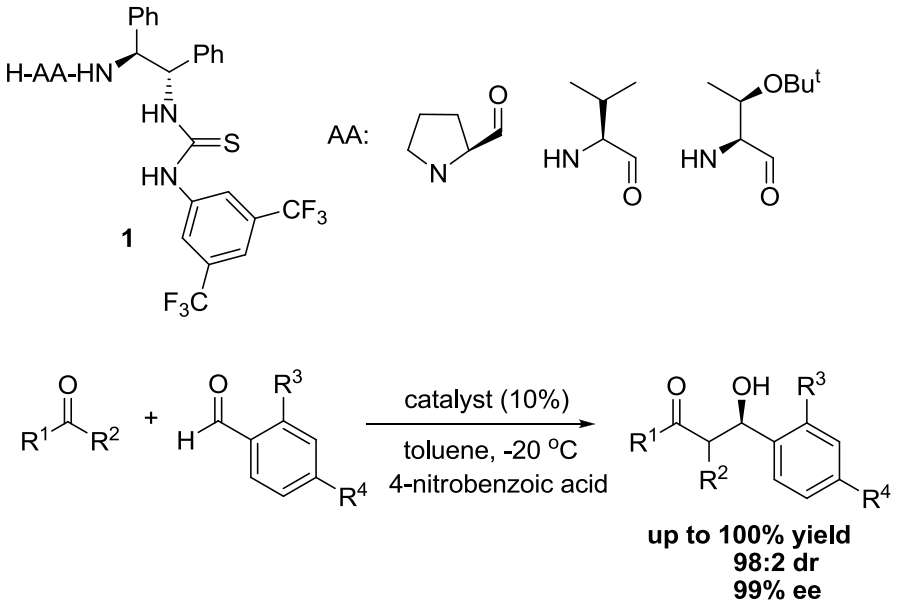
17th European Symposium on Organic Chemistry (ESOC), 10-15 Ιουλίου 2011, Χερσόνησος, Κρήτη

Prolinamides Carrying a Thiourea Group as New Catalysts for the Asymmetric Aldol Reaction

Stamatis Fotaras, Christoforos G. Kokotos, George Kokotos*
Laboratory of Organic Chemistry, Department of Chemistry, University of Athens, Panepistimiopolis, Athens 15771 Greece
email: gkokotos@chem.uoa.gr

At the beginning of the 21st century, organocatalysis has emerged as a new powerful methodology for the synthesis of enantiopure organic compounds. The breakthrough of proline-catalyzed asymmetric direct aldol reaction together with the pioneering work on catalytic thioureas and imidazolidinones opened new directions in asymmetric catalysis. The five-membered secondary amine structure of proline is considered as a"privileged" structure able to activate carbonyl compounds through the formation of enamine intermediates. In an attempt to develop new organocatalysts, we thought of combining a thiourea group with prolinamide or an α-amino acid amide unit. Thiourea group is a well known double hydrogen bond donor and recently we have shown that chiral thioureas based on *tert*-butyl esters of α-amino acids are excellent catalysts for the asymmetric Michael reaction.[1] In the present work, we describe the synthesis of various α-amino acid amides based on a chiral diamine carrying a thiourea group (general structure 1). The catalytic efficiency of the new organocatalysts was evaluated in the aldol reaction between acetone and 4-nitrobenzaldehyde. Prolinamide derivative was more efficient than the valinamide and the threonine amide derivatives. The catalyst based on (*S*)-proline and (1*S*,2*S*)-diphenylethylenediamine proved to be an excellent catalyst providing the products between ketones and aromatic aldehydes in high to quantitative yield and high stereoselectivities.[2]



1) Kokotos, G. C.; Kokotos, G. *Adv. Synth. Catal.* **2009**, *351*, 1355-1362.
2) Fotaras, S.; Kokotos, G. C.; Tsandi, E.; Kokotos, G. *Eur. J. Org. Chem.* **2011**, 1310-1317.

PROLINAMIDES CARRYING A THIOUREA GROUP AS NEW CATALYSTS FOR THE ASYMMETRIC ALDOL REACTION

Stamatis Fotaras, Christoforos G. Kokotos and George Kokotos

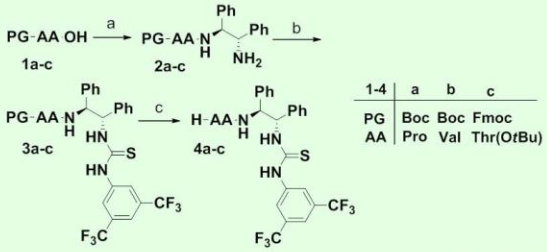
Laboratory of Organic Chemistry, Department of Chemistry, University of Athens, Panepistimiopolis, Athens 15771, Greece

INTRODUCTION

At the beginning of the 21st century, organocatalysis has emerged as a new powerful methodology for the synthesis of enantiopure organic compounds.[1] The breakthrough of proline-catalyzed asymmetric direct aldol reaction together with the pioneering work on catalytic thioureas and imidazolidinones opened new directions in asymmetric catalysis. The five-membered secondary amine structure of proline is considered as a "privileged" structure able to activate carbonyl compounds through the formation of enamine intermediates. In an attempt to develop new organocatalysts, we thought of combining a thiourea group with a prolinamide or an α-amino acid amide unit. Thiourea group is a well known double hydrogen bond donor and recently we have shown that chiral thioureas based on *tert*-butyl esters of α-amino acids are excellent catalysts for the asymmetric Michael reaction.[2] In the present work, we describe the synthesis of various α-amino acid amides based on a chiral diamine carrying a thiourea group and the evaluation of the resulting catalysts in asymmetric aldol reactions.[3]

RESULTS AND DISCUSSION

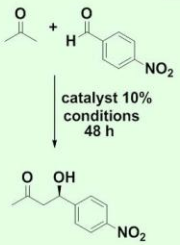
Boc-L-proline (**1a**), Boc-L-valine (**1b**), and Fmoc-L-threonine *O*-*tert*-butyl ether (**1c**) were each coupled with (1*S*,2*S*)-diphenylethylenediamine using 1-[3-dimethylamino)propyl]-3-ethylcarbodiimide (WSCI) as a condensing agent in the presence of 1-hydroxybenzotriazole (HOBt). The amides **2a**–**c** were then treated with the commercially available 3,5-bis(trifluoromethyl)phenyl isothiocyanate to give the thiourea derivatives **3a**-**c**. The Boc group was removed from **3a** and **3b** by treatment with HCl in methanol, whereas the Fmoc group was removed with piperidine in DMF.



Scheme 1. *Reagents and conditions.* (a) (1*S*,2*S*)-diphenylethylenediamine,WSCI, HOBt, Et_3N, CH_2Cl_2, 24 h, r.t. (b) 3,5-bis(trifluoromethyl)phenyl isothiocyanate, CH_2Cl_2, 24 h, r.t. (c) 4N HCl/MeOH, r.t. for **3a**,**b** and piperidine/DMF, r.t. for **3c**.

The catalytic activities of **4a-c** were first evaluated in the reaction between acetone and 4-nitro-benzaldehyde at various temperatures in toluene that as we have shown is the optimum solvent for this reaction.[3] In all cases, the best enantioselectivities were achieved at -20 or -50 °C. The prolinamide catalyst **4a** (entries 1-3, Table 1) was more efficient than the valinamide **4b** (entries 4-6, Table 1) and the threonamide **4c** (entries 7-9, Table 1), indicating that a secondary amino group rather than a primary one is required for catalytic efficiency in the aldol reaction.

Table 1. Effect of temperature on the direct asymmetric aldol reaction between acetone and 4-nitro-benzaldehyde in the presence of catalysts **4a-c**.



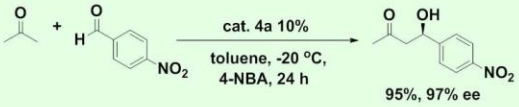
Entry	Catalyst	Solvent, temp. [°C]	Yield [%][a]	*ee* [%][b]
1	**4a**	toluene, room temp.	50[c]	42
2	**4a**	toluene, -20	90	83
3	**4a**	toluene, -50	66	90
4	**4b**	toluene, room temp.	76	55
5	**4b**	toluene, -20	60	77
6	**4b**	toluene, -50	21	73
7	**4c**	toluene, room temp.	48	57
8	**4c**	toluene, -20	33	86
9	**4c**	toluene, -50	20	83

[a] Isolated yield after column chromatography. [b] The *ee* was determined by HPLC with a Diacel Chiralpak AD-RH column. [c] Reaction time: 18 h.

ACKNOWLEDGEMENT

This research has been co-financed by the European Union (European Social Fund – ESF) and Greek national funds through the Operational Program "Education and Lifelong Learning" of the National Strategic Reference Framework (NSRF) - Research Funding Program: Heracleitus II. Investing in knowledge society through the European Social Fund.

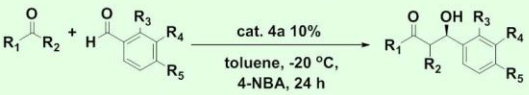
Using toluene as the solvent and reaction temperature at -20 °C, we continued our research studying the effect of different additives and catalyst loading on the reaction between acetone and 4-nitro-benzaldehyde in the presence of catalyst **4a** and we found that the best results were obtained when a medium acidity additive as the 4-nitro-benzoic acid (4-NBA) was used at 10% catalyst loading.[3]

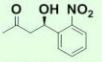
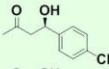
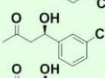
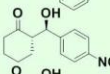
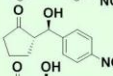
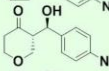
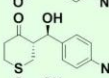
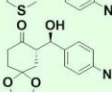


Scheme 2. Optimum conditions on the direct asymmetric aldol reaction between acetone and 4-nitro-benzaldehyde in the presence of catalyst **4a**.

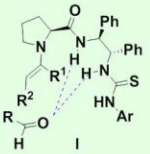
The aldol reaction substrate scope for the new catalyst **4a** was studied then and the results are summarized in Table 2. Electron-poor aldehydes (entries 1-3, Table 2) reacted easily with acetone, providing the products in high to quantitative yields (79-100%) and with high enantioselectivities (94-99% *ee*). When cyclohexanone or cyclopentanone were used as the donors and 4-nitro-benzaldehyde as the acceptor, the products were obtained both in quantitative yields and with excellent enantioselectivities (entry 4,5). A number of cyclic ketones reacted with 4-nitro-benzaldehyde to provide the products in varying yields (61-98%), with high diastereoselectivities (93:7 to 98:2) and excellent enantioselectivities (98-99% *ee*, entries 6-8, Table 2).

Table 2. Direct asymmetric aldol reactions between ketones and various aldehydes in the presence of catalyst **4a**.

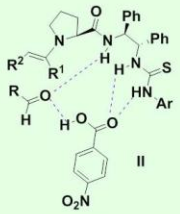


Entry	Product	Yield [%][a]	*dr*[b]	*ee* [%][c]
1		100	-	99
2		100	-	94
3		79	-	99
4		100	97:3	99
5[d]		100	30:70	99[e]
6[d,f]		98	98:2	99
7[d,f]		61	93:7	98
8[d]		64[g]	94:6	98

[a] Isolated yield after column chromatography. [b] The diastereomeric ratio was determined by ^1H NMR spectroscopy and refers to the *anti*/*syn* ratio. [c] The *ee was* determined by chiral HPLC. [d] 10 equiv. of ketone were used. [e] 99% *ee* for *anti*, 92% *ee* for *syn*. [f] Reaction time 48 h. [g] 91% yield after 4 d.



Scheme 3. Proposed transition state model for the aldol reaction in the absence of additive.



Scheme 4. Proposed transition state model for the aldol reaction in the presence of additive.

The catalytic mechanism in the case of **4a** is likely to proceed through enamine activation of the ketone by the pyrrolidine functionality and subsequent nucleophilic attack to the aldehyde that is oriented and activated through the formation of a double hydrogen bond involving the amide hydrogen and one of the thiourea hydrogen atoms (scheme 3). Additives as 4-nitro-benzoic acid might enhance enantioselectivity indicating that the acid might play a key role in the catalytic mechanism (scheme 4).

REFERENCES

1. For books see: (a) Berkessel, A.; Groger. H.; *Asymmetric Organocatalysis-From Biomimetic Concepts to Powerful Methods for Asymmetric Synthesis,* Wiley-VCH, Weinheim, **2005**; (b) Dalko, P. I.; *Enantioselective Organocatalysis. Reactions and Experimental Procedures*, Wiley-VCH, Weinheim, **2007**; For reviews see: (a) Liu, X.; Lin, L.; Feng, X.; *Chem. Commun.* **2009**, 6145; (b) Trindade, A.; Gois, P. M. P.; Afonso, C. A. M.; *Chem. Rev.* **2009**, *109,* 418.
2. Kokotos, G. C.; Kokotos, G.; *Adv. Synth. Catal.* **2009**, *351*, 1355.
3. Fotaras, S.; Kokotos, G. C.; Tsandi, E.; Kokotos, G.; *Eur. J. Org. Chem.* **2011**, 1310.