



Review

Coinage metal complexes as chiral catalysts for 1,3-dipolar cycloadditions



Carmen Nájera*, José M. Sansano*

Departamento de Química Orgánica, Facultad de Ciencias, and Instituto de Síntesis Orgánica (ISO), Universidad de Alicante, Apdo 99, 03080 Alicante, Spain

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ABSTRACT

In this account, we describe the experience of our research group in the implementation of chiral coinage metal complexes into the efficient enantioselective 1,3-DC of azomethine ylides derived from α -amino acids and azlactones with different dipolarophiles. The corresponding chiral metallodipoles were generated *in situ* and next focused on the synthesis of highly substituted prolines. For this purpose, privileged ligands such as phosphoramidites and binap with silver(I), gold(I) and copper(II) salts are described. Depending from the ligand and mainly from the metal salt it can be possible to control the facial *endo/exo*-diastereoselectivity and the enantioselectivity of these types of processes. The synthetic processes are also supported by DFT calculations in order to elucidate the most plausible mechanism and the stereochemical results.

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Introduction

Coinage metals as salts and complexes attract particular interest from many scientific areas [1,2]. In particular, they can be useful catalysts in synthetic organic chemistry for preparing the core of many important drugs containing heterocyclic structures [3]. Good chemoselectivity, good functional group compatibility, stability, are the main features of noble metal complexes which are crucial for application in complex molecular environments. One of the representative examples concerns the synthesis of enantiomerically enriched prolines [4–6] through the catalytic enantioselective 1,3-dipolar cycloadditions (1,3-DC) [7–14] between azomethine

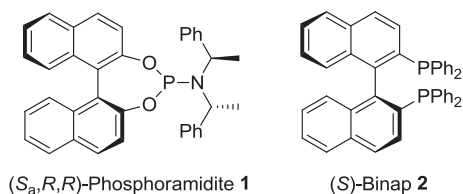
ylide and alkenes. In fact, silver and copper catalyzed 1,3-DC are very well known and constitute the most reliable, and direct enantioselective methodology to built up to four stereogenic centers of the resulting proline derivatives [6,15–18], in only one operation step. In addition, they exhibit more versatility and wider scope than the analogous enantioselective organocatalyzed 1,3-dipolar cycloadditions [19–25]. However, chiral gold complexes [26–28] have not so extensively employed and just a very efficient enantioselective cycloaddition of münchnones with electron-deficient alkenes has been described. In this transformation, followed by an ester/amide formation, Δ^1 -pyrrolines were obtained in very high enantioselectivity [29].

In this account, we will describe the experience of our research group in the implementation of chiral coinage metal complexes into the efficient enantioselective 1,3-DC of azomethine ylides derived from α -amino acids with different dipolarophiles. The

* Corresponding authors. Tel.: +34 96 5903728; fax: +34 96 5903549.

E-mail addresses: cnajera@ua.es (C. Nájera), jmsansano@ua.es (J.M. Sansano).

corresponding chiral metallodipoles were generated *in situ* and next focused on the synthesis of highly substituted prolines. For this purpose, privileged ligands [30] such as and (*S_a,R,R*)-phosphoramidite **1**(*R*)- or (*S*)-binap **2** and their enantiomers will be evaluated.



Silver-catalyzed 1,3-DC of azomethine ylides

Silver-catalyzed enantioselective 1,3-DCs of stabilized azomethine ylides have been demonstrated to be very high diastereoselective processes affording mainly *endo*-cycloadducts. Since the pioneering works [31] of Zhang [32] and Jørgensen [33] many examples of chiral silver complexes have been documented [34–39] in this silver-mediated asymmetric cycloaddition. In general, chiral bidentate ligands such as bisphosphines, aminophosphines, sulfur-containing phosphines, bisoxazolines and diimines were used as chiral ligands, but not monodentate ligands were tested in this 1,3-DC [40].

Chiral monodentate phosphoramidites were chosen as ligands for silver(I) salts. These complexes were successfully used in the enantioselective 1,3-DC employing azomethine ylides and electrophilic alkenes [41,42]. The new 1:1 and 2:1 complexes of AgClO₄ and phosphoramidite (*S_a,R,R*)-**1** could be characterized by single crystal X-ray crystallographic diffraction and were tested in the enantioselective 1,3-DC obtaining excellent results when employing the equimolar mixture. The reaction between imino esters **3** derived from glycine (R¹ = H) and *tert*-butyl acrylate occurred at

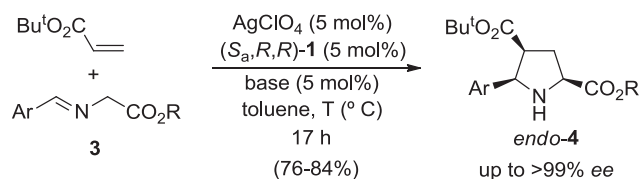
0 or –20 °C in the presence of a 5 mol% of (*S_a,R,R*)-**1**·AgClO₄ complex, giving good yields and very high enantioselections of the exclusive *endo*-cycloadduct **4** (Scheme 1). However, the catalyst formed by 2 equivalents of silver(I) perchlorate and 1 equivalent of chiral ligand gave very poor enantioselections in cycloadducts **4**. The employment of the enantiomeric form of the chiral ligand (*R_a,S,S*)-**1** furnished in identical chemical yield, diastereo- and enantioselectivity *endo*-**4**.

Different dipolarophiles were allowed to react with benzylidene-glycine methyl ester modifying the temperature and the base. Triethylamine was the more appropriate base working at –20 °C with diisopropyl fumarate and chalcone as dipolarophiles (Fig. 1, compounds **5** and **7** respectively), but DABCO was a more effective base than triethylamine, at room temperature, in those reactions involving maleimides (for example see Fig. 1, compound **6a**). In the case of α -substituted imino esters the reaction with *tert*-butyl acrylate, *N*-methylmaleimide, and chalcone, took place at room temperature giving cycloadducts **8–10** in moderate to excellent *ee*'s (Fig. 1). These results reflected that a possible steric hindrance at this position of the dipole, which could avoid a perfect enantio-discrimination in the transition state.

Concerning the most favored transition state the two possible *endo*-**TS1** saddle points were much closer in energy. **TS1–SSR** was calculated to be 1.31 kcal/mol lower in energy than **TS1–RRS**. However, a large energy gap was obtained for **TS1–SRR** (Fig. 2). It is observed that the dihedral angle formed by the two naphthyl groups is of ca. 57–58°. In the case of **TS1–SSR**, this lead to the blockage of the Re–Si face of the dipole (Fig. 4). These calculations were in good agreement with the experimental results and also support that the whole process occurred through a stepwise mechanism [42].

It has been demonstrated that enantiomerically pure proline derivative **11** is the key precursor to a series of antiviral agents inhibitors of the hepatitis C virus (HCV) polymerase [18,43,44] such as prolinamide **13** [45,46]. The intermediate prolinamide **12** was synthesized in 88% yield (estimated by ¹H NMR) from enantiomerically enriched **11** by a simple amidation reaction with 4-(trifluoromethyl)benzoyl chloride in refluxing dichloromethane during 19 h. After subsequent hydrolysis, the resulting dicarboxylic acid **13** (a first generation GSK-antiviral agent) was finally obtained in 81% yield (50% overall yield from iminoester **11**) in 86% *ee* (Scheme 2).

This type of phosphoramidite–silver complexes opened new perspectives in this and other reactions because is capable to perform cycloadditions involving sterically hindered components with moderate enantioselections, the fine-tuning being achieved



Scheme 1.

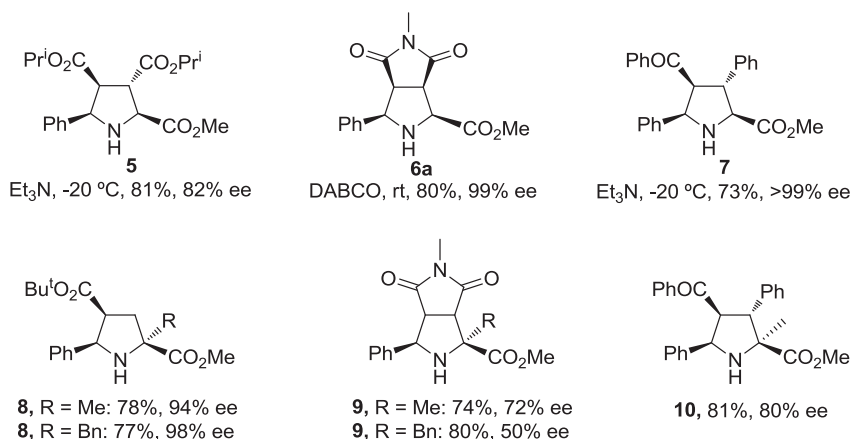


Fig. 1. Scope of the 1,3-DC between imino esters **3** and alkenes catalyzed by (*S_a,R,R*)-**1**·AgClO₄ complex.

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