First Advances in the Asymmetric Synthesis of Biologically Active 2-Amino-3-cyano-4*H*-chromen-4-yl Phosphonates

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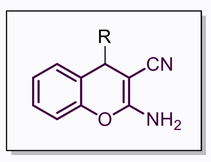
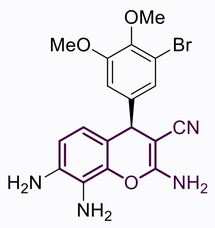
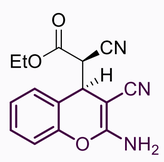
Background and Objective of the Present Research



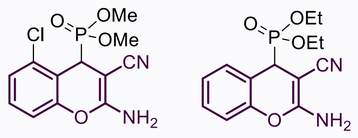
4*H*-2-amino-3-cyano-chromene scaffold



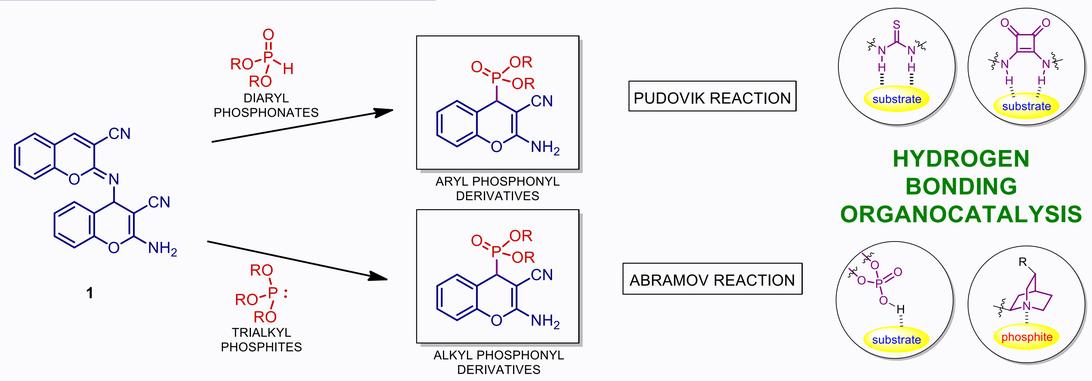
Crolibulin
antitumour activity



HA14-A
pro-apoptotic activity



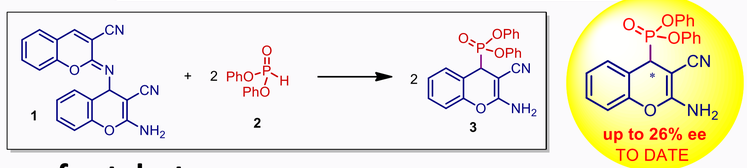
PHOSPHONYL DERIVATIVES



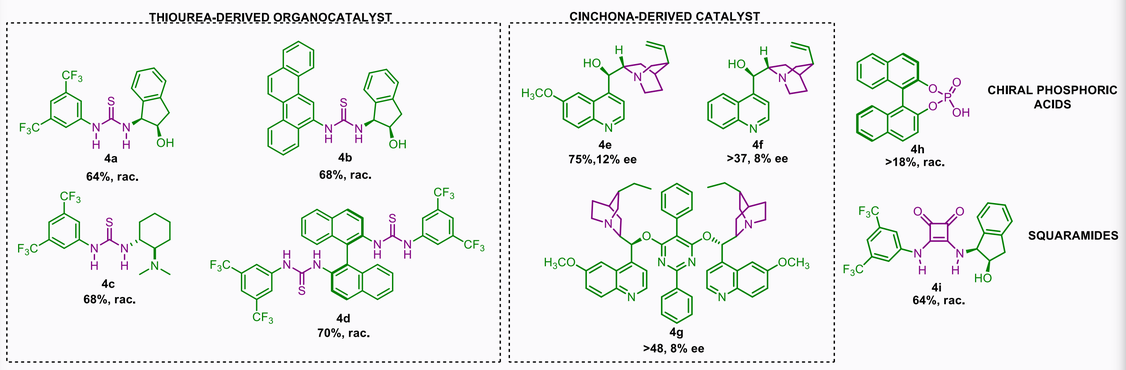
Substituted 4*H*-2-amino-3-cyanochromene derivatives have recently played an important role in the search of new pharmaceuticals. On the basis of recent studies, 4-fosfonyl derivatives became of particular interest due to different biological activities that these compounds exhibit.[1,2,3] However, the enantioselective synthesis of these interesting products has not been reported to date.[4]

Due to the importance of these scaffolds, the present research explores the use of different chiral hydrogen bonding organocatalysts in the asymmetric synthesis of alkyl and aryl fosfonyl 4*H*-2-amino-3-cyano chromenes. For this purpose, a new electrophilic substrate **1** is employed in the study of two pioneering catalytic strategies, which involve the use of trialkyl phosphites and diarylphosphonates.

Pudovik Reaction Approach



1. Screening of catalysts

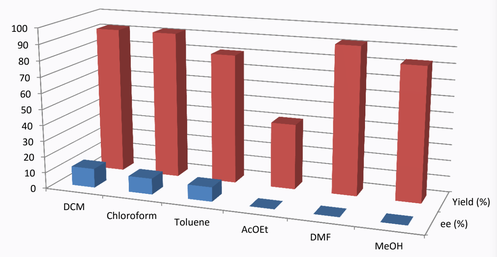


In order to explore the catalytic addition of diarylphosphonate **2** to dimer **1**, the activity of several organocatalysts **4a**-**i** was tested. To our delight, the diarylphosphonate **2**, which has not been previously used as reagent in the synthesis of these compounds, reacted in presence of 10-20 mol% of catalyst to give the desirable product **3**. In addition, an appreciable enantioselectivity can be observed in presence of the cinchona-derived catalysts **4e**-**g**.

2. Optimization of reaction conditions

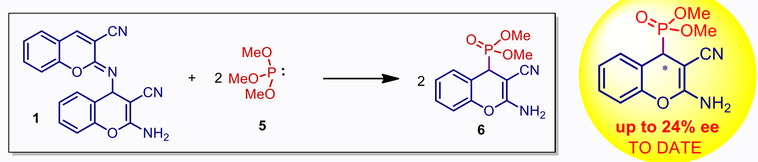
Variation of reaction conditions.

Eq. **2**	Catalyst **4e** (%)	Solvent (µl)	T (˚C)	Time (h)	Yield (%)	ee (%)
2	20	DCM (250)	r.t.	24	75	12
2	20	DCM (500)	r.t.	24	74	14
2	20	DCM (500)	0	24	92	12
1	20	DCM (500)	0	48	61	18
1	40	DCM (500)	0	12	61	26

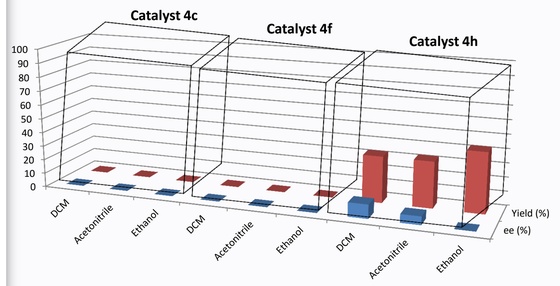


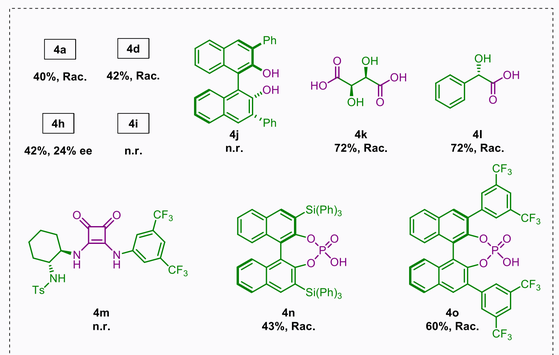
With the aim of improving the selectivity provided by catalyst **4e**, different solvents and reaction conditions were explored. In this way, DCM was chosen as the best solvent for the catalysis. In the other hand, the use of less equivalents of phosphite as well as higher amounts of catalyst have provided better selectivities. To date, an unprecedented enantiomeric excess of 26% has been obtained.

Abramov Reaction Approach



1. Screening of catalysts

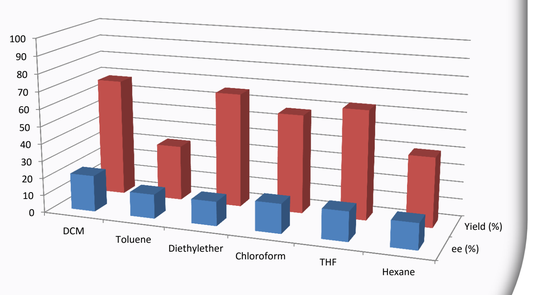




Organocatalysts **4c**,**f** and **h** were tested in three different solvents at room temperature, in order to study their catalytic activation of the addition of trialkylphosphite **5** to dimer **1**. Interestingly, in presence of phosphoric acid **4h**, the reaction gives product **6** with an appreciable enantioselectivity. In contrast, in the presence of organocatalysts **4c** and **4f**, with a trialkylamino moiety in their structures, the reaction does not occur. After the preliminary study, different acidic organocatalysts **4a**,**d**,**h**-**o** were tested, at low temperature and in DCM as solvent. The best results of selectivity were obtained in presence of catalyst **4h**.

2. Screening of solvents

Other solvents were explored in order to improve the catalytic results provided by catalyst **4h** in the previous studies. However, similar results of selectivity were obtained. To date, an unprecedented enantiomeric excess of 24% has been obtained.



References

[1]Rajasekhar, M.; Rao, K. U. M.; Sundar, S.; Reddy, N. B.; Nayak, S. K.; Reddy, C. S. *Chem. Pharm. Bull.*, **2012**, *60*, 854-858.
[2]Kalla, R. M. N.; Choi, J.-S.; Yoo, J.-W.; Byeon, S. J.; Heo, M. S.; Kim, I. *Eur. J. Med. Chem.*, **2014**, *76*, 61-66.
[3]Kour, P.; Kumar, A.; Sharma, R.; Chib, R.; Khan, I. A.; Rai, V. K. *Res. Chem. Intermed.*, **2017**, https://doi.org/10.1007/s11164-017-3077-2.
[4]For a review about enantioselective organocatalyzed synthesis of 2-amino-3-cyano-4*H*-chromene derivatives, see: Sonsona, I. G.; Marqués-López, E.; Herrera, R. P. *Symmetry*, **2015**, *7*, 1519-1535.

Acknowledgements

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