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Cooperative Catalysis

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Asymmetric Alkynylation of Imines by Cooperative Hydrogen Bonding and Metal Catalysis**

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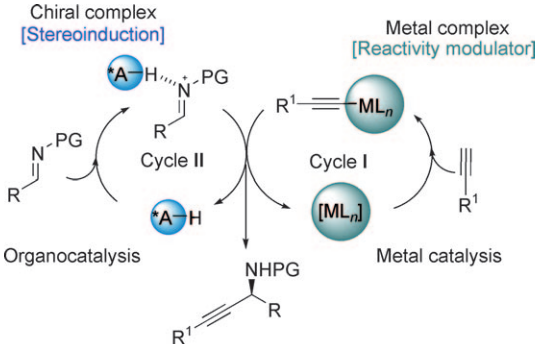
asymmetric catalysis · Brønsted acids · cooperative catalysis · organocatalysis · transition metals

Chiral propargyl amines are important building blocks for the total synthesis of complex natural products,[1] pharmaceuticals,[2] and plant pesticides (herbicides and fungicides).[3] In addition to their synthetic utility, some propargylic amine derivatives display interesting biological properties.[4] The most direct access to these important synthetic blocks relies on the asymmetric alkynylation of imines. In spite of their importance, the number of available methodologies for their preparation remains scarce.[5] They are mainly based on organometallic protocols involving copper,[6] zinc,[7] zirconium,[8] or boron,[9] and Lewis bases as chiral ligands. Typically, these ligands are complex chiral molecules obtained by a multistep synthesis, and their optimization by structural/functional modifications is often not easy as it requires time-consuming functional group manipulations. Thus, alternative catalytic models based on the use of simple chiral ligands that can be assembled in a fast and easy manner would be highly desirable. Cooperative catalytic models based on chiral Brønsted acids and metal catalysis have emerged as such an alternative. Recent studies[10,11] have shown that high enatioselective alkynylations of imines can be performed according to the cooperative catalytic model shown in Scheme 1. The model comprises two well-differentiated and parallel catalytic cycles: the addition of metallic alkynylides to imines (cycle **I**)[12] and the use of chiral Brønsted acids as chiral imine activators (cycle **II**).[13]

Whereas the organometallic cycle **I** has the task of supplying the achiral metallic alkynylide reactant, the organocatalytic cycle **II** delivers the chiral ion pair bearing the activated imine component. The reaction of both components should lead to the corresponding propargyl amine, liberating the catalysts to reinitiate the cycles. This catalytic model features two important practical properties: firstly, chiral catalyst accessibility—a large pool of chiral Brønsted acids is commercially available (amino acids, natural carboxylic acids, chiral phosphoric acids), and secondly, metal/ligand simplicity—commercial achiral ligands are much more accessible than their more elaborate chiral homologues, and therefore, the metal reactivity can be much more easily modulated. In spite of its apparent power, the number of described cooperative catalytic systems involving both Brønsted acids and metals is scarce.[14] Actually, only a few systems operating under this paradigm have been implemented.[15]



Scheme 1. Combined enantioselective Brønsted acid and metal catalyzed alkynykation of imines. PG = protecting group.

Rueping et al.[10] have implemented a cooperative Brønsted acid/metal catalytic system for the enantioselective alkynylation of α-imino esters catalyzed by silver salts and chiral binol hydrogen phosphates (Scheme 2). The reaction of aryl-substituted alkynes and N-protected α-imino esters in the presence of catalytic amounts of a silver salt (5 mol %) and a chiral phosphoric acid (10 mol %) generates propargylic α-amino acids **2** in good yields (60–93 %) and good enantioselectivities (e.r. up to 96:4). Two remarkable properties of alkynyl/silver salts render them optimal for this system: 1) they are not hydrolyzed by the phosphoric acid catalyst and 2) they do not add to non-activated imines.[16] These two properties ensure the independence of the two catalytic cycles and reinforce their cooperativity.

Scheme 2 outlines the best experimental conditions found for this system. The nature of the metallic counterion proved to be important to regulate the reactivity of the metallic

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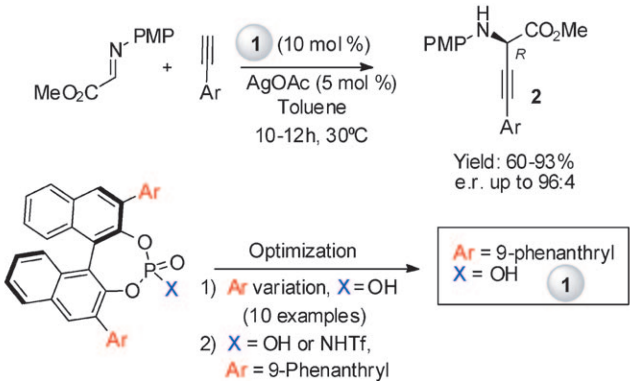
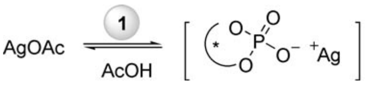


Scheme 2. Catalytic enantioselective alkynylation of α-imino esters with aryl-substituted alkynes. PMP = *para*-methoxyphenyl, Tf = trifluoromethanesulfonyl.

alkynylide, and silver acetate salts gave the best results in terms of yield and enantioselectivity. Other counterions (nitrate, triflate, or tetrafluoroborate) did not perform well, presumably because of their ability to catalyze the reaction in the absence of Brønsted acids.[12,16] Brønsted acid catalyst screening was performed with 12 binol-based catalysts having structural variations in the scaffold at the aromatic appendage to the binol core, or at the phosphoric functional group (acid or amide; Scheme 2). Extensive structural variation of these catalysts is not a simple task and it requires time-consuming chemical transformations of more simple, commercially available binol precursors. From the set of chiral phosphoric acid assayed, catalyst **1**, featuring a chiral binol scaffold having a phosphoric acid group flanked by two bulky 9-phenanthryl substituents, gave the best results in terms of yield and enantioselectivity.

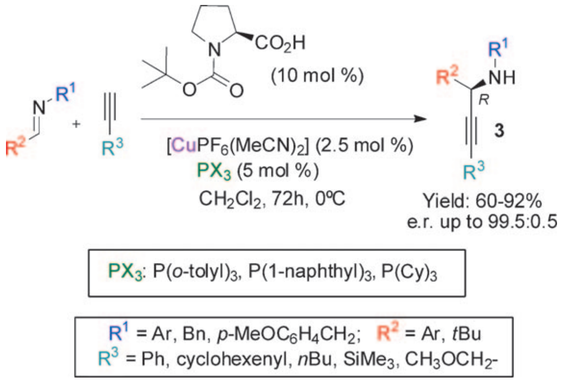
With regard to the reaction mechanism, the authors propose a mechanism combining two different catalytic processes: 1) a cooperative chiral Brønsted acid and achiral metal complex (depicted in Scheme 1), and 2) a complex involving chiral counterions to the metal catalyst [Eq. (1)].[17]



(1)

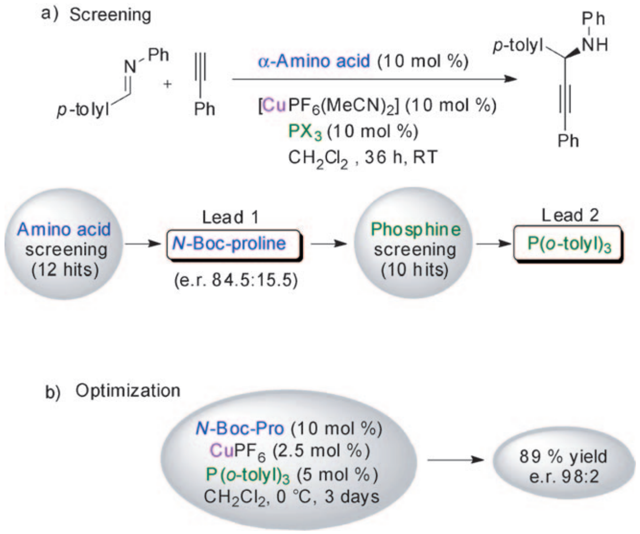
The second model would arise from an exchange of the metal counterion (acetate for chiral phosphate) leading to the formation of a chiral silver complex which would in turn lead to a chiral silver alkynylide salt. It is remarkable that when chiral silver–binol complexes were used in combination with achiral diphenyl hydrogen phosphates, racemic amino acids were obtained. This fact seems to confirm that a chiral organocatalytic cycle **II** is required for enantioinduction independent of the nature of the silver salt participating in the organometallic cycle **I** (Scheme 1). If this model could be confirmed, the chiral phosphate would be rendering chirality to both the metal salt (cycle **I**) and the H-bonded imine complex (cycle **II**). It would be a nice example of a reaction catalyzed by a chiral metal complex in combination with a chiral Brønsted acid catalyst. However, more experimental work remains to be done to confirm it.

A more recent discovery has been recently reported by Arndtsen and co-workers,[11] in which they implement a cooperative catalytic model involving α-amino acids as chiral catalysts, copper/alkynylides as nucleophiles, and N-protected imines as substrates (Scheme 3). The catalytic manifold generates propargyl amines in good-to-excellent yields (up to 92 %) and high enantioselectivity (e.r. up to 99.5:0.5) from the reaction of appropriate N- and C-aryl imines with terminal alkynes in the presence of catalytic amounts of *N*-Boc-proline (Boc = *tert*-butoxycarbonyl), copper salts, and tertiary phosphines. The accelerating influence of the amino acid allows use of electron-rich N-alkylimines which have been reported to be unreactive toward alkynylation (likely because of their reduced electrophilicity). The authors report that the combination of *N*-Boc-proline and [Cu{P(1-naphthyl)$_3$}]PF$_6$ catalyzes the reaction of *N*-benzyl-*p*-tolylimine and ethynylbenzene to give the corresponding propargyl amine in excellent yield (92 %) and enantioselectivity (e.r. 96.5:3.5).



Scheme 3. H-bonding asymmetric metal catalysis with α-amino acids. Cy = cyclohexyl, Bn = benzyl.

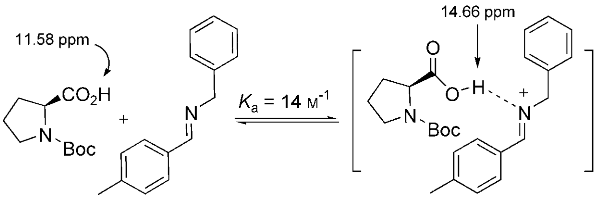
The most significant advantage of this approach is its flexibility and practicality. Although the primary source of stereoinduction is brought about by the α-amino acid, which is directly involved in the chiral H-bonding complex with the imine, the steric bulk of the copper catalyst also has a significant influence on the stereoselectivity. Because the number of commercially avalaible α-amino acids and tertiary phosphines is large, the screening for the optimal catalyst combination for a given substrate can be performed in a straightforward and direct manner from these materials. Scheme 4 outlines a remarkable example. Direct screening using a pool of 12 commercially avialable *N*-Boc-protected α-amino acids allowed identification of *N*-Boc-proline as the optimal α-amino acid for this reaction (see Lead 1 in Scheme 4 a). As the authors declare, a single day of labor is enough to perform this screening. The second screening for ligand optimization was also straightforward, using ten commercially available tertiary phosphines and *N*-Boc-proline as the chiral imine activator. From this screening, P(*o*-tolyl)$_3$ was selected as the optimal ligand for this reaction (see



Scheme 4. Screening and optimization for the optimal catalyst combination.

Lead 2 in Scheme 4a). Once the best catalyst combination was discovered, optimization of the reaction conditions resulted in obtaining the corresponding propargyl amine in 89% yield and 98:2 e.r. (Scheme 4b). In contrast to other catalytic systems using complex chiral ligands,[5] the modularity exhibited by this system can be used to create a large number of different catalysts by using different members of the available pools of amino acids and phosphines, with screening often limited only by the rate of HPLC analysis.

Preliminary studies on the reaction mechanism are consistent with α-amino acid/imine association during catalysis. A ^{1}H NMR titration of *N*-Boc-proline with (*p*-tolyl)HC=N(Bn) showed a significant downfield shift in the proton signal for -CO_2H (from $\delta = 11.58$ to 14.66 ppm) as anticipated by a H-bonding interaction [Eq. (2)]. Titration studies gave a



(2)

value for the association constant of $14\,\text{M}^{-1}$. Consistent with this weak interaction to form the corresponding chiral H-bonding complex during catalysis (see Scheme 1), kinetic studies revealed that the rate of reaction was first order in *N*-Boc-proline (in the range of 3 to 50 mol%) and independent of the $CuPF_6$ concentration (in the range of 10 to 60 mol%). These data are consistent with the catalytic model displayed in Scheme 1, with two different catalytic cycles working in parallel and without mutual interference. Although a secondary coordination α-amino acid/Cu should be expected to occur in this chemical scenario, the observed zero-order dependence of the reaction rate with the $CuPF_6$ concentration suggests that Cu and α-amino acid can be playing separate roles in this reaction. It is remarkable that the enantiomeric excess remains constant in the range of concentrations used in these experiments.

The role played by the α-amino acid was corroborated by the inhibition observed when triethylamine (20 mol%) was added to the reaction mixture. The expected acid/base reaction between the base and the α-amino acid inhibits the cycle **II** and therefore, the overall catalysis. This data is consistent with the observed low product yield (16%) obtained when the reaction is performed in the absence of an acid catalyst. Although a model for the observed stereoinduction has not been advanced, the role played by the α-amino acid seems to be essential. Other chiral H-bonding acids were also able to catalyze the reaction but with reduced enantioselectivity [i.e., (*S*)-mandelic acid, e.r. 59.5:40.5; L-2-pyrrolidone-5-carboxylic acid, e.r. 1:1].

Taken together, the two systems present a new manner for the incorporation of chirality into metal catalysis, namely, forming chiral H-bonding complexes between a chiral Brønsted acid derivative and the substrate imine (organocatalysis) in the presence of an achiral metal/alkynylide salt (metalo-catalysis). Some interesting questions regarding the mechanism remain to be addressed, particularly that related to the possible participation of the Brønsted acid as a chiral counterion in the organometallic catalytic cycle (chiral counterion catalysis). Both reports are very appealing examples of how developments in metal and organocatalysis can be combined to elicit simple and high efficient catalytic systems. The combination of α-amino acids and metal catalysis is particularly attractive because of its practicality and efficiency. It will be interesting to see if future developments of this strategy will enable the expansion of the reaction scope. Doubtless, the asymmetric catalysis toolbox has been nicely increased with two spectacular examples of a novel and powerful model of cooperative catalysis.[18]

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Please note: Minor changes have been made to this manuscript since its publication in *Angewandte Chemie* Early View. The Editor.