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The debut of chiral cyclic (alkyl)(amino)carbenes (CAACs) in enantioselective catalysis†

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The popularity of NHCs in transition metal catalysis has prompted the development of chiral versions as electron-rich neutral stereodirecting ancillary ligands for enantioselective transformations. Herein we demonstrate that cyclic (alkyl)(amino)carbene (CAAC) ligands can also engage in asymmetric transformations, thereby expanding the toolbox of available chiral carbenes.

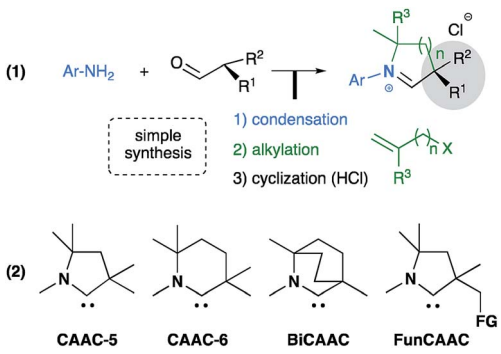
1. Introduction

The success of stable N-heterocyclic carbenes (NHCs) as ligands for transition metal catalysts, and as organocatalysts in their own right, has triggered the development of chiral versions.[1–3] Surprisingly, as recently noted by Glorius and co-workers,[4] despite the existence of a variety of stable heterocyclic carbenes,[5] only diaminocarbenes, namely imidazol-2-ylidenes,[6] imidazolidin-2-ylidenes[7] and 1,2,4-triazol-5-ylidenes[8] have been used as ligands for enantioselective transformations. In 2005 our group discovered cyclic (alkyl)(amino)carbenes (CAACs).[9,10] We and others have demonstrated that their unique electronic (more σ-donating and π-accepting than NHCs) and steric properties allow for the improvement of known catalytic processes (Ru,[11] Pd,[9,12] and Rh[13]) as well as promoting novel reactions with coinage metals (Cu[14] and Au[15]). The direct protonated precursors of CAACs are readily available in one pot from an aldehyde and a primary amine (Scheme 1(1)).[16] We have shown that our versatile synthetic methodology facilitates access to a library of 5-membered (CAAC-5), 6-membered (CAAC-6),[12] bicylic (BiCAAC)[17] and even bifunctional CAACs (FunCAAC)[14b] (Scheme 1(2)). Of particular importance, the CAAC family features a quaternary carbon adjacent to the carbene carbon, thus allowing the introduction of a chiral center in closer proximity to the active site than NHCs. Herein, we report the first examples of chiral CAAC ligands in asymmetric catalysis.

In our initial paper on CAACs,[9] we showed that the enantiopure ***L*-$^{\text{Menth}}$CAAC** could be prepared without time-consuming enantio- or diastereoselective separation from the inexpensive (−)-menthol (Scheme 2). The key step of the synthesis was based on the well-known propensity of relatively bulky reactants to approach the cyclohexane moiety selectively from the equatorial direction.

2. Results and discussion

Years ago, we tested ***L*-$^{\text{Menth}}$CAAC** transition metal complexes in a variety of asymmetric catalytic reactions without any success. Given our recent mechanistic work on copper-catalysis, we decided to revive this topic. We considered benchmarking the ***L*-$^{\text{Menth}}$CAAC** in the copper-catalysed Asymmetric Conjugate Borylation (ACB) reaction. Over the past decade, this chemical transformation has emerged as a stalwart method for the preparation of chiral organoboron building blocks, which are



Scheme 1 Synthetic route to cyclic (alkyl)(amino)carbenes, and existing families of CAACs.

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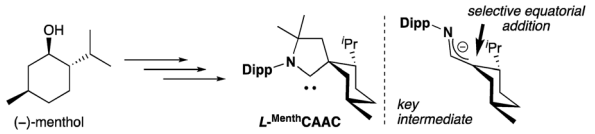
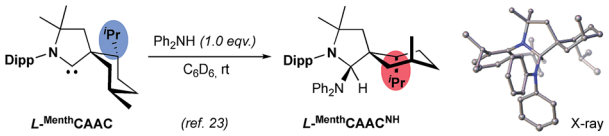
† Electronic supplementary information (ESI) available: Experimental procedures, NMR spectra. CCDC 1919315. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9sc02810b



Scheme 2 Synthesis of *L*-^{Menth}CAAC highlighting the key step.



Scheme 4 Conformational inversion of the menthyl ring.[23]

sought after in organic synthesis.[18] Although pioneered by Yun[19] and others using chiral phosphine ligands,[18d] Fernández,[20] Hoveyda[21] and others[18d] have successfully shown that carbene ligands, specifically NHCs, could also be utilized in this process.

As can be seen in Scheme 3, although the ***L*-^{Menth}CAAC** copper complex **1** was found to be highly active in the addition of bis(pinacolato)diboron (B_2pin_2) to various α,β-unsaturated esters, an almost complete lack of asymmetric induction was observed. In comparison, the known non C_2-chiral NHC copper complex **2**,[22] derived from (*S*)-1-(naphthalen-1-yl)ethan-1-amine, gave a 55% ee for the borylated adduct $\mathbf{P_1}$. Examining the X-ray crystal structure of **1**,[9] we expected some asymmetric induction since for many years we believed that a conformational inversion of the menthyl ring was energetically inaccessible. However, we recently found that in the solid state the menthyl group of the ***L*-^{Menth}CAAC** amine adduct ***L*-^{Menth}CAAC^{NH}** existed as the other conformer with the methyl and isopropyl substituents in axial position (Scheme 4).[23] We were able to confirm with DFT calculations that the inverted menthyl conformer is also readily accessible in complex **1** (Fig. 1). The existence of the two conformers **1** and **1′** readily explains the lack of asymmetric induction since they have antagonistic stereo-inducing effects.

To circumvent this issue, we sought to prepare a more rigid chiral CAAC. Among the number of readily available molecules derived from the chiral pool, we selected the steroid backbone for its bulk, structural diversity, and tunability. We also reasoned that owing to a three-dimensional skeleton composed of four fused rings (three six-member cyclohexane rings – A, B, C- and one five-member cyclopentane ring D), this steroid motif

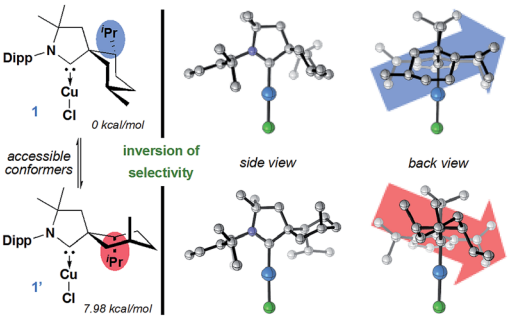


Fig. 1 Proposed justification for the lack of asymmetric induction in catalyst **1**.

would provide the desired rigid structural features while keeping the chirality intact during the synthesis (Fig. 2).

Before proceeding further, we confirmed that our synthetic methodology[16] extends to the readily available decahydronaphthalene, a model substrate mimicking the first two fused cyclohexane (A and B) rings of a steroid skeleton (Scheme 5). CAAC-decahydronaphthyl iminium ***rac*-^{Naph}CAAC** was obtained in 7 steps and 50% yield as a white powder.

Reassured by these results, we applied the same synthetic strategy to 5α-cholestan-3-one, an inexpensive enantiopure

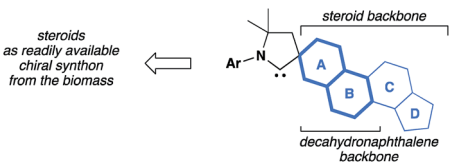
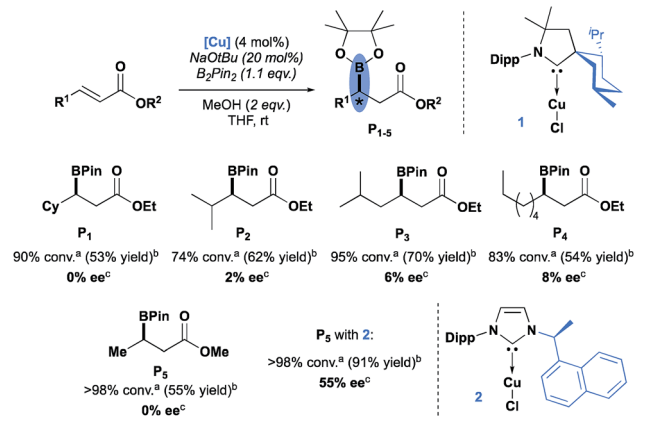
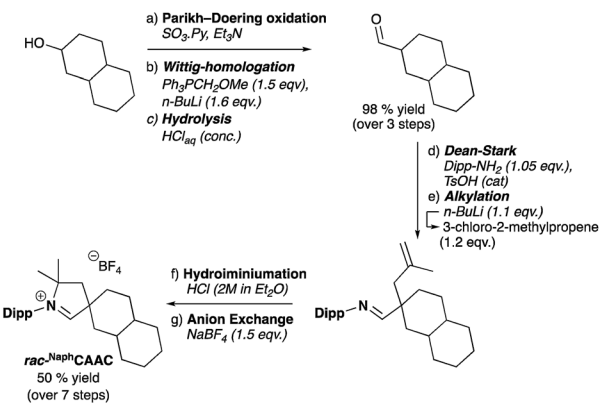


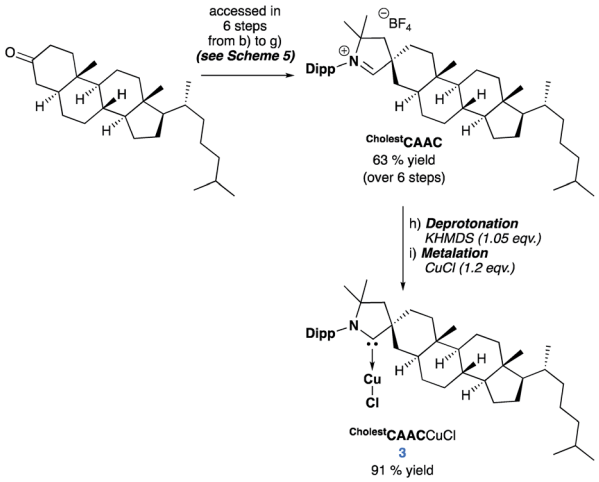
Fig. 2 Steroid CAACs as versatile chiral ligand frameworks.



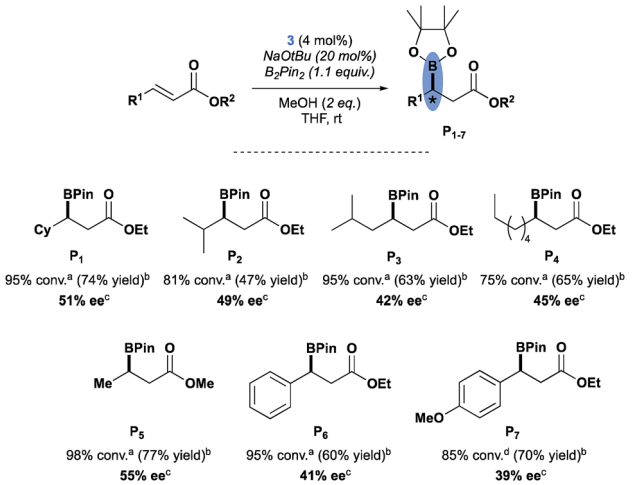
Scheme 3 Comparing *L*-^{Menth}CAACCuCl **1** and NHC–CuCl **2** in the Asymmetric Conjugate Borylation (ACB) reaction. [a]Determined by ^{1}H NMR spectroscopy using mesitylene as an internal standard. [b]Isolated yield after SiO_2 purification. [c]Determined by GC on a chiral stationary phase (see ESI for details†).



Scheme 5 Preparation of *rac*-^{Naph}CAAC.



Scheme 6 Preparation of ^{Cholest}CAAC and complex **3**.



Scheme 7 Evaluation of ^{Cholest}CAACCuCl complex **3** in ACB reaction. [a]Determined by ^{1}H NMR spectroscopy using mesitylene as an internal standard. [b]Isolated yield after SiO_2 purification. [c]Determined by GC on a chiral stationary phase (see ESI for details†). [d]Anthracene was used as internal standard.

steroid derived from coprostanol (Scheme 6). The CAAC-cholestanyl iminium ^{Cholest}**CAAC** was obtained in 6 steps and 63% yield as a white fluffy powder.[24] The corresponding copper complex **3** was prepared by deprotonation of the ^{Cholest}**CAAC** iminium with KHDMS followed by addition of copper chloride in THF. Single crystals were obtained by slow diffusion of diethyl ether in acetonitrile, and an X-ray diffraction study confirmed the formation of ^{Cholest}**CAAC**CuCl complex **3** (Fig. 3). It crystallized in the $P2_1$ space group with one molecule in the asymmetric unit cell.

The absolute stereochemistry was conclusively established using anomalous dispersion with a Flack parameter of 0.002(7) from refinement. The X-ray data of **3** show a distinctive orientation of the cholestanyl backbone, which gives rise to the topographic steric map showed in Fig. 3.[25,26] As can be seen, the corresponding quadrant diagram could support facial stereoselectivity in catalyst-substrate adducts.

We next evaluated complex **3** in the ACB reaction (Scheme 7). As with ***L***-^{Menth}**CAAC**CuCl **1**, the steroid copper complex ^{Cholest}**CAAC**CuCl **3** efficiently catalyzes the addition of B_2pin_2 to various β-substituted α,β-unsaturated esters, affording the corresponding 1,4-adducts in moderate to good isolated yields (47 to 77%). More importantly, we were pleased to observe enantioinductions with enantioselectivities reaching 55%.

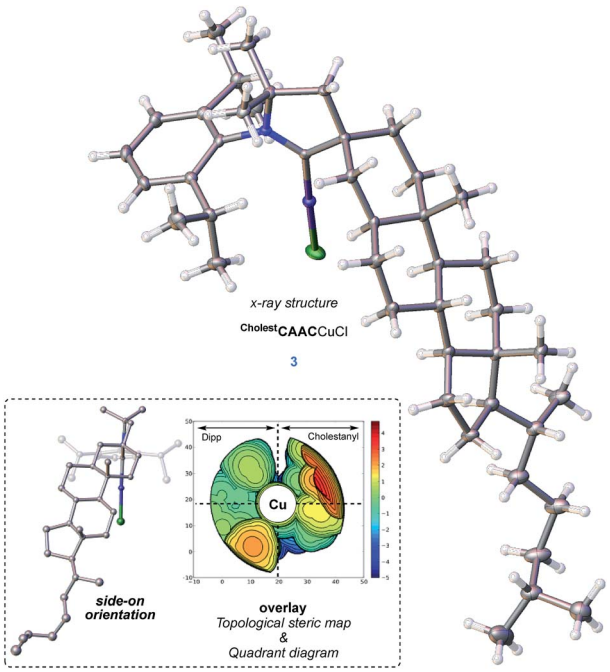


Fig. 3 X-ray crystal structure of **3** (top) with the side-on orientation (omitting hydrogen for clarity) and an overlaid topological steric map with a quadrant diagram.

3. Conclusions

This work rationalizes the inability of ***L***-^{Menth}**CAAC** to induce enantiomeric excess, and indicates that upon providing the right steric environment, the use of chiral CAACs should not be overlooked in metal-catalyzed asymmetric transformations. This new family of stereo-directing chiral carbene ligands are readily available from inexpensive precursors belonging to the chiral pool, and it is noteworthy that the chirality is not restricted to chiral amines (as is the case of NHCs), but extends to chiral aldehydes, a much larger feedstock.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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