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Organocatalytic Synthesis of Chiral 1,4-Dihydropyridines with Potential Biological Properties

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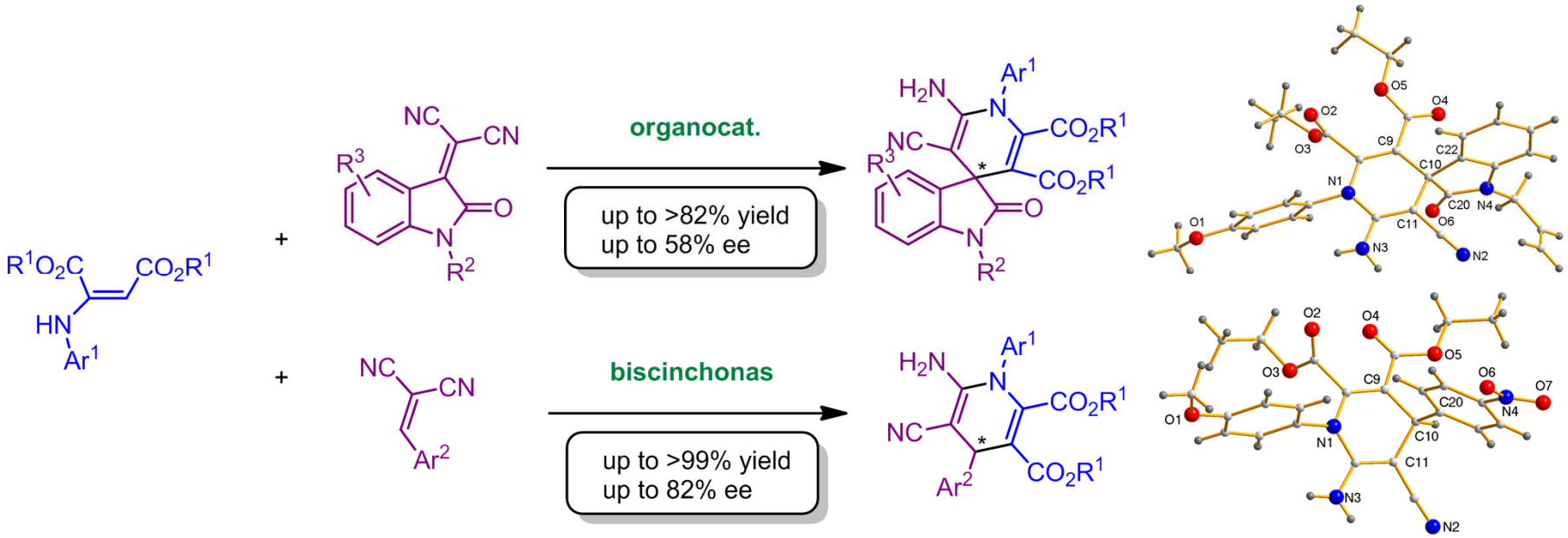
Organocatalytic Synthesis of Chiral 1,4-Dihydropyridines with Potential Biological Properties

Graphical Abstract

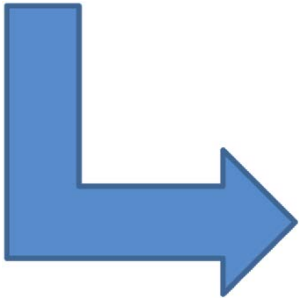


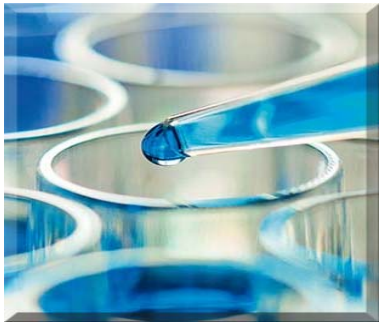
Abstract:
The 1,4-dihydropyridine core is a widely studied privileged scaffold. Molecules containing this structure are well known calcium channel blockers and are being used already as drugs in the treatment of heart disease. Moreover, recent advances have demonstrated their potential to act against many other diseases. The recent research concerning their activity as multidrug-resistance reversing agents should be highlighted. In the chemistry field, they are soft reducing agents and have been used in asymmetric reductions.
As shown before, these molecules contain a chiral center in their C4 position. Nowadays, it is well known that living matter can discern between stereoisomers of the same compound. Nevertheless, there are scarce examples of procedures leading to enantiomerically enriched 1,4-DHPs, most of them being based on the use of chiral auxiliaries or chiral resolutions. Finding more environmental-friendly processes is also an interesting matter in chemistry, organocatalytic procedures are a perfect tool to achieve this goal.
Herein, we report our recent advances in the development of new organocatalytic methodologies to produce enantiomerically enriched 1,4-DHPs. Interestingly, one of them brings out another privileged scaffold, such as the oxindole motif. Our methodologies could be perfect keystones leading to further research on the biological properties of these promising compounds.

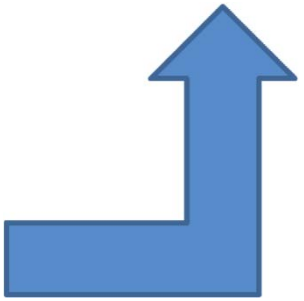
Keywords: 1,4-dihydropyridines; 1,4-DHPs; organocatalysis; cinchona; (thio)ureas

Introduction

DRUG DISCOVERY







Introduction

CATALYSIS AS A KEY TOOL

GREEN CHEMISTRY

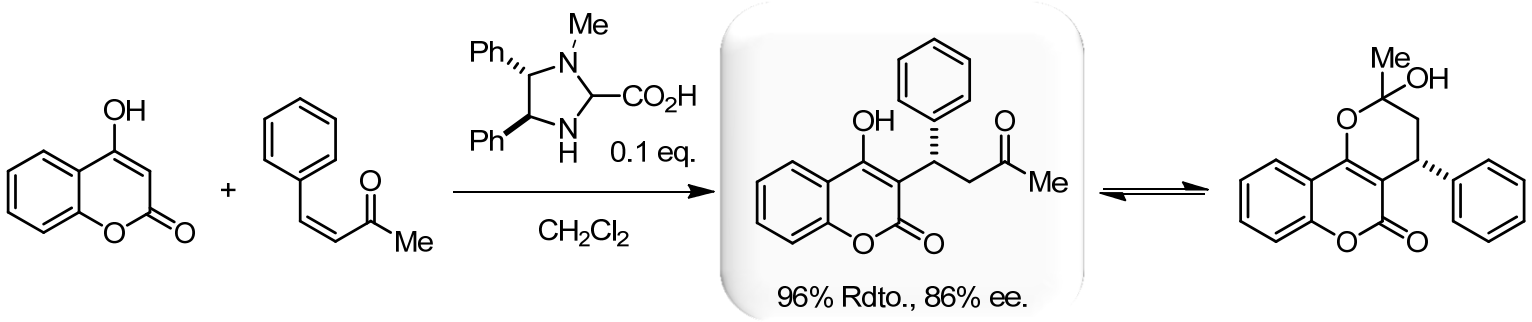
"The invention, design and application of chemical products and processes to reduce or eliminate the use and the production of harmful substances."

IUPAC

ORGANOCATALYSIS

"The acceleration of chemical reactions with a substoichiometric amount of organic molecules, which do not contain a metal element."

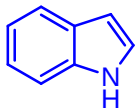
Organocatalysis (Eds.: M. T. Reetz, B. List, S. Jaroch, H. Weinmann). Springer, Berlín-Heidelberg, New York, **2007**.



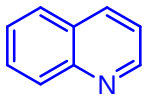
Organocatalytic step of the enantioselective synthesis of (S)-Warfarin

Introduction

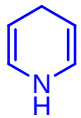
Privileged scaffolds



Indol



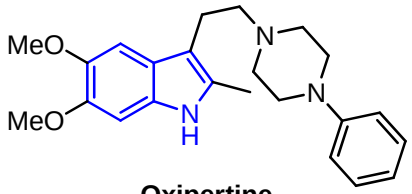
Quinoline



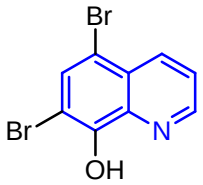
Dihydropyridine

Curr. Opin. Chem. Biol. **2010**, *14*, 347.

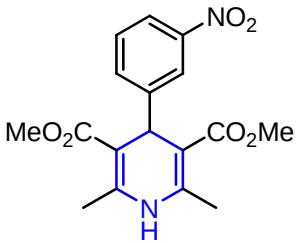
DRUGS



Oxipertine
Antidepressant

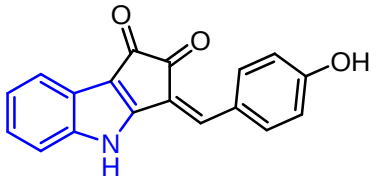


Broxiquinoline
Antiseptic

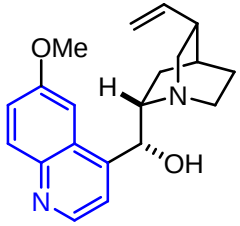


Nifedipine
Antihypertensive

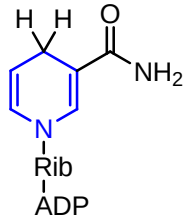
NATURAL PRODUCTS



Nostodione A
Mitotic spindle poison



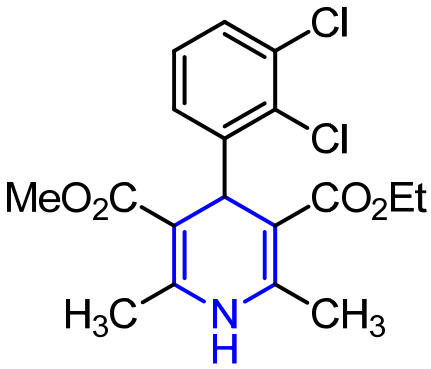
Quinine
Antimalarial



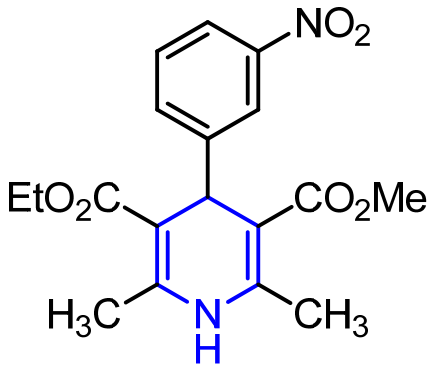
NADH
Coenzime

Introduction

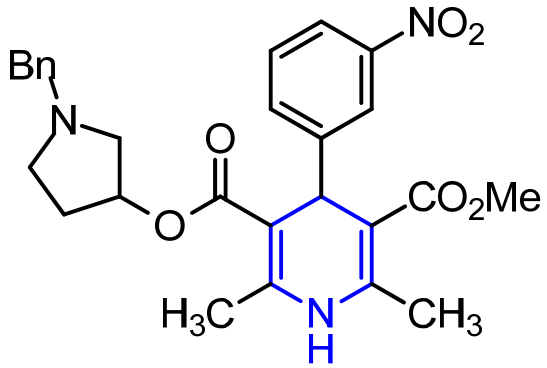
Classic activity of DHPs: Ca Channel Blockers



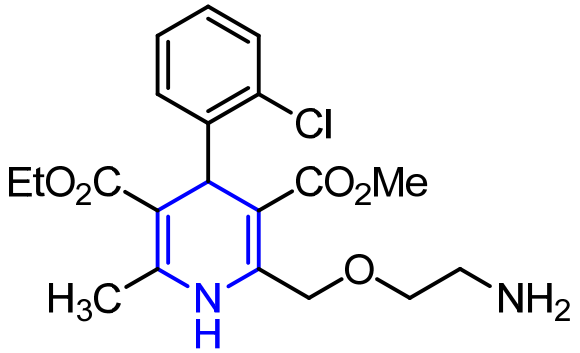
Felodipine



Nitredipine



Barnidipine

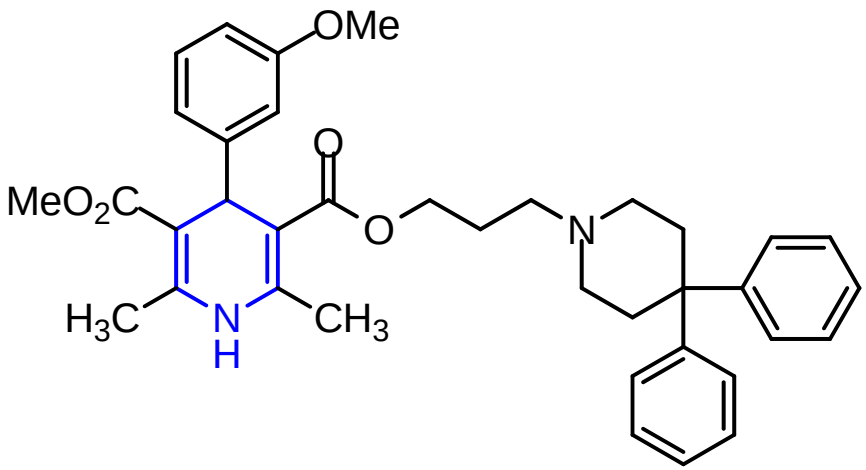


Amlodipine

Introduction

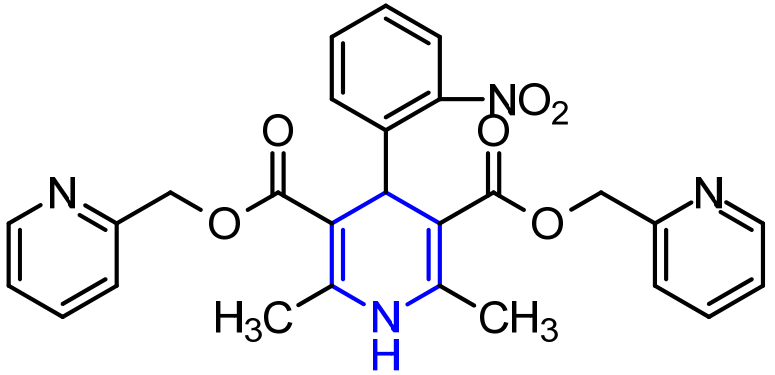
Multidrug-resistance reversing agents

Classical MDR



Morris, M. E. *J. Pharm. Sci*. **2005**, *94*, 2256-2265.

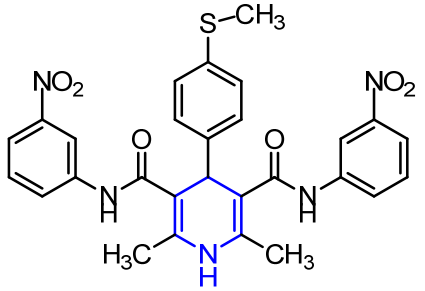
Atypical MDR



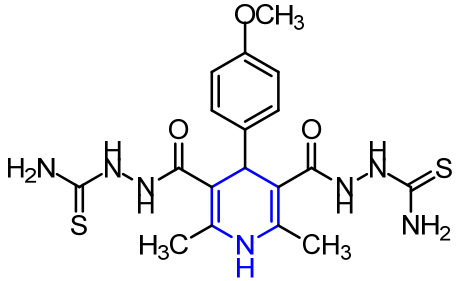
Mehdipour, A.R. *et al*. *Chem. Biol. Drug Des*. **2007**, *70*, 337–346.

Introduction

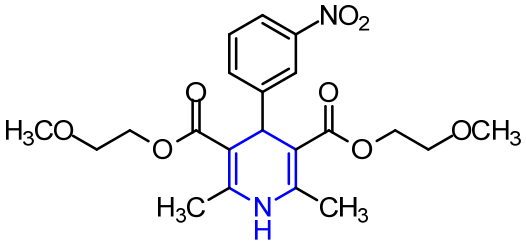
DHPs, more than Ca channel blockers



ANTITUBERCULAR
Desai, B. *et al*. *Bioorg. Med. Chem*. **2001**, *9*, 1993-1998.



ANTITUMOR
Surendra Kumar, R. *Indian J. Chem. Sect. B. 2011*, **50**, 1140-1144.

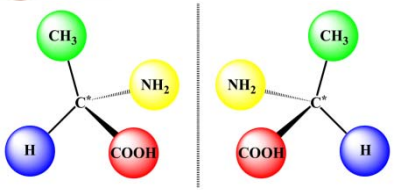


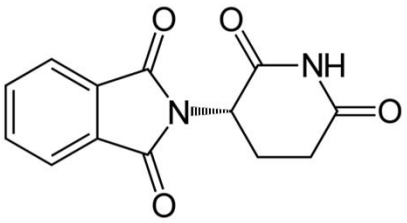
ALZHEIMER TREATMENT
López-Arrieta, J.M. and Birks, J. *Cochrane Database Syst. Rev.* **2002**, *3* CD000147.

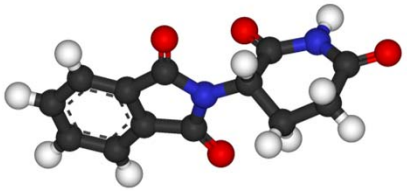
Introduction

Chirality on farmacology and 1,4-DHPs

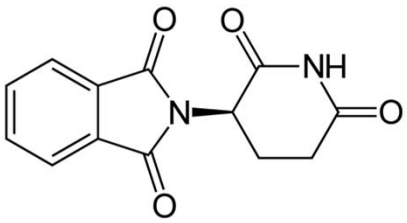
DIFFERENTIATION

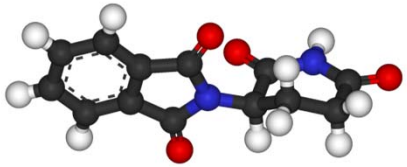




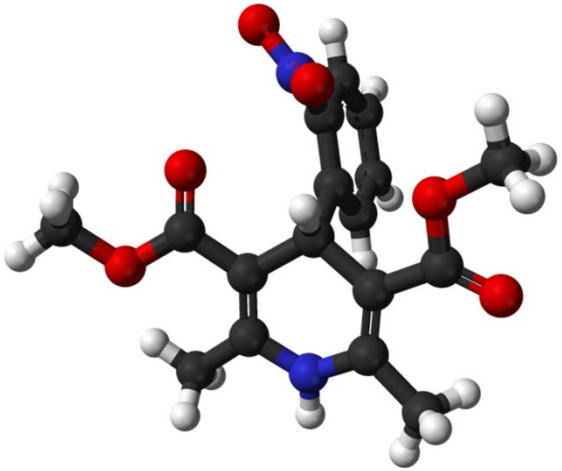


TERATOGENIC





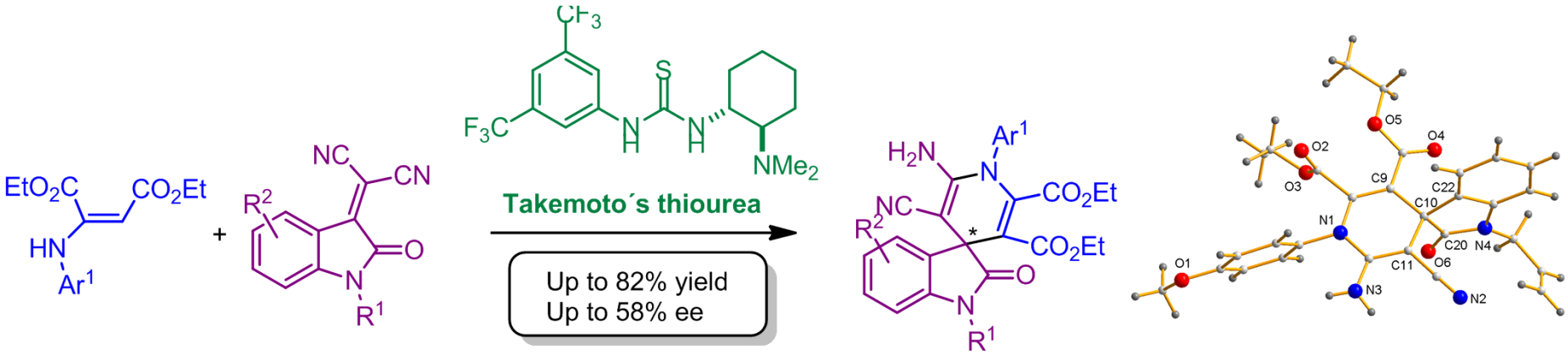
SEDATIVE



SCARCE EXAMPLES OF ENANTIOSELECTIVE PROCEDURES

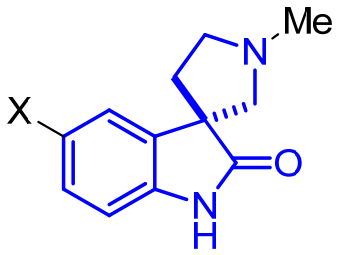
Organocatalytic synthesis of chiral 1,4-dihydropyridines.
Herrera, R. P. *et al*
Adv. Synth. Catal. **2017**, *359*, 2161-2175.

Results and discussion

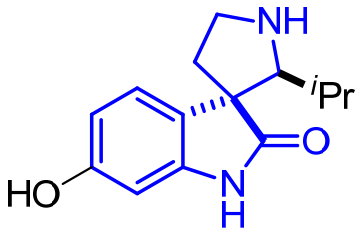


Herrera, R. P. *et al Molecules*, **2015**, *20*, 15807-15826.

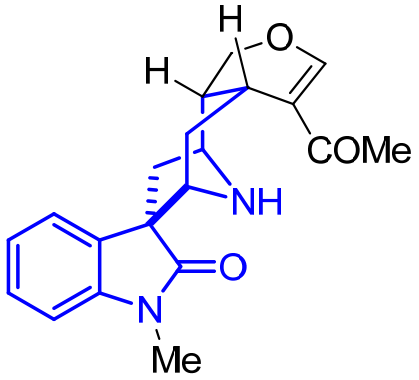
SPIROOXINDOLE



horsfiline (X = MeO)
coerulescine (X = H)



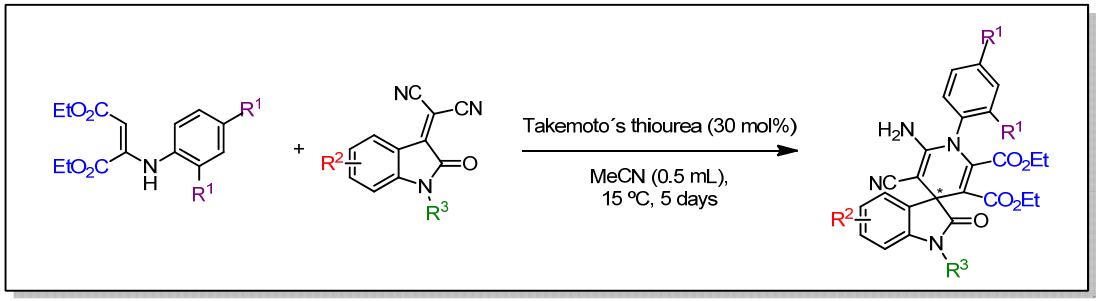
(+)-elacomine



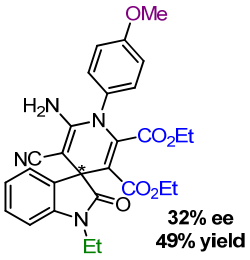
alstonisine

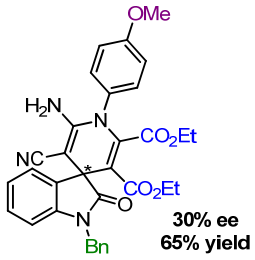
Results and discussion

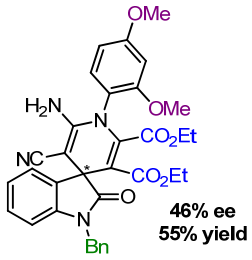
Reaction scope

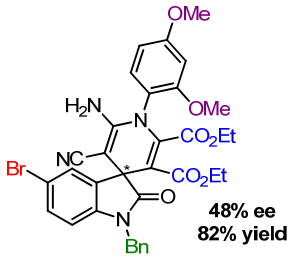


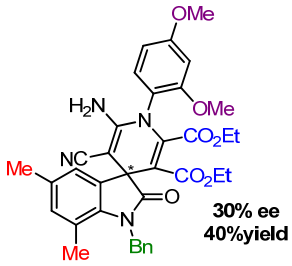
Up to 82% yield
Up to 58% ee


32% ee
49% yield


30% ee
65% yield


46% ee
55% yield


48% ee
82% yield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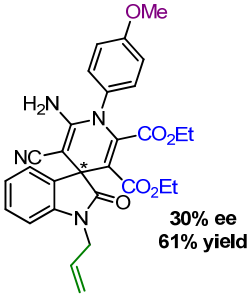
40%yield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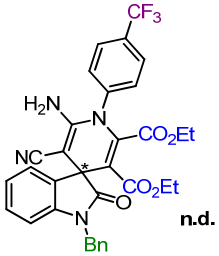
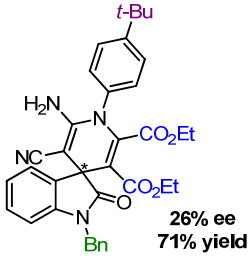
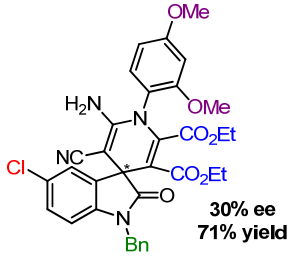
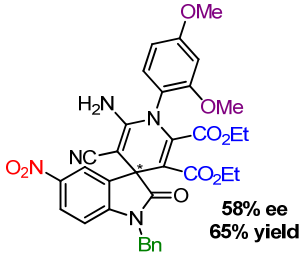
61% yield


n.d.

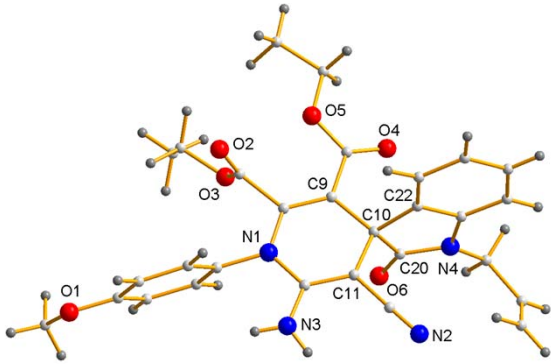

26% ee
71% yield


30% ee
71% yield


58% ee
65% yield

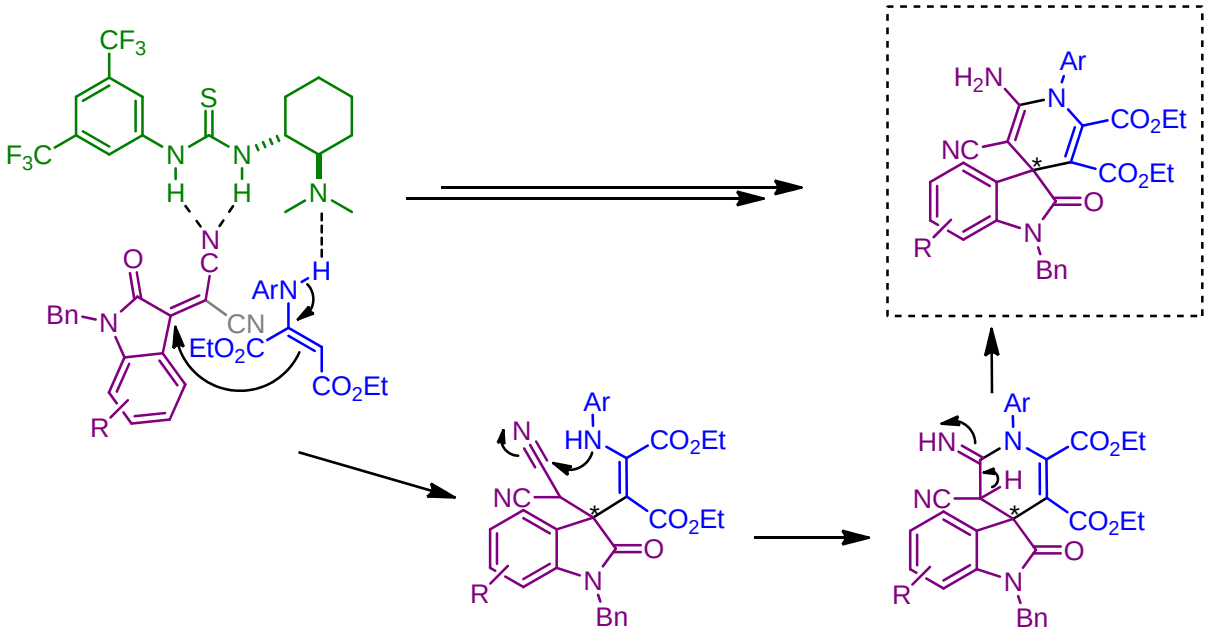
Results and discussion

X ray structure

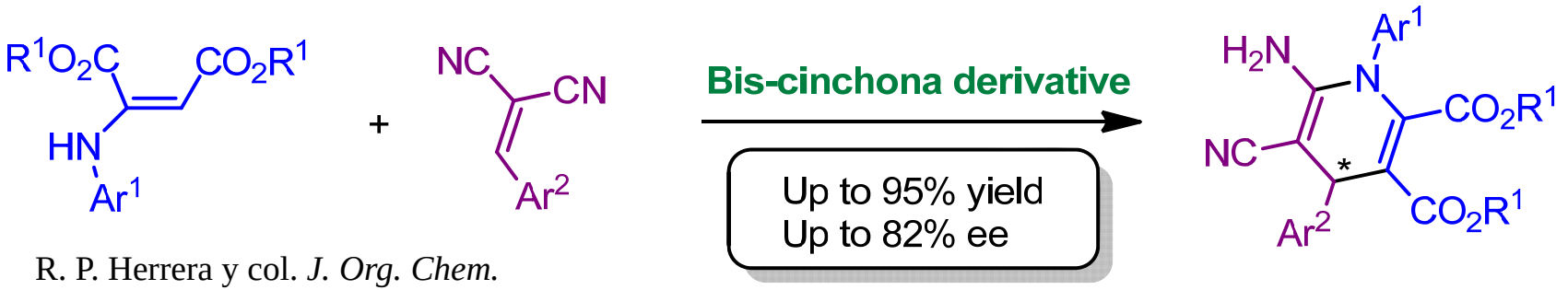


Prof. Gimeno, M. C. (ISQCH, CSIC)

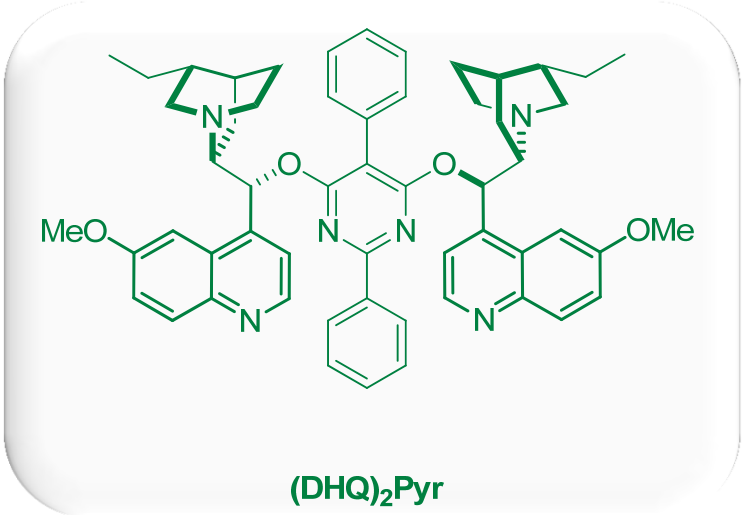
Mechanistic proposal

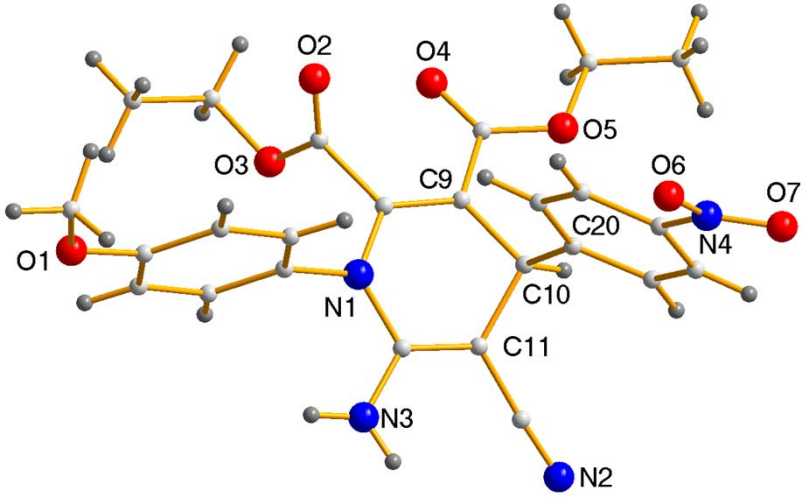


Results and discussion



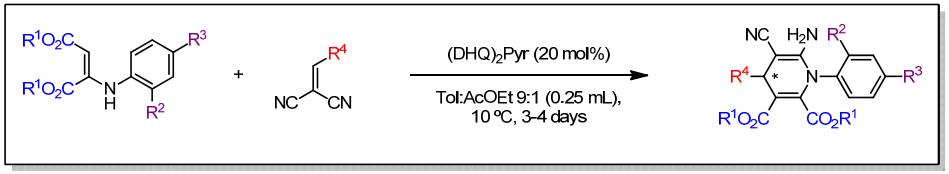
R. P. Herrera y col. *J. Org. Chem.* **2017**, *82*, 5516-5523.



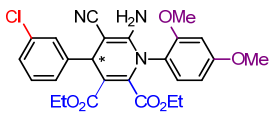


Results and discussion

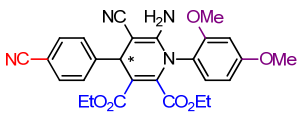
Reaction scope



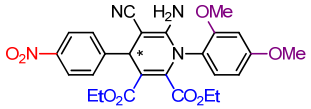
Up to 99% yield
Up to 82% ee



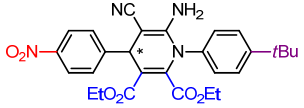
99% yield
74% ee



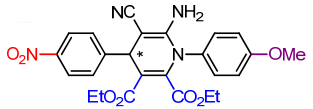
96% yield
74% ee



97% yield
76% ee



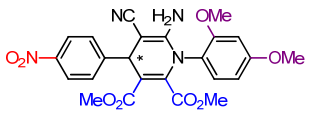
62% yield
74% ee



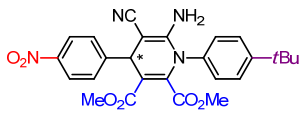
71% yield
73% ee

Ethyl ester derivatives

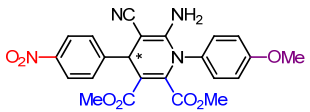
Methyl ester derivatives



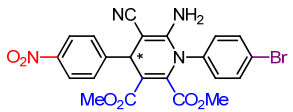
88% yield
82% ee



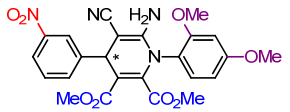
76% yield
62% ee



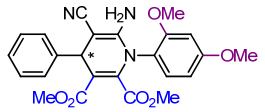
69% yield
74% ee



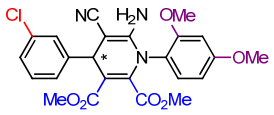
89% yield
64% ee



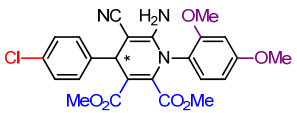
99% yield
77% ee



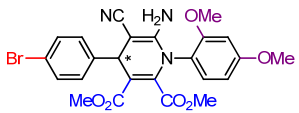
21% yield
80% ee



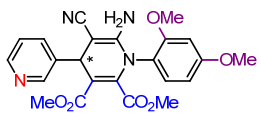
82% yield
74% ee



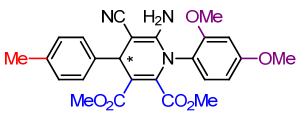
36% yield
72% ee



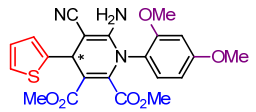
43% yield
76% ee



79% yield
82% ee



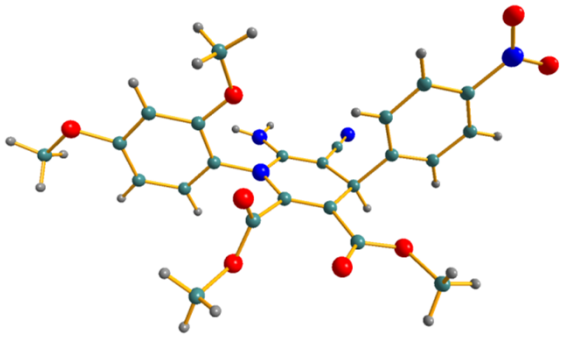
22% yield
72% ee



15% yield
76% ee

Results and discussion

X ray structure



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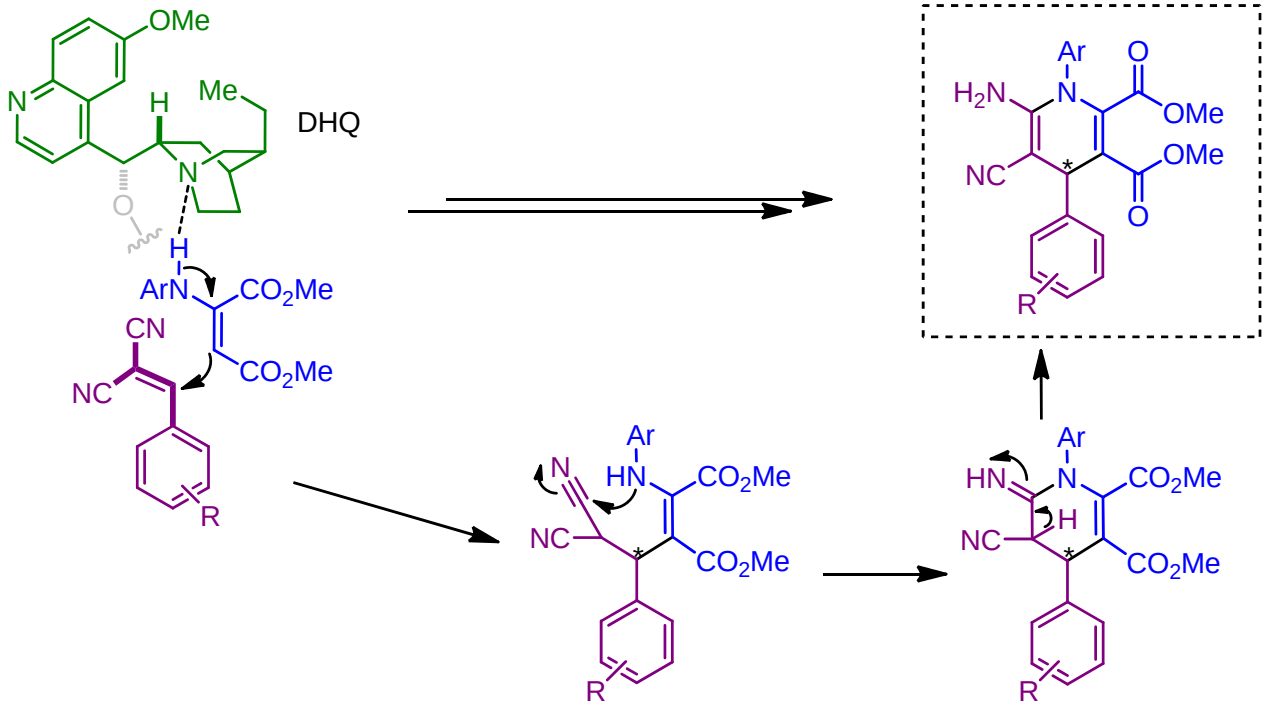
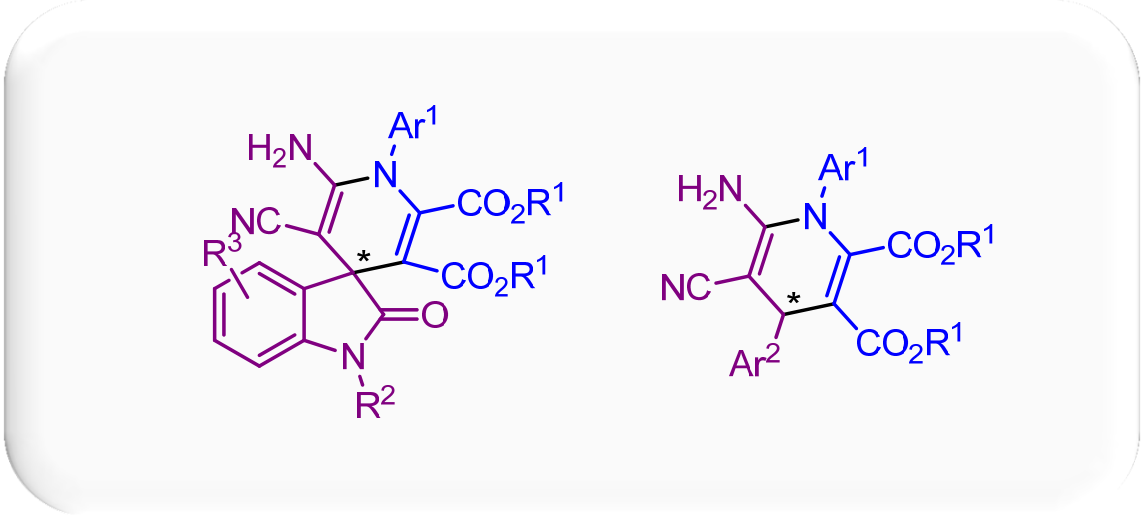
Mechanistic proposal



Conclusions



- ✓ Pioneering catalytic strategies leading to 1,4-DHPs.
- ✓ Mild conditions and operational simplicity.
- ✓ Promising results.
- ✓ Great structural diversity.

Acknowledgments

DGA group (E-104) Organocatálisis Asimétrica. https://hoca.unizar.es

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