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Chiral Catalyst Design: Cyclopentadiene-Based Brønsted Acids

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The introduction of BINOL-based (BINOL = [1,1′-binaphthalene]-2,2′-diol) phosphoric acids **1** as chiral catalysts of Mannich reactions by Akiyma et al.[1] as well as by Uraguchi and Terada[2] marks the beginning of the quickly progressing research field of asymmetric Brønsted acid catalysis (Figure 1).[3] The substrates are activated by protonation, which

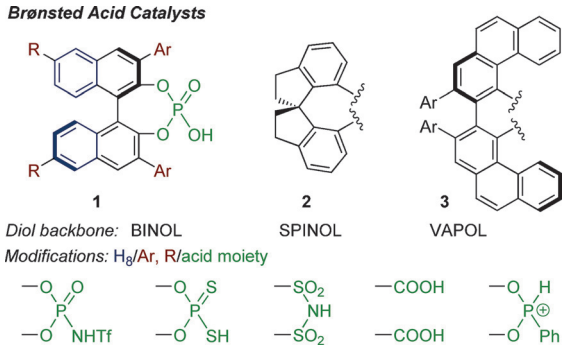
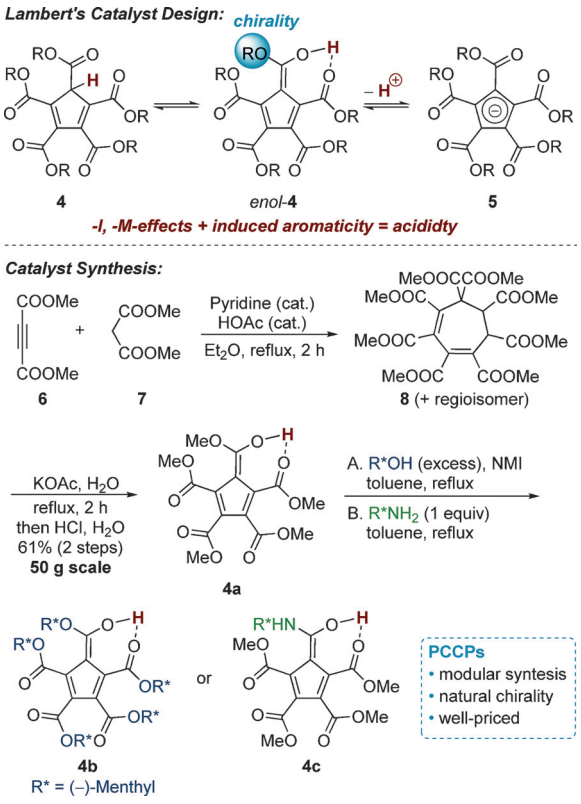


Figure 1. Common chiral Brønsted acid catalysts and their structural variations. Tf = triflate.

leads to a lowering of the energy of the lowest unoccupied molecular orbital (LUMO) and facilitates reaction with a nucleophile. Whereas most of the research in this area has focused on method development, the generation of conceptually new catalysts has attracted much less attention. Clearly, BINOL-based acids **1** still constitute the state-of-the-art structural motifs of catalysts.[4] Their reactivity and selectivity can, in general, be modulated by varying the 3,3′-substituents or the acidic moiety, as exemplified by the stronger *N*-phosphoramide-based acids.[5] Other frameworks, such as VAPOL [2,2′-diphenyl-(3,3′-biphenanthrene)-4,4′-diol, **2**][6] and SPINOL [2,2′,3,3′-tetra-hydro-1,1′-spirobi(indene)-7,7′-diol, **3**][7] have also been introduced. However, the unnatural chirality of these structures requires a chiral resolution during the synthesis, which often consists of multiple steps, including protecting-group manipulation. This drawback of these useful catalysts is reflected in their limited commercial availability and high price.

A fundamentally new catalyst design was reported by Lambert and co-workers.[8] This catalyst not only overcomes the drawbacks of the known chiral Brønsted acids, it also represents an old, yet innovative, concept to stabilize the conjugate base through a combination of electron-withdrawing groups and induced aromaticity, thus leading to acidity comparable to mineral acids. The new catalyst class is based on 1,2,3,4,5-pentacarboxycyclopentadiene (PCCP) **4**, which preferably exists in the enol form and its deprotonation leads to the stable aromatic cyclopentadienyl anion **5** (Scheme 1). The pentamethyl ester **4a** was originally described by Diels[9] and later investigated by others mainly because of its



Scheme 1. Design and synthesis of PCCP catalysts. NMI = *N*-methylimidazole.

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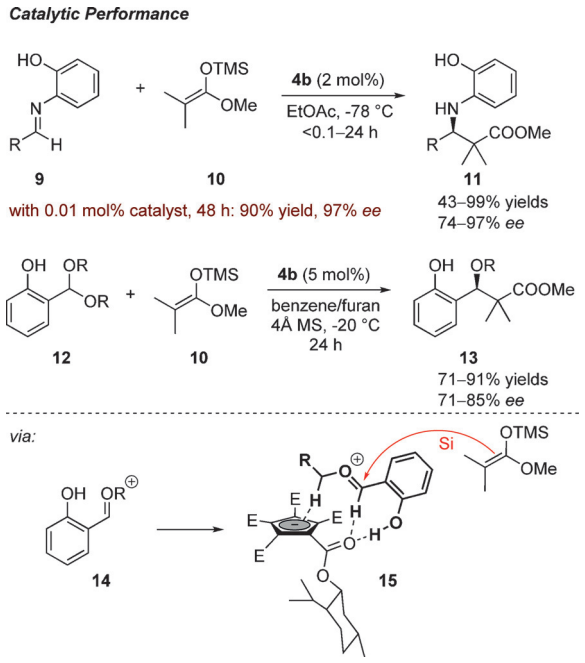
reactivity and simply for curiosity.[10] Lambert and co-workers envisioned modifying **4a** by using chiral alcohols and amines to generate a new type of chiral acid catalyst.

The synthesis of several examples was accomplished in three steps from commercially available starting materials. First, dimethyl malonate (**7**) was reacted with dimethylacetylene dicarboxylate (**6**) in the presence of pyridinium acetate to yield a mixture of cycloheptadiene **8** and its regioisomer. This mixture was directly treated with KOAc to provide the pentamethyl ester **4a** in good yield after an acidic workup. This simple procedure, which was originally developed and mechanistically investigated in the 1980s by Bruce et al.,[10c] allowed for a scale-up to access more than 50 g of the synthetic intermediate **4a**. Further functionalization with (−)-menthol resulted in the formation of chiral pentaester **4b** in high yield. The reaction of **4a** with one equivalent of a chiral amine led to amides **4c** being produced. The measured pK_a values of some of the compounds ranged from 8.85 (**4a**) to 11.7 (**4c**), which are comparable to those of known Brønsted acid catalysts.[11] This range also shows that it is possible to vary the acidity through the choice of the alcohol or amine.

The performance of the new PCCP catalysts was then evaluated in the known Mukaiyama–Mannich reaction of imines **9** and silyl ketene acetal **10** (Scheme 2).[1] It was found that the pentamenthyl ester **4b** not only outperformed the reported BINOL acid in terms of the enantioselectivity achieved (97% versus 89% *ee*), it also displayed astonishing activity, and the catalyst loading could be reduced to only 0.01 mol%, which is rare in organocatalysis.[12] Furthermore, the related challenging transformation of acetals **12** was realized to demonstrate the potential of PCCPs in discovering new reactivity (Scheme 2). In this reaction, the oxocarbenium ions **14**, which are known to be problematic intermediates in enantioselective acid catalysis,[13] are the actual electrophiles



Scheme 2. Catalyst **4b** in the Mukaiyama–Mannich and Mukaiyama–oxocarbenium aldol reactions. TMS = trimethylsilyl.

formed in situ. The authors were able to achieve good yields and enantioselectivities by using 5 mol% of catalyst **4b** to convert different acetals **12** with ketene silyl acetal **10** into the β-alkoxy esters **13** in good yields and enantioselectivities. They also showed that the *ortho*-hydroxy group was essential for the stereoselectivity.

No experimental or computational evidence to account for the observed stereochemistry were reported in this study. The crystal structure of the ammonium salt of **4b** showed a propeller-like orientation of the ester groups around the planar cyclopentadienyl core. The menthyl groups point in one direction to form a hydrophobic pocket, while the carbonyl groups are oriented in the opposite direction. Further investigations are necessary to uncover if this arrangement can be applied to solution. However, the authors suggested stereochemical models for both investigated reactions. The model of the new oxocarbenium aldol reaction (**15**) is depicted in Scheme 2. The oxocarbenium species **14** can only form one hydrogen bond between the OH group and the carbonyl oxygen atom of the catalyst. However, additional interactions might contribute to the stabilization of the transition state and result in the observed good enantioselectivity.

Undoubtedly, the pentacarboxycyclopentadienes have the potential to become valuable alternatives to the established Brønsted acid catalysts. Their greatest advantages are their straightforward and modular synthesis from cheap building blocks and the possibility to utilize the natural chiral pool. In addition, Lambert and co-workers demonstrated that the menthol-based ester **4b** is a highly selective and active catalyst in selected transformations. It is very likely that this study will inspire researchers to synthesize and evaluate more members of this catalyst class, which together with detailed mechanistic studies will help to understand their performance. Their applicability as chiral counterions in homogeneous metal and organocatalysis should also be investigated.

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