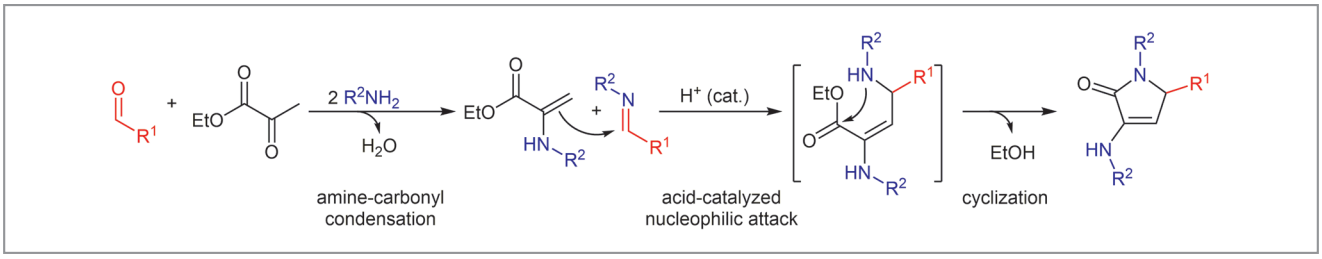
Brønsted Acid Catalyzed Asymmetric Three-Component Reaction of Amines, Aldehydes and Pyruvate Derivatives: Enantioselective Synthesis of Highly Functionalized γ-Lactam Derivatives

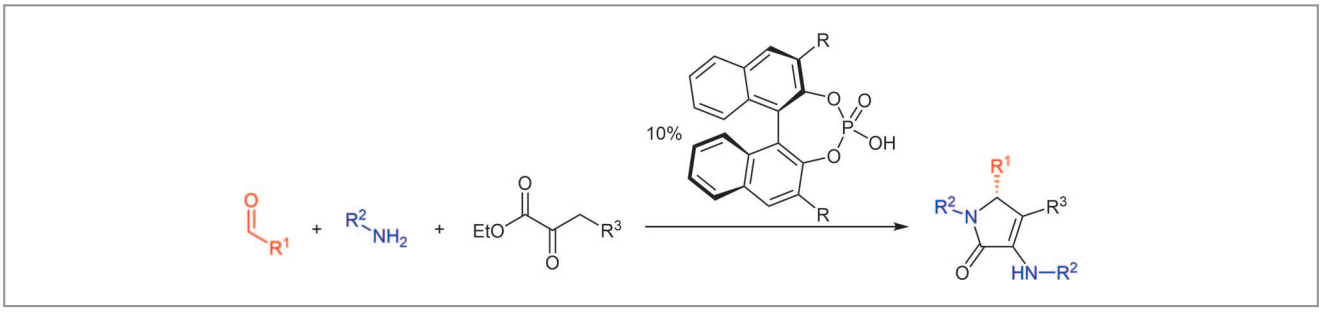
Org. Lett. **2018**, *20*, 317–320

At the heart of diversity-oriented synthesis, multicomponent reactions (MCRs) are valuable synthetic protocols where three or more components react together in a single vessel to afford densely functionalized substrates, where a substantial part of the structure of all the starting materials can be found in the final substrate. Hantzsch dihydropyridine synthesis, Biginelli, Ugi, Passerini, Gröbcke–Blackburn–Bienaymé, Kabachnik–Fields or Strecker reactions are notorious examples of extremely useful MCR protocols. As a contribution to this field, the research group of Professor Francisco Palacios (University of the Basque Country, Vitoria-Gasteiz, Spain) reported a few years ago an acid-catalyzed three component reaction of amines, aldehydes and ethyl pyruvate to afford 3-amino-1,5-dihydro-1*H*-pyrrol-2-ones (*Eur. J. Org. Chem.* **2006**, 2843). "As shown in Scheme 1, this reaction consists of an initial double condensation of amines with aldehydes and ethyl pyruvate, followed by an acid-catalyzed nucleophilic addition of the resulting enamines to imines with a final intramolecular formation of amide bond, due to the addition of resulting amine to carboxylic group," explained Professor Palacios. He continued: "The resulting 1,5-dihydro-2*H*-pyrrol-2-ones contain a γ-lactam ring and are the core structures in the skeleton of many bioactive natural products and a wide range of drug candidates that show assorted pharmacological activities."

Considering the fast development of organocatalysis during recent decades and particularly the Brønsted acid catalyst, the group was intrigued whether the stereocontrolled formation of the C–C bond in their three-component reaction could be achieved if chiral phosphoric acids were used as catalytic species. "Although only a modest enantioselectivity was obtained in the preliminary studies, later on, we were shocked when we discovered that, using diethyl ether as solvent, the enantiomeric excesses were substantially raised," remarked Professor Palacios.



Scheme 1 Three-component reaction of amines, aldehyde and ethyl pyruvate



Scheme 2 Phosphoric acid catalyzed three component reaction

This remarkable behavior was attributed to the participation of ether molecules in the transition state for the nucleophilic addition process, which may coordinate with the chiral catalyst or even the nucleophile species. Although the enantiomeric excesses were already excellent in diethyl ether, the group tested other ether solvents in order to shed some light on this matter, but no further improvement of the enantioselectivity was observed.

"The optimized experimental conditions were applied to the multicomponent reaction using easily available or commercial starting reagents such as amines, aldehydes and pyruvate derivatives," said Professor Palacios. Some selected examples are shown in Figure 1. Professor Palacios noted that regarding the amine substrate, excellent enantiomeric excesses are obtained when weakly activated or deactivated anilines are used as substrates (*p*-toluidine, *p*-bromoaniline, *m*-chloroaniline or *o*-fluoraniline). "Very good enantioselectivity is also observed when a strongly activated aromatic amine such as *p*-anisidine is used. Regarding the aldehyde component, good enantioselectivities are obtained using the less electrophilic benzaldehyde and good reactivity and enantioselectivity is also achieved using other electron-poor aldehydes such as *p*-trifluoromethylbenzaldehyde," said Professor Palacios. He continued: "Moreover, although *ortho* substitution is not allowed in the aldehyde substrate, which may be due to steric issues, using *meta*-substituted aromatic aldehydes in the

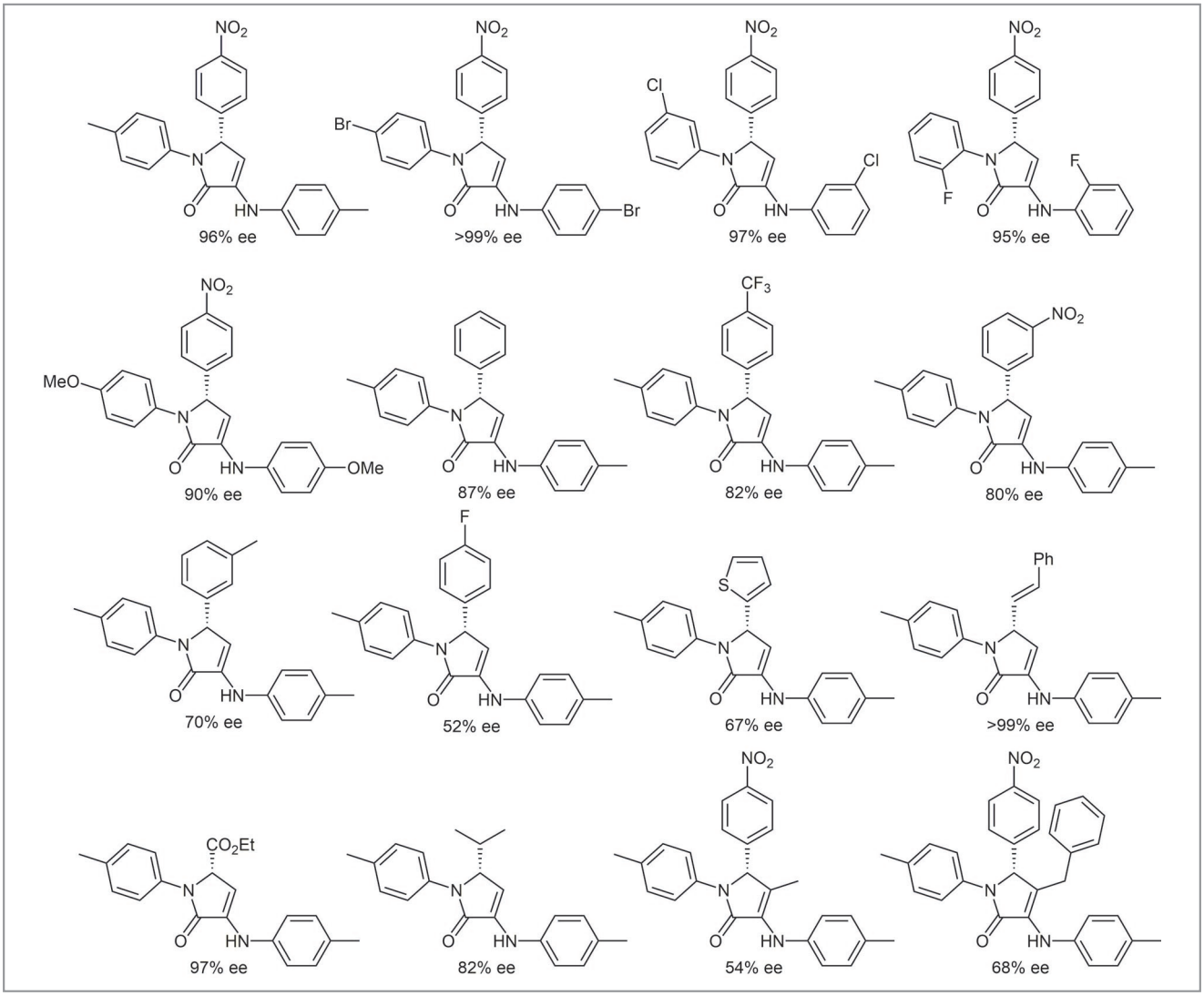


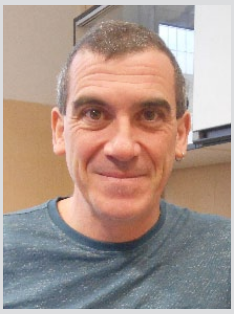
Figure 1 Selected examples for the enantioselective three component reaction

three-component reaction leads to the formation of lactam substrates in good yields." In these cases, while a good ee is observed when *m*-nitrobenzaldehyde is used as substrate, the use of less electrophilic *m*-tolualdehyde requires heating of the reaction, which results in a drop in the ee. "A substantial drop in the ee together with an increase in the reaction time is observed when deactivated *p*-fluorobenzaldehyde is used as substrate. A similar drop in the enantioselectivity, attributed to heating, is observed when heteroaromatic, 2-thiophenecarboxaldehyde is used as electrophile substrate," explained Professor Palacios.

The reaction can also be extended to the use of aliphatic aldehydes as electrophiles, such as cinnamaldehyde or ethyl glyoxalate as well as enolizable aldehydes as *iso*-butyraldehyde, with good to excellent enantioselectivities. Finally, the reaction can be applied to the use of substituted pyruvates as enamine precursors. "However, lower enantioselectivities are obtained, which may possibly be again attributed to the necessity of performing the reaction at higher temperature," Professor Palacios commented.

"In conclusion, this is the first report of a highly enantioselective three-component reaction of pyruvate derivatives, amines and aldehydes to efficiently afford 3-amino-1,5-dihydro-2*H*-pyrrol-2-ones. The enamine chemistry of these lactam substrates is currently under investigation, with special focus on diastereoselective transformations. Moreover, some fluorine- and phosphorus-substituted substrates have been synthesized and the biological activity of racemic and enantiopure substrates is also being investigated," said Professor Palacios.

About the authors



Dr. J. Vicario

Javier Vicario grew up in Imíruri, a small village next to Vitoria-Gasteiz (Basque Autonomous Community, Spain). He graduated in Chemistry in 1998 and then completed his PhD in 2003 under the guidance of Professor Francisco Palacios, at the Faculty of Pharmacy of the University of the Basque Country (Spain), struggling with the chemistry of phosphorated enamines and hydrazones. Then he joined Ben Feringa's research group at the University of Groningen (The Netherlands), where he completed a two-year postdoctoral period, working mainly in the design of light-driven molecular motors and their attachment to surfaces. In 2006, he moved back to the Faculty of Pharmacy in Vitoria-Gasteiz, where he is currently Associate Researcher in Organic Chemistry. His main research interests include the preparation of new enantiopure amino acid and aminophosphonic acid derivatives, using organocatalytic processes.

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Edorta Martinez de Marigorta was born in Vitoria-Gasteiz (Basque Autonomous Community, Spain), graduated in Chemistry in 1984 and received his PhD at the University of Basque Country (Spain) under the guidance of Dr. Esther Domínguez on the chemistry of isoquinolines and protoberberines. In 1991–1992 and 1996 he worked with Professor Ian Fleming at the University of Cambridge (UK) on the use of silyl anions in synthesis. By the end of 1996, he joined the Faculty of Pharmacy and Professor Palacios' group at the University of Basque Country where he is now Associate Professor of Organic Chemistry. His research interests include the chemistry of fluorine- and phosphorus-containing compounds and the preparation of enantioenriched cyclic and acyclic compounds.

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Prof. F. Palacios

Francisco Palacios was born in Vitoria-Gasteiz (Basque Autonomous Community, Spain). He graduated in Chemistry in the University of Zaragoza (Spain) and received his PhD degree in the University of Oviedo (Spain) in 1977 under the supervision of Professor José Barluenga. After two years (1979–1981) of postdoctoral work with Professor Dr. Rolf Huisgen in the Organic Chemistry Institute of the Ludwig Maximilians University (Munich, Germany) working on cycloaddition reactions, he came back to the University of Oviedo as Assistant Professor and became Associate Professor in 1983 at the same University. Since 1991 he has been Full Professor of Organic Chemistry in the University of the Basque Country (Faculty of Pharmacy in Vitoria-Gasteiz, Spain). He has held visiting professorships at the Ecole Nationale Supérieure de Chimie of Montpellier (France) and at the Department of Chemistry of the University of Coimbra (Portugal). His research interests are organic synthesis, organophosphorus chemistry, fluorine chemistry, heterocyclic chemistry, cycloaddition reactions, solid-phase synthesis, design and development of enzyme inhibitors and drug discovery (cancer and neglected tropical diseases).

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Xabier Del Corte was born and grew up near Bilbao (Basque Autonomous Community, Spain). He graduated in Pharmacy at the University of the Basque Country (Spain) in 2017, with a final degree project related to organocatalytic multicomponent reactions. Currently he is carrying out his PhD thesis in Professor Palacios' research group at the Faculty of Pharmacy of the University of Basque Country in Vitoria-Gasteiz. His current research comprises the development of new organocatalytic processes for the preparation of enantiopure amino acid derivatives.

A. Maestro

Aitor Maestro was born in Vitoria-Gasteiz (Basque Autonomous Community, Spain). He graduated in Chemistry in 2015 and then completed his Master degree in Synthetic Chemistry in 2016 at the University of Basque Country (Spain), working in enantioselective synthesis of aminophosphonates. Then he joined Professor Palacios' research group at the Faculty of Pharmacy of the University of Basque Country in Vitoria-Gasteiz where he is currently carrying out his PhD thesis. His research interests include the synthesis of new amino acid and aminophosphonic acid derivatives and organocatalytic asymmetric processes.

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