Synthesis of Chiral Thiourea-Phosphine Organocatalysts derived from L-Proline

Thi-Huong Nguyen, Martial Toffano, Chloée Bournaud and Giang Vo-Thanh*

Laboratoire de Catalyse Moléculaire, Institut de Chimie Moléculaire et des Matériaux d'Orsay (ICMMO), UMR CNRS 8182, Université Paris-Sud, 91405 Orsay Cedex, France

Email: giang.vo-thanh@u-psud.fr

Abstract: A novel class of thiourea-phosphine was prepared from L-Proline as a chiral renewable resource. The original structure of the chiral framework offers an interesting potential to the construction of bifunctional organocatalysts for asymmetric transformations.

Key words: L-Proline, Organocatalyst, Thiourea, Phosphine, Asymmetric [3+2] annulation.

Due to their weaker basicity and stronger nucleophilicity than amines, phosphines have been used with success in catalytic processes, especially, in nucleophilic catalysis.[1] Many research groups have been focusing on the design and synthesis of new chiral monophosphine compounds. Among them, Binepine and FerroPHANE appear as efficient catalysts for [3+2] annulation of allenoates (Figure 1).[1b]

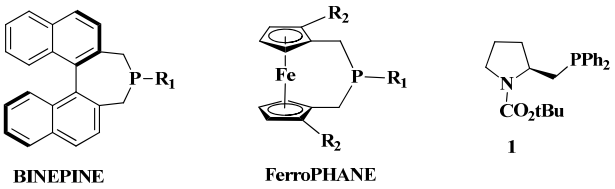
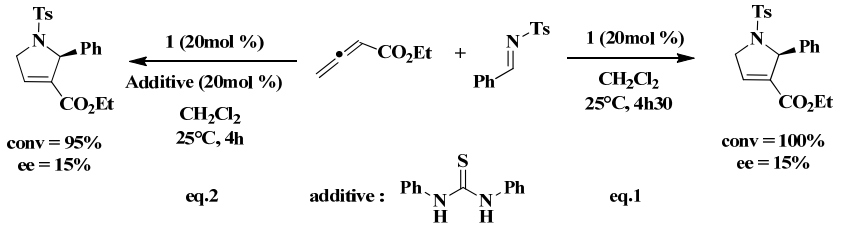


Figure 1: Structure of some chiral monophosphines.

The development of suitable, inexpensive, modular chiral catalysts has attracted considerable interest in recent years. Many chiral thiourea-phosphine compounds derived from natural or unnatural products have been reported in the literature. However, the synthesis and applications of monophosphines derived from L-proline have not been reported in catalytic asymmetric [3+2] annulation. Moreover, the potentiality and effectiveness of L-proline derivatives as organocatalysts have demonstrated very broad applications.[2] Thus, in the course of our study to promote the use of natural and inexpensive compounds to elaborate catalytic systems, we focus first on the use of simple and well-known (*S*)-*N*-(terbutylcarbonyl)-2-(diphenylphosphinomethyl) pyrrolidine **1**. Its easy preparation and the potential to functionalize the nitrogen atom are of interest for future developments.

As we can observe in Scheme 1, the best preliminary results showed that using **1** as the catalyst in asymmetric [3+2] annulation between ethyl 2,3-butadienoate and *N*-benzylidene-*p*-toluenesulfonamide led to the formation of pyrrolidine in a few hours with excellent conversion but low enantioselectivity (15% ee) (Scheme 1, eq.1). Moreover, the presence of diphenylthiourea as a co-catalyst did not improve at all the asymmetric induction (Scheme 1, eq.2).



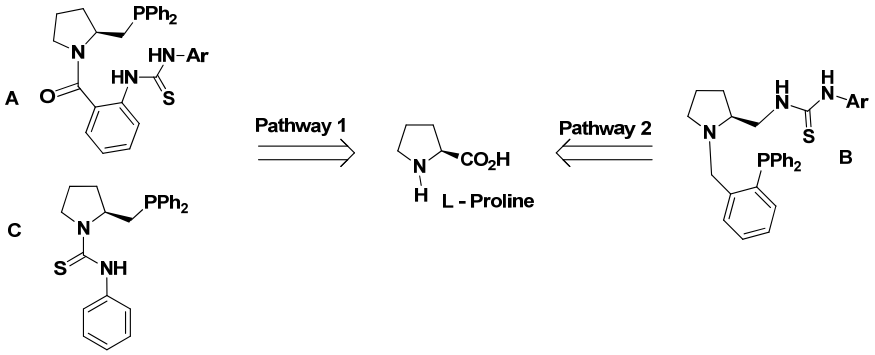
Scheme 1: Asymmetric [3+2] annulation.

The results demonstrated that using urea and phosphine functions separately did not synergistically activate the substrates in a controlled chiral environment. This led us to develop a new family of bifunctional chiral thiourea-phosphine organocatalysts.

Thiourea-phosphines have received considerable attention due to their high efficiency in asymmetric induction for [3+2] annulation reaction and other enantioselective transformations. These catalysts have been prepared based on unnatural skeletons (cyclohexane[3], binaphthyl[4]), or natural compounds such as amino-acids.[5]

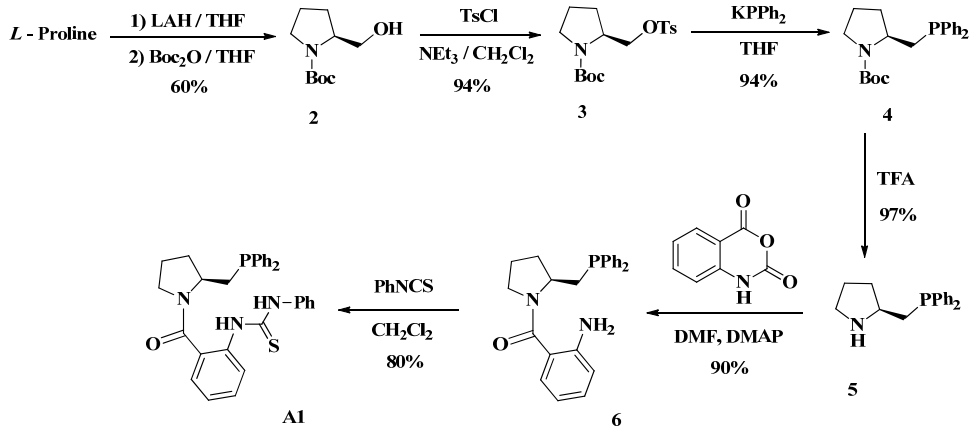
Herein, we report the synthesis of a new family of bifunctional chiral thiourea-phosphine organocatalysts, derived from L-proline and their first application in asymmetric organocatalysis. Our design of modular catalyst involves: 1) an urea function for interaction between catalyst and substrates; 2) a phosphorus center that is responsible for catalytic activity; 3) a stereogenic center that is ensured by the natural chirality of L-proline; 4) a chiral carbon framework which offers potential modularity of a catalyst.

Two synthetic pathways were investigated for the preparation of original organocatalysts **A**, **B** and **C** (Scheme 2).



Scheme 2. Retrosynthetic pathway to thiourea-phosphines **A**, **B** and **C**.

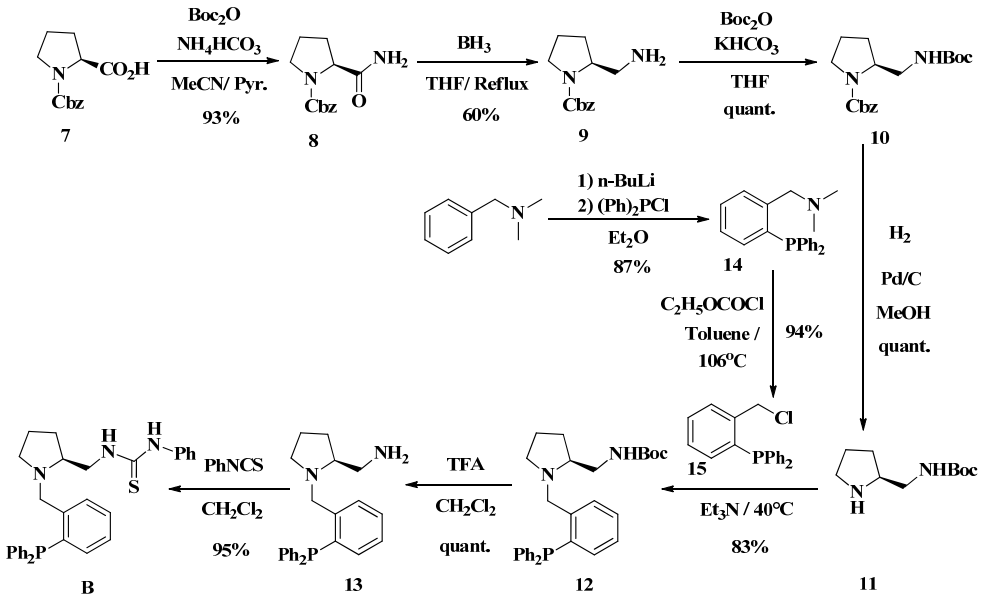
In the first pathway, the phosphine moiety is located on the lateral chain fixed on position 2 of the pyrrolidine cycle, whereas the thiourea group is attached to the *N*-substituent of L-proline. The synthesis of chiral thiourea-phosphine **A1** is shown in Scheme 3.



Scheme 3. Synthetic strategy of thiourea-phosphine **A1** (Ar = Ph).

In this pathway, the key step of the synthesis is the reaction of phosphine **5** with isatoic anhydride.[6] First, enantiopure *N*–Boc prolinol **2** was obtained in two steps in 60% overall yield by reduction of L-proline with LAH, followed by the protection of amine function. The hydroxyl group was then activated as its tosylate by treatment with tosyl chloride using an excess of triethylamine affording tosylate **3** in 94% yield. Subsequently, tosylate **3** was treated with $KPPh_2$ *via* a SN_2 substitution reaction, and the protecting group was removed by TFA to give phosphine **5** in very good yield (91% over two steps). The next step in the synthesis is transforming phosphine **5** into thiourea-phosphine **A1** by reacting **5** with isatoïc anhydride, followed by a condensation of amine function with phenylisothiocyanate. Thiourea-phosphine **A1** was isolated in good overall yield of 37% over 7 steps from L-proline.

In pathway 2, the phosphine moiety is attached to the *N*-substituent of L-proline, whereas the thiourea group is located on the lateral chain fixed on position 2 of the heterocycle (Scheme 4).



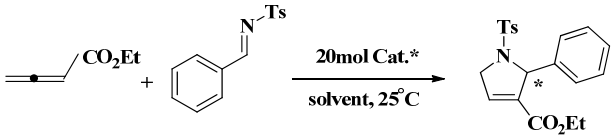
Scheme 4. Synthesis of thiourea-phosphine **B**.

The key intermediate in the synthesis is tert-butyl–*N*–(pyrrolidin-2-ylmethyl)carbamate **11**. This compound was prepared from commercially available and inexpensive *N*–benzyloxycarbonyl pyrrolidine **7** in four steps. Our synthesis was initiated by transforming

carboxylic acid **7** into amide **8,** followed by reducing of amide function, without affecting the Cbz protecting group, into amine **9** by treatment with BH_3. Amine **9** was isolated in 56% yield over two steps. Protection of the primary amine in **9** with Boc_2O gave **10** in quantitative yield. Palladium-catalyzed hydrogenolysis removed the Cbz protecting group to afford **11** in quantitative yield. Introduction of the phosphorus group was ensured by nucleophilic substitution of **11** by **15** to give **12** (63%). Chloride **15** was easily prepared in two steps by ortho-lithiation of *N*, *N*–dimethylbenzylamine followed by reaction with Ph_2PCl to conduct to **14** in 87% yield. Chorination in the presence of ethyl chloroformate gave **15** in 94% yield. Deprotection of *N*-protected Boc group of **12** led to the formation of phosphine-amine **13** as an enantiopure form.[7] The enantiomeric excess was determined by chiral HPLC analysis. Treatment of the phosphine-amine with phenylisothiocyanate gave the expected thiourea-phosphine **B** in 95% yield.

The efficiency of thiourea-phosphine **A1** and **B** as organocatalysts was investigated in the asymmetric [3+2] cyclisation between ethyl-butan-2,3-dienoate and *N*-benzylidene-*p*-toluenesulfonamide. The results are summarized in Table 1.

Table 1. Asymmetric [3+2] cyclisation between ethyl butan-2,3-dienoate and *N*-benzylidene-*p*-toluenesulfonamide.[a]



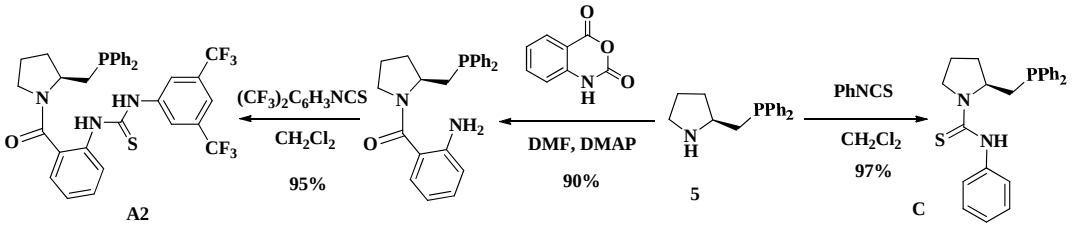
Entry	Cat	solvent	Time (h)	Isolated yield (%)	Ee (%)[b]
1	**A1**	$PhCH_3$	6	90	3
2	**A1**	Hexane	24	90	2
3	**A1**	THF	6	70	0
4	**A1**	CH_2Cl_2	6	80	14
5[c]	**A1**	CH_2Cl_2	4 days	70	5
6[d]	**A1**	CH_2Cl_2	40	78	0
7	**B**	$PhCH_3$	29	85	0
8	**B**	Hexane	24	80	5
9	**B**	THF	29	82	5
10	**B**	CH_2Cl_2	29	78	20

[a] Reactions were conducted under an argon atmosphere and in degassed solvent with a concentration of 0.3 mol/L of substrate at 25°C except otherwise noted. [b] Enantiomeric excesses were determined by chiral HPLC analysis. [c] Reaction was carried out at -30°C for 4 days. [d] Concentration 0.02mol/L.

As we can observe, thiourea-phosphine **A1** catalyzed the reaction. The pyrrolidine adduct was obtained with good to excellent conversions in a few hours, but with low enantiomeric excesses. Changing concentration, catalyst loading or temperature did not improve enantioselectivity at all (entries 5-6).[8] The best result was obtained (80% yield, 14% ee) when the reaction was carried out, in dichloromethane (entry 4). Catalyst **B** was then tested under similar reaction conditions resulting in the same activity compared to catalyst **A1**.

Dichloromethane was again the best solvent for this reaction in which, 20% ee along with 78% yield were obtained (entry 10).

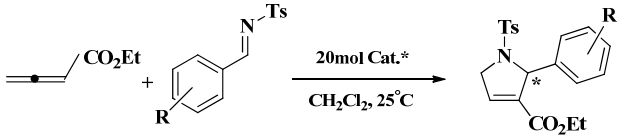
The low enantioselectivity observed led us to modify the structure of catalysts, namely **A2** and **C**, hoping to have a better ee (Scheme 5). The act of adding trifluoromethyl group on aromatic ring in thiourea moiety seems to be of interest. It was demonstrated that the acidity of mobile hydrogens plays an important role in increasing reaction rates and stereochemical control in some asymmetric transformations involving thiourea.[9] Furthermore, we suggest synthesizing a catalyst **C** with a complete modification of the structure of *N*-substituent on heterocycle. The thiourea-phosphine **A2** and the thioamide-phosphine **C** were easily obtained in good yields from phosphine **5** (Scheme 5).



Scheme 5. Synthesis of **A2** and **C** catalysts.

With these new catalysts in hand, we were interested in testing their potential in asymmetric [3+2] cyclization between ethyl-butan-2,3-dienoate and *N*-substituted-benzylidene-*p*-toluenesulfonamide described above (R = H). Unfortunately, unlike we expected, the presence of trifluoromethyl groups has no positive effect on selectivity (Table 2, entries 1-4). Next, the influence of nitro group on aromatic ring was investigated in this model reaction (R = NO_2 in ortho or in para position). Four catalysts **A1**, **A2**, **B** and **C** were tested. Generally speaking, good yields were obtained along with very low enantiomeric excesses. The presence of *p*-NO_2 group on imine in almost all cases led to the loss of asymmetric induction (entries 5,6,7,8 vs 1,2,3,4). No remarkable positive effect is observed either when it is located in ortho position. However, we observed good catalytic activity and regular ee values with catalyst **C** for all substrates (entries 4,8,12). The results are summarized in Table 2.

Table 2. Asymmetric [3+2] cyclisation between ethyl butan-2,3-dienoate and *N*-substituted-benzylidene-*p*-toluenesulfonamide.[a]



Entry	Cat	R	Time (h.)	Isolated yield (%)	Ee (%)[b]
1	**A1**	H	6	80	14
2	**A2**	H	29	75	3
3	**B**	H	29	78	20
4	**C**	H	18	84	11
5	**A1**	4-NO_2	6	61	6
6	**A2**	4-NO_2	29	65	3
7	**B**	4-NO_2	28	87	0
8	**C**	4-NO_2	16	Quant.	15

9	**A1**	2-NO_2	4	70	12
10	**A2**	2-NO_2	24	89	12
11	**B**	2-NO_2	24	76	9
12	**C**	2-NO_2	18	Quant.	15

[a.] Reactions were conducted under an argon atmosphere and in degassed solvent with a concentration of 0.3 mol/L of substrate at 25°C except otherwise noted. [b] Enantiomeric excesses were determined by chiral HPLC analysis.

In summary, we have developed a short and efficient procedure for the synthesis of 4 chiral thiourea-phosphine organocatalysts derived from L-proline. Good overall yields were obtained in all cases. These catalysts were evaluated in asymmetric [3+2] cyclization between ethyl butan-2,3-dienoate and an imine. Although the low enantioselectivity was observed, the results clearly demonstrated that these catalysts present good catalytic activity. Furthermore, the efficiency of thiourea-phosphine has been evaluated in asymmetric Baylis-Hillman and aza-Baylis Hillman reactions. The results of these studies will be communicated in due course.

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7. The enantiomeric excess of compound 12 was determined by chiral HPLC (ee > 98%).

8. In the presence of 10mol% of catalyst, the enantiomeric excess of the adduct decrease to 5%ee for catalyst B and the product is obtained in a racemic form for catalyst A.

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