to the success of their NHC cousins, featuring the same type of fused side chain 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.

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