Catalytic Asymmetric Formal [3+2] Cycloaddition of 2-Isocyanatomalonate Esters and Unsaturated Imines: Synthesis of Highly Substituted Chiral γ-Lactams

Miguel Espinosa,[a] Gonzalo Blay,*[a] Luz Cardona,[a] M. Carmen Muñoz,[b] and José R. Pedro*[a]

Abstract: Unlike their isocyano and isothiocyanato analogues, isocyanato esters remain almost unexplored as formal 1,3-dipoles in asymmetric catalytic reactions. In this communication, the first asymmetric formal [3+2] cycloaddition involving isocyanato esters and electrophilic alkenes is reported. Diisopropyl 2-isocyanatomalonate reacts with α,β-unsaturated *N*-(*o*-anisidyl) imines in the presence of a $Mg(OTf)_2$-BOX complex to give highly substituted chiral pyrrolidinones featuring a conjugate exocyclic double bond with excellent yields and enantiomeric excesses up to 99%. Several transformations of the resulting heterocycles, including the synthesis of a pyroglutamic acid derivative have been carried out.

Pyrrolidinones (γ-lactams) and, in particular, 2-alkoxycarbonylpyrrolidinones (pyroglutamic acid derivatives) have been extensively used as building blocks in synthetic chemistry[1] and as chiral ligands in asymmetric catalysis.[2] They are also structural units frequently encountered in numerous biologically active natural products and pharmaceuticals (Figure 1). Examples include the marine metabolite (-) salinosporamide A, currently tested as an anticancer drug candidate,[3] the proteasome inhibitors antiprotealide and lactacystin,[4] the antibiotic and antitumoral compound neooxazolmycin, isolated form a strain of *Streptomyces*,[5] the neuroexcitotoxic dysibetaine, isolated from the Micronesian sponge *Dysidea herbacea*,[6] or the lipooligosaccharides found in the cell wall of different mycobacteria.[7]

Given the widespread chemical significance of these scaffolds, the development of new efficient and atom economy processes for the construction of these heterocyclic systems, especially in an enantioselective manner, constitutes an important challenge in current organic synthesis. Besides procedures based on the structural modification of nitrogen-containing heterocycles such as pyrrolidinones, pyroglutamic acid or succinimides,[8] cyclization procedures in which the pyrrolidinone heterocycle is formed from acyclic precursors result especially appealing. The Michael addition/lactamization reaction of 2-amino acids and unsaturated acid derivatives is one of the first used procedures for the synthesis of γ-lactams.[9]

[a] Mr. M. Espinosa, Prof. Dr. G. Blay, Prof. Dr. L. Cardona, and Prof. Dr. J. R. Pedro
Departament de Química Orgànica, Facultat de Química
Universitat de València,
C/ Dr. Moliner 50, E-46100-Burjassot, Spain.
E-mail: jose.r.pedro@uv.es; gonzalo.blay@uv.es
[b] Prof. Dr. M. C. Muñoz
Departament de Física Aplicada
Universitat Politècnica de València
Camí de Vera, S/N, E-46071 València, Spain.

Supporting information for this article is given via a link at the end of the document.

Recently, the double Michael addition of amide-tethered diacids with alkynones[10] and the Conia-ene reaction of alkynyl amidomalonates[11] have been used in the synthesis of pyroglutamic acid derivatives. However, most of the methods for the enantioselective synthesis of pyrrolidinones are still based on chiral starting materials or stoichiometric reagents,[12] and only few asymmetric catalytic procedures are available. Among them, enantioselective versions of the Michael addition/lactamization reaction of 2-amino acids and unsaturated acid derivatives have been reported by several groups.[13] Chiral γ-lactams have been obtained with excellent enantioselectivities via *N*-heterocyclic carbene catalyzed coupling of imines with unsaturated aldehydes.[14] Finally, the reaction between 2-aminomalonates and Morita-Baylis-Hillman carbonates catalyzed by chiral Lewis bases to give α-methylene-γ-lactams with moderate enantioselectivity has been recently reported.[15]

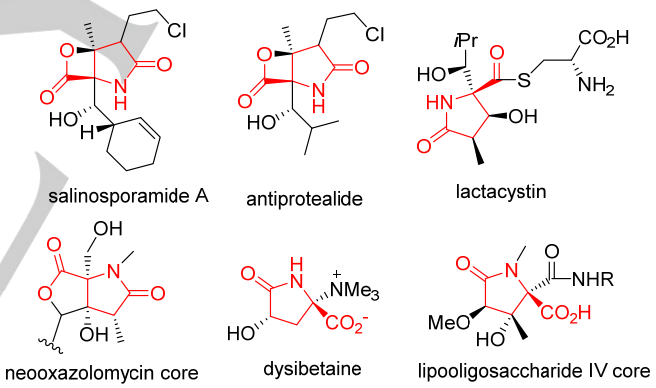
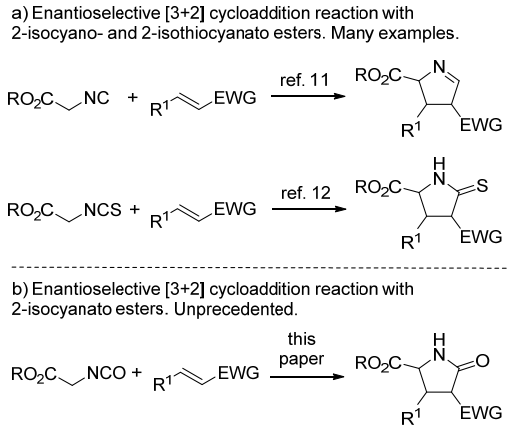


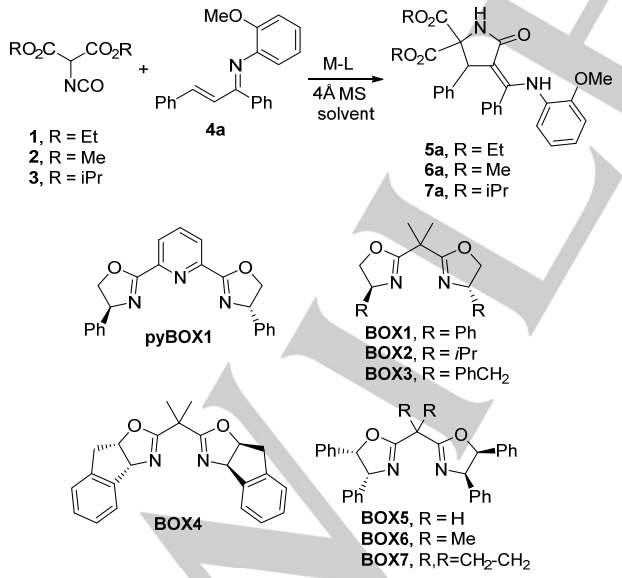
Figure 1. Examples of bioactive natural compounds incorporating a pyrrolidinone unit.

On the other hand, 2-isocyano-[16] and 2-isothiocyanato[17] esters have been increasingly used as formal 1,3-dipoles in asymmetric synthesis over the last years. These compounds react with different unsaturated groups to give a variety of five-membered nitrogen-containing heterocycles. In particular, their participation in asymmetric catalytic formal [3+2] cycloaddition reactions with conjugate carbonyl compounds has provided a strightforward access to enantiomerically enriched pyrrolidines[18] or thiopyrrolidinones,[19] respectively (Scheme 1). Following these antecedents, we envisaged that a formal [3+2] cycloaddition between a 2-isocyanato esters and a proper Michael acceptor may be used for the efficient and atom-economy enantioselective synthesis of 2-alkoxycarbonylpyrrolidinones (Scheme 1). However, the use of 2-isocyanato esters in reactions that combine both nucleophilic and electrophilic behavior (1,3-dipole-like behavior) is

challenging due to the higher reactivity of the isocyanate group compared to the isocyano and isothiocyanate groups. In fact, 2-isocyanato esters have been mainly used as electrophiles for the preparation of ureas and carbamates,[20] while reactions making use of their 1,3-dipole-like character are almost inknown. To the best of our knowledge, the organocatalytic reaction of 2-isocyanatomalonate esters and aldehydes to give oxazolidinones developed by Takemoto,[21] is the only example reported in the literature, so far.[22] Following our research on the use of 1-aza-butadienes as electrophiles,[23] we report here the first example of enantioselective formal [3+2] cycloaddition of 2-isocyanato esters with alkenes to give highly substituted α,β-unsaturated γ-lactams. The reaction is carried out by using unsaturated imines, 2-isocyanatomalonate esters and a Mg-BOX complex as catalyst (Scheme 2).



Scheme 1. Formal [3+2] cycloadditions



Scheme 2. Formal [3+2] cycloaddition between 2-isocyanatomalonates and unsaturated imines, and ligands used in this study.

We initially investigated the activity of the La^{III}-**pyBOX1**, Ca^{II}-**pyBOX1** and Mg^{II}-**BOX1** complexes in the reaction between diethyl 2-isocyanatomalonate (**1**) and imine **4a** derived from *o*-anisidine (Table 1, entries 1-3).[24] In all the cases, the reaction proceeded smoothly to give pyrrolidinone **5a**, which features a conjugated exocyclic double, a structural moiety that is present in a large number of antitumor compounds. Compound **5a** was obtained as a single geometric isomer having the *Z* configuration at the double bond. Regarding enantioselectivity, the La^{III}-**pyBOX1** complex gave compound **5a** in almost racemic form, while the Ca^{II}-**pyBOX1** and Mg^{II}-**BOX1** complexes showed similar enantioselectivities (ee = 67%), although the magnesium complex seemed slightly more active. Further research was continued by testing several Mg-BOX complexes. The best result was obtained with **BOX6** that provided compound **5a** in 98% yield with 71% ee (Table 1, entry 8). A decrease of temperature to 0 °C increased the ee up to 80%, however further decrease of temperature to -20 °C produced a dramatic drop of enantioselectivity (Table 1, entries 9 and 10). With the optimal temperature (0 °C), the effect of the alcoxy group in the 2-isocyanatomalonate ester was tested (Table 1, entries 9, 11 and 12).

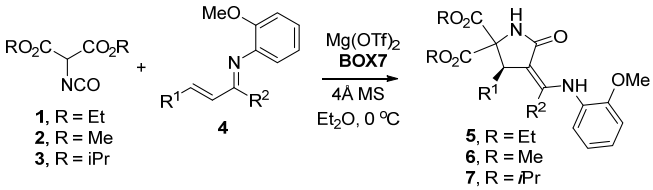
Table 1. Enantioselective [3+2] cycloaddition of isocyanatomalonate esters with unsaturated imine **2a**. Optimization of reaction conditions.[a]

entry	M	L	solvent	R	T [°C]	t (h)	Yield [%][b]	ee [%][c]
1	$La(OTf)_3$	**pyBOX1**	CH_2Cl_2	Et	25	3	81	3
2	$Ca(OTf)_2$	**pyBOX1**	CH_2Cl_2	Et	25	3.5	89	-67
3	$Mg(OTf)_2$	**BOX1**	CH_2Cl_2	Et	25	2	97	-67
4	$Mg(OTf)_2$	**BOX2**	CH_2Cl_2	Et	25	2.5	83	-5
5	$Mg(OTf)_2$	**BOX3**	CH_2Cl_2	Et	25	2.5	89	-5
6	$Mg(OTf)_2$	**BOX4**	CH_2Cl_2	Et	25	3	94	63
7	$Mg(OTf)_2$	**BOX5**	CH_2Cl_2	Et	25	3	97	29
8	$Mg(OTf)_2$	**BOX6**	CH_2Cl_2	Et	25	2.5	97	71
9	$Mg(OTf)_2$	**BOX6**	CH_2Cl_2	Et	0	3	96	80
10	$Mg(OTf)_2$	**BOX6**	CH_2Cl_2	Et	-20	45	68	43
11	$Mg(OTf)_2$	**BOX6**	CH_2Cl_2	Me	0	2	98	49
12	$Mg(OTf)_2$	**BOX6**	CH_2Cl_2	*i*Pr	0	2	98	89
13	$Mg(OTf)_2$	**BOX6**	$(ClCH_2)_2$	*i*Pr	0	2.5	98	76
14	$Mg(OTf)_2$	**BOX6**	$CHCl_3$	*i*Pr	0	2.5	89	91
15	$Mg(OTf)_2$	**BOX6**	Et_2O	*i*Pr	0	2.5	96	91
16	$Mg(OTf)_2$	**BOX7**	Et_2O	*i*Pr	0	1.5	97	97

[a] Reaction conditions: **1-3** (0.19 mmol), **4a** (0.125 mmol, C=N geometry isomer mixture), **L** (0.0125 mmol, $M(OTf)_2$ (0.0125 mmol), 4Å MS (110 mg), solvent (1.1 mL). [b] Yield of isolated product. [c] Determined by HPLC with chiral stationary phases; opposite sign indicates opposite enantiomers.

It was found that the diisopropyl ester **3** underwent a more enantioselective reaction than diethyl or dimethyl 2-isocyanatomalonates, giving lactam **7a** in 98% yield with 89% ee. Next, the effect of the solvent was checked. The use of diethyl ether as the solvent in the addition of **3** to **4a** allowed increasing the ee of compound **7a** up to 91% (Table 1, entry 15). Finally, in view of the important effect of the substitution at the central carbon of the BOX ligand on the enantioselectivity of the reaction (Table 1, entry 7 *vs* entry 8), the cyclopropylic **BOX7** ligand was prepared and tested providing compound **7a** in excellent 97% yield and 97% ee (Table 1, entry 16).

Table 2. Enantioselective [3+2] cycloaddition of 2-isocyanatomalonate esters with unsaturated imines **2**. Scope of the reaction.[a]



Entry	R	R^1	R^2	t[h]	5-7	Yield [%][b]	ee [%][c]
1	*i*Pr	Ph	Ph	1.5	**7a**	97	97
2	*i*Pr	*p*-ClC_6H_4	Ph	1.5	**7b**	93	96
3	*i*Pr	*p*-$NO_2C_6H_4$	Ph	1.5	**7c**	98	98
4	*i*Pr	*p*-$MeOC_6H_4$	Ph	1.5	**7d**	98	96
5	*i*Pr	2-furanyl	Ph	1	**7e**	98	88
6	*i*Pr	*t*Bu	Ph	20	**7f**	26	23
7	*i*Pr	Ph	*p*-ClC_6H_4	1.5	**7g**	94	99
8	*i*Pr	Ph	*p*-$NO_2C_6H_4$	1	**7h**	98	95
9	*i*Pr	Ph	*p*-$MeOC_6H_4$	1	**7i**	97	98
10	*i*Pr	Ph	*m*-$NO_2C_6H_4$	3	**7j**	87	97
11	*i*Pr	Ph	*o*-ClC_6H_4	1.5	**7k**	98[d]	98[e]
12	*i*Pr	Ph	*o*-$NO_2C_6H_4$	27	**7l**	98[d]	99
13	*i*Pr	Ph	2-furanyl	1	**7m**	98	83
14	*i*Pr	Ph	2-naphthyl	1	**7n**	98	98
15	Et	Ph	Ph	1	**5a**	96	77
16	Me	Ph	Ph	1	**6a**	97	76
17[f]	*i*Pr	Ph	Ph	1.5	**7a**	96	94

[a] Reaction conditions: **1-3** (0.19 mmol), **4** (0.125 mmol), **BOX7** (0.0125 mmol, $Mg(OTf)_2$ (0.0125 mmol), 4Å MS (110 mg), Et_2O (1.1 mL), 0 °C. [b] Yield of isolated product. [c] Determined by HPLC with chiral stationary phases. [d] Obtained as a *ca.* 1:1 mixture of *Z/E* isomers. [e] Determined after enamine hydrolysis. [d] Reaction carried out with 1.6 mmol of **4a**.

With the best conditions available the scope of the reaction of diisopropyl 2-isocyanatomalonate (**3**) and α,β-unsaturated *N*-(*o*-methoxyphenyl)imines **4**[25] using the $Mg(OTf)_2$-**BOX7** complex as catalyst was studied. The results are gathered in Table 2. The reaction can be carried out with imines bearing at the β carbon an aromatic ring substituted with either electron-withdrawing (Table 2, entries 2 and 3) or electron-donating groups (Table 2, entry 4), to give the expected products **7b-d** with excellent yields and enantioselectivities. R^1 can be also a heterocyclic furanyl ring (Table 2, entry 5). In this case, compound **7e** was obtained in almost quantitative yield and slightly lower ee (88%). The introduction of a bulky *tert*-butyl group at the β-carbon brought about a decrease on the reaction rate and the expected lactam **7f** was obtained with low yield and enantioselectivity (Table 2, entry 6).

The R^2 group attached to the azomethinic carbon was also amenable to variation (Table 2, entries 7-14). Aromatic rings bearing either electron-withdrawing or electron-donating groups were permitted without showing much influence on the enantioselectivity of the reaction. Again, when R^2 was a 2-furanyl group, compound **7m** was obtained with lower ee, although with high yield (Table 2, entry 13). A naphthyl group attached to the imine was also tolerated, compound **7n** being obtained in 98% yield and 98% ee (Table 2, entry 14). As anticipated, diethyl and dimethyl 2-isocyanatomalonates reacted with **4a** to give the expected lactams with lower enantioselectivity than diisopropyl 2-isocyanatomalonate (Table 2, entries 15 and 16). To further demonstrate the practicality of this newly developed procedure, the reaction of **3** and **4a** was carried out on a 1.6 mmol scale (500 mg). Product **7a** was obtained in 96% yield with minimal erosion in the enantioselectivity (94% ee, Table 2, entry 17).

In all the examples studied except with imines **4k** and **4l**, which have an *o*-substituted phenyl ring attached to the azomethinic carbon, compounds **5-7** were obtained as a single diastereomer. Compound **7b** (Table 2, entry 2) could be crystallized and subjected to X-ray analysis,[26] what allowed to stablish the geometry of the enamine double bond as *Z* and the configuration of the stereogenic center as *R* (Figure 2). The absolute stereochemistry of all compounds **5-7** was assigned by analogy upon the assumption of a uniform stereochemical pathway.

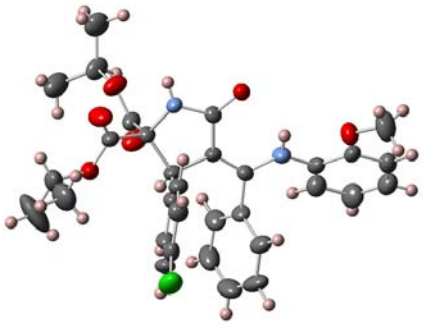
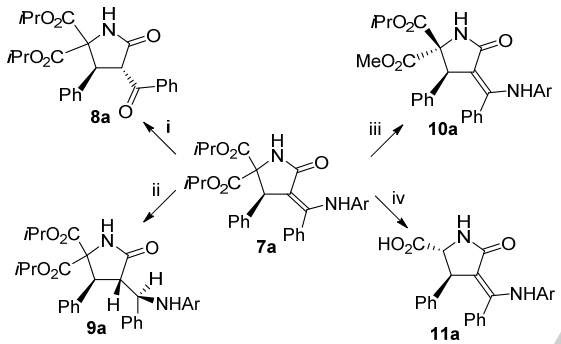


Figure 2. Ortep plot for the X-ray structure of compound **7b**. The thermal ellipsoids are drawn at the 50% probability level. Flack parameter -0.16(8)

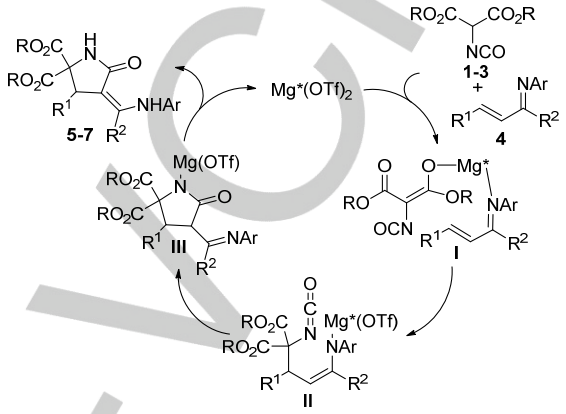
Some transformations were carried out on compound **7a** (Scheme 3). Thus, aqueous hydrolysis of the enamine with concentrated HCl in THF gave ketone **8a** in 90% yield. On the other hand, treatment of **3a** with $NaBH_3CN$-AcOH in EtOH provided a major amine **9a**[26] in 75% yield, together with an isomeric amine **9a'**, whose stereochemistry could not be assigned, in 11% yield. Also, the chemoselective transesterification of the diisopropyl ester **7a** to give the mixed diester **10a** was efficiently achieved in 89% yield by treatment with NaOMe/MeOH. Finally, the pyroglutamic acid derivative **11a** was obtained in 87% yield after hydrolysis/decarboxylation upon treatment of **7a** with an excess of tetraethylammonium hydroxyde in DMSO at 80 °C. All these reactions took place without noticeable loss of enantiomeric excess with respect to starting **7a**.



Scheme 3. Ar = *o*-$MeOC_6H_4$. i: HCl, THF, rt, **8a**: 90%. ii: $NaBH_3CN$, AcOH, EtOH, 0 °C, **9a**: 75%, **9a'** (a diasteromer of **9a**):11%. iii: NaOMe/MeOH, 65 °C, **10a**: 89%. iv: Et_4NOH, DMSO, 80 °C, **11a**: 87%.

A simplified mechanistic proposal for the [3+2] cycloaddition is outlined in Scheme 4. Thus, initial coordination of both reaction partners to the Mg^{II}-BOX complex would bring about nucleophilic activation of the malonate ester via enolization together with electrophilic activation of the imine (intermediate **I**). Conjugate addition would lead to enamine intermediate **II** which would undergo nucleophilic addition to the isocyanate group giving lactam **III**. Finally, imine/enamine tautomerization and decoordination would give the final products and release the catalyst.

In summary, we have reported the first enantioselective formal [3+2] cycloaddition of 2-isocyanatomalonate esters with electrophilic alkenes. Using a $Mg(OTf)_2$-BOX complex as catalyst, diisopropyl isocyanatomalonate reacted with α,β-unsaturated *N*-(*o*-anisidyl) imines to give highly substituted chiral pyrrolidinones featuring a conjugate exocyclic double bond. The reaction products, which are derivatives of pyroglutamic acid, were obtained with excellent yields and high to excellent enantioselectivities, for a significative number of unsaturated imines. The use of the *N*-(*o*-anisidyl) group was essential for the success of the reaction as neither the unsaturated ketone nor the unsaturated *N*-tosyl imine were reactive with this catalyst. Furthermore, the reaction does not requires the use of diastereomerically pure imines, instead mixtures of C=N geometric isomers can be used. The application of nonexpensive and nontoxic Mg(II) salts as Lewis acids is another advantage of this procedure. We believe that this reaction will open new possibilities for the potential application of isocyanato esters as formal 1,3-dipoles in asymmetric catalytic reactions. Research toward this goal is currently under progress in our laboratory



Scheme 4. Simplified mechanistic proposal for the [3+2] cycloaddition. Mg* = Mg-BOX

Experimental Section

General procedure for the formal [3+2] reaction: $Mg(OTf)_2$ (4.0 mg, 0.0125 mmol) was dried in a Schlenk tube under vacuum. **BOX7** (6.1 mg, 0.0125 mmol) was introduced and the Schlenk tube was filled with nitrogen. Et_2O (0.55 mL) was added via syringe and the mixture was stirred for 30 min. The tube was introduced in a bath at 0 °C, 4 Å MS (110 mg) was then added followed by the imine (0.125 mmol) dissolved in dry Et_2O (0.5 mL), and by diisopropyl 2-isocyanatomalonate (37 μL, 0.19 mmol). The mixture was stirred at 0 ºC for the indicated time and chromatographed on silica gel eluting with hexane/EtOAc mixtures to give compounds **7**. Compounds **5** and **6** were prepared following the same procedure using diethyl or dimethyl 2-isocyanatomalonate, respectively.

Acknowledgements

Financial support (CTQ2013-47494-P) from the Ministerio de Economía y Competitividad (MINECO-Gobierno de España). M.E. thanks the Generalitat Valenciana for a predoctoral grant. Access to NMR and MS facilities from the Servei Central de Suport a la Investigació Experimental (SCSIE)-UV is also acknowledged.

Keywords: nitrogen heterocycles • lactams • asymmetric catalysis • nucleophilic addition • enantioselectivity

[1] Reviews: a) S. Hanessian, L. Auzzas, *Acc. Chem. Res.* **2008**, *41*, 1241; b) C. Najera, M. Yus, *Tetrahedron: Asymmetry* **1999**, 10, 2245; c) A. Stefanucci, E. Novellino, R. Costante, A. Mollica, *Heterocycles* **2014**, *89*, 1801. Selected examples: d) C. Zanato, S. Watson, G. S. Bewick, W. T. A. Harrison, M. Zanda, *Org. Biomol. Chem.* **2014**, *12*, 9638; e) S.

V. Pansare, K. G. Kulkarni, *RSC Adv.* **2013**, *3*, 19127; K. Yamada, T. Sato, M. Hosoi, Y. Yamamoto, K. Tomioka, *Chem. Pharm. Bull.* **2010**, *58*, 1511. f) A. Hameed, A. J. Blake, C. J. Hayes, *Synlett* **2010**, 535.

[2] P. Geoghegan, P. O'Leary, *Tetrahedron: Asymmetry* **2010**, *21*, 867.

[3] a) R. H. Feling, G. O. Buchanan, T. J. Mincer, C. A. Kauffman, P. R. Jensen, W. Fenical, *Angew. Chem. Int. Ed.* **2003**, *42*, 355; *Angew. Chem.* **2003**, *115*, 369**;** b) T. A. M. Gulder, B. S. Moore, *Angew. Chem. Int. Ed.* **2010**, *49*, 9346; *Angew. Chem.* **2010**, *122*, 9534.

[4] a) S. Omura, T. Fujimoto, K. Otoguro, K. Matsuzaki, R. Moriguchi, H. Tanaka, Y. Sasai, *J. Antibiot.* **1991**, *44*, 113; b) S. Omura, K. Matsuzaki, T. Fujimoto, K. Kosuge, T. Furuya, S. Fujita, A. Nakagawa, *J. Antibiot.* **1991**, *44*, 117; c) G. Fenteany, S. L. Schreiber, *J. Biol. Chem.* **1998**, *273*, 8545. d) R. R. Manam, V. R. Macherla, G. Tsueng, C. W. Dring, J. Weiss, S. T. C. Neuteboom, K. S. Lam, B. C. Potts, *J. Nat. Prod.* **2009**, *72*, 295.

[5] T. Mori, K. Takahashi, M. Jashiwabara, D. Uemura, *Tetrahedron Lett.* **1985**, *26*, 1073; b) M. G. Moloney, P. C. Trippier, M. Yaqoob, A. Wang. *Curr. Drug Discovery Technol.* **2004**, *1*, 181.

[6] a) R. Sakai, C. Oiwa, K. Takaishi, H. Kamiya, M. Tagawa, *Tetrahedron Lett.* **1999**, *40*, 6941; b) R. Sakai, K. Suzuki, K. Shimamoto, H. Kamiya, *J. Org*. Chem. **2004**, *69*, 1180.

[7] Y. Rombouts, E. Elass, C. Biot, E. Maes, B. Coddeville, A. Burguiere, C. Tokarski, E. Buisine, X. Trivelli, L. Kremer, Y. Guerardel, *J. Am. Chem. Soc.* **2010**, *132*, 16073.

[8] a) Q. Yuan, D. Liu, W. Zhang, *Org. Lett.* **2017**, *19*, 1144; b) V. Pace, J. P. Rae, D. J. Procter, *Org. Lett.* **2014**, *16*, 476; c) P. Moutevelis-Minakakis, E. Papavassilopoulou, T. Mavromoustakos, *Molecules* **2013**, *18*, 50; d) J.-F. Bai, L.-L. Wang, L. Peng, Y.-L. Guo, L.-N. Jia, F. Tian, G.-Y. He, X.-Y. Xu, L.-X. Wang, *J. Org. Chem.* **2012**, *77*, 2947; e) M. J. Just, S. Tekkam, M. A. Alam, S. C. Jonnalagadda, J. L. Johnson, V. R. Mereddy, *Tetrahedron Lett.* **2011**, *52*, 5349.

[9] B. G. Chatterjee, D. P. Sahu, *J. Org. Chem.* **1977**, *42*, 3162; b) J. Yang, X. Zhou, Y. Zeng, C. Huang, Y. Xiao, J. Zhang, *Chem. Commun.* **2016**, *52*, 4922; c) D. Deredas, L. Albrecht, H. Krawczyk, *Tetrahedron Lett.* **2013**, *54*, 3088.

[10] M. Sccansetti, X. Hu, B. P. Mc Dermott, H. W. Lam, *Org. Lett.* **2007**, *9*, 2159.

[11] K. Takahashi, M. Midori, K. Kawano, J. Ishihara, S. Hatakeyama, *Angew. Chem. Int. Ed.* **2008**, *47*, 6244; *Angew. Chem.* **2008**, *120*, 6340; b) H. A. Keane, W. Hess, J. W. Burton, *Chem. Commun.* **2012**, *48*, 6496; c) W. Hess, J. W. Burton, *Adv. Synth. Catal.* **2011**, *353*, 2966.

[12] a) C. H. Yoon, D. L. Flanigan, B.-D. Chong, K. W. Jung, *J. Org. Chem.* **2002**, *67*, 6582; b) M. Oba, N. Nishiyama, K. Nishiyama, *Chem. Commun.* **2003**, 776; c) V. A. Soloshonok, H. Ueki, R. Tiwari, *J. Org. Chem.* **2004**, *69*, 4984; d) M. K. Ghorai, D. P. Tiwari, *J. Org. Chem.* **2010**, *75*, 6173.

[13] a) M. S. Taylor, E. N. Jacobsen, *J. Am. Chem. Soc.* **2003**, *125*, 11204; b) S. Vellalath, K. N. Van, D. Romo, *Angew. Chem. Int. Ed.* **2013**, *52*, 13688; *Angew. Chem.* **2013**, *125*, 13933; c) L. Chen, Z.-J. Wu, M.-L. Zhang, D.-F. Yue, X.-M. Zhang, X.-Y. Xu, W.-C. Yuan, *J. Org. Chem.* **2015**, *80*, 12668; d) Z.-Y. Xue,Z.-M Song, C.-J. Wang, *Org. Biomol. Chem.* **2015**, *13*, 5460.

[14] a) D. E. A. Raup, B. Cardinal-David, D. Holte, K. A. Scheidt, *Nat. Chem.* **2010**, *2*, 766; b) X. Zhao, D. A. DiRocco, T. Rovis, *J. Am. Chem. Soc.* **2011**, *133*, 12466

[15] X. Companyo, P.-Y. Geant, A. Mazzanti, A. Moyano, R. Rios, *Tetrahedron* **2014**, *70*, 75.

[16] Selected examples with aldehydes and ketones: a) Y. Ito, M. Sawamura, T. Hayashi, *J. Am. Chem. Soc.* **1986**, 10*8*, 6405; b) A. Togni, S. D. Pastor, *J. Org. Chem.* **1990**, *55*, 1649; c) M. Sawamura, Y.Nakayama, T. Kato, Y. Ito, *J. Org. Chem.* **1995**, *60*, 1727; d) M. Sawamura, H.Hamashima, Y. Ito, *J. Org. Chem.* **1990**, *55*, 5935; e) S. Gosiewska, M. F. I. Veld, J. J. M. de Pater, P. C. A. Bruijnincx, M. Lutz, A. L. Spek, G. van Koten, R. J. M. Klein Gebbink, *Tetrahedron: Asymmetry* **2006**, *17*, 674; f) N. Lin, Y.-Q. Deng, Z.-W. Zhang, Q. Wang, G. Lu, *Tetrahedron: Asymmetry* **2014**, *25*, 650; g) F. Sladojevich, A. Trabocchi, A. Guarna, D. J. Dixon, *J. Am. Chem. Soc*. **2011**, *133*, 1710; h) R. de la Campa, I. Ortin, D. J. Dixon, *Angew. Chem. Int. Ed.* **2015**, *54*, 4895; *Angew. Chem.* **2015**, *127*, 4977. Selected examples with imines: i) X.-T. Zhou, Y.-R. Lin, L.-X. Dai, J. Sun, L.-J. Xia, M.-H. Tang, *J. Org. Chem.* **1999**, *64*, 1331; j) Z.-W. Zhang, G. Lu, M.-M. Chen, N. Lin, Y.-B. Li, T. Hayashi, A. S. C. Chan, *Tetrahedron: Asymmetry* **2010**, *21*, 1715; k) S. Nakamura, Y. Maeno, M. Ohara, A. Yamamura, Y. Funahashi, N. Shibata, *Org. Lett.* **2012**, *14*, 2960; l) I. Ortin, D. J. Dixon, *Angew. Chem. Int. Ed.* **2014**, *53*, 3462; *Angew. Chem.* **2014**, *126*, 3530; m) P.-L. Shao, J.-Y. Liao, Y. A. Ho, Y. Zhao, *Angew. Chem. Int. Ed.* **2014**, *53*, 5435; *Angew. Chem.* **2014**, *126*, 5539; n) M. Hayashi, M. Iwanaga, N. Shiomi, D. Nakane, H. Masuda, S. Nakamura, *Angew. Chem. Int. Ed.* **2014**, *53*, 8411; *Angew. Chem.* **2014**, *126*, 8551; o) M.-X. Zhao, L. Jing, H. Zhou, M. Shi, *RSC Adv.* **2015**, *5*, 75648; p) S. Nakamura, R. Yamaji, M. Iwanaga, *Chem. Commun.* **2016**, *52*, 7462; q) R. de la Campa, A.D. Gammack Yamagata, I. Ortin, A. Franchino, A. L. Thompson, B. Odell, D. J. Dixon, *Chem. Commun.* **2016**, *52*, 10632.

[17] Selected examples with aldehydes and ketones: a) M. C. Willis, G. A. Cutting, V. J.-D. Piccio, M. J. Durbin, M. P. John, *Angew. Chem. Int. Ed.* **2005**, *44*, 1543; *Angew. Chem.* **2005**, *117*, 1567; b) L. Li, E. G. Klauber, D. Seidel, *J. Am. Chem. Soc.* **2008**, *130*, 12248; c) T. Yoshino, H. Morimoto, G. Lu, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2009**, *131*, 17082; d) X. Jiang, Y. Cao, Y. Wang, L. Liu, F. Shen, R. Wang, *J. Am. Chem. Soc.* **2010**, *132*, 15328; e) X. Chen, Y. Zhu, Z. Qiao, M. Xie, L. Lin, X. Liu, X. Feng, *Chem. Eur. J*. **2010**, *16*, 10124; f) Y.-M. Cao, F.-F. Shen, F.-T. Zhang, J.-L. Zhang, R. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 1862; *Angew. Chem.* **2014**, *126*, 1893. Selected examples with imines: g) L. Li, M. Ganesh, D. Seidel, *J. Am. Chem. Soc.* **2009**, *131*, 11648; h) X. Chen, S. Dong, Z. Qiao, Y. Zhu, M. Xie, L. Lin, X. Liu, X. Feng, *Chem. Eur. J.* **2011**, *17*, 2583; i) G. Lu, T. Yoshino, H. Morimoto, S. Matsunaga, M. Shibasaki, *Angew. Chem. Int. Ed.* **2011**, *50*, 4382; *Angew. Chem.* **2011**,*123*, 4474; j) S. Kato, T. Yoshino, M. Shibasaki, M. Kanai, S. Matsunaga, *Angew. Chem. Int. Ed.* **2012**, *51*, 7007; *Angew. Chem.* **2012**, *124*, 7113; k) D. Du, Q. Xu, X-G. Li, M. Shi, *Chem. Eur. J.* **2016**, *22*, 4733.

[18] a) W.-T. Wei, C.-X. Chen, R.-J. Lu, J.-J. Wang, X.-J. Zhang, M. Yan, *Org. Biomol. Chem.* **2012**, *10*, 5245; b) L.-L. Wang, J.-F. Bai, L. Peng, L.-W. Qi, L.-N. Jia, Y.-L. Guo, X.-Y. Luo, X.-Y. Xu, L.-X. Wang, *Chem. Commun.* **2012**, *48*, 5175. c) J.-Y. P.-L. Shao, Y. Zhao, *J. Am. Chem. Soc.* **2015**, *137*, 628; d) X.-J. Peng, Y. A. Ho, A.-P. Wang, P.-L. Shao, Y. Zhao, Y. He, *Org. Chem. Front.* **2017**, *4*, 81.

[19] a) Y. Cao, X. Jiang, L. Liu, F. Shen, F. Zhang, R. Wang, *Angew. Chem. Int. Ed.* **2011**, *50*, 9124; *Angew. Chem.* **2011**, *123*, 9290; b) B. Tan, X-Zeng, W. W. Y. Leong, Z. Shi, C. F. Barbas, G. Zhong, *Chem. Eur. J.* **2012**, *18*, 63; c) H. Wu, L.-L. Zhang, Z.-Q. Tian, Y.-D. Huang, Y.-M. Wang, *Chem. Eur. J*. **2013**, *19*, 1747; d) Q. Chen, J. Liang, S. Wang, D. Wang, R. Wang, *Chem. Commun.* **2013**, *49*, 1657; e) Y.-M. Cao, F.-F. Shen, F.-T. Zhang, J. L. Zhang, R. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 1862; *Angew. Chem.* **2014**, *126*, 1893; f) D. Du, Y. Jiang, Q. Xu, X.-Y. Tang, M. Shi, *ChemCatChem* **2015**, *7*, 1366; g) H.-W. Zhao, T. Tian, H.-L. Pang, B. Li, X.-Q. Chen, Z. Yang, W. Meng, X.-Q. Song, Y.-D. Zhao, Y.-Y. Liu, *Adv. Synth. Catal.* **2016**, *358*, 2619; h) R. Chowdhury, M. Kumar, S. K. Ghosh, *Org. Biomol. Chem.* **2016**, *14*, 11250.

[20] a) L. Senica, K. Stopar, M. Friedrich, U. Groselj, J. Plavec, M. Pockaj, C. Podlipnik, B. Stefane, J. Svete, *J. Org. Chem.* **2016**, *81*, 146; b) E. R. Shore, M. Awais, N. M. Kershaw, R. R. Gibson, S. Pandalaneni, D. Latawiec, L. Wen, M. A. Javed, D. N. Criddle, N. Berry, P. M. O'Neill, L.-Y. Lian, R. S. Sutton, *J. Med. Chem.* **2016**, *59*, 2596; c) G. Singh, J. Aube, *Org. Biomol. Chem.* **2016**, *14*, 4299.

[21] S. Sakamoto, N. Kazumi, Y. Kobayashi, C. Tsukano, Y. Takemoto, *Org. Lett.* **2014**, *16*, 4758.

[22] A related reaction involving addition of bis(silyl)methylisocyanates to aldehydes and imines has been reported: G. Barbaro, A. Battaglia, P. Giorgianni, A. Guerrini, G. Seconi, *J. Org. Chem.* **1995**, *60*, 6032.

[23] a) M. Espinosa, G. Blay, L. Cardona, J. R. Pedro, *Chem. Eur. J.* **2013**, *19*, 14861; b) M. Espinosa, G. Blay, L. Cardona, J. R. Pedro, *Chem.*

Eur. J. **2013**, *19*, 17632; c) M. Espinosa, A. Garcia-Ortiz, G. Blay, L. Cardona, M. C. Muñoz, J. R. Pedro, *RSC Adv.* **2016**, *6*, 15655.

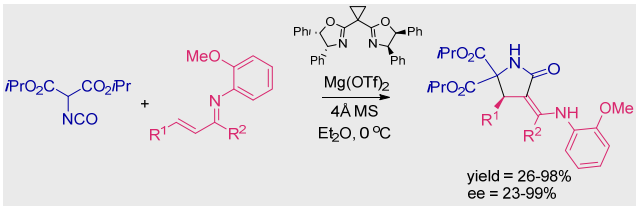
[24] Preliminary experiments on the reaction of diethyl 2-isocyanatomalonate with chalcone or its *N*-tosyl imine showed that these were not reactive in the presence of Mg-**BOX** complexes.

[25] Imines **4** have the *E*-geometry at the C=C bond, but were prepared and used as 2:1 to 7:3 mixtures of C=N geometric isomers.

[26] See the Supporting Information for further details. CCDC 1544707 (**7b**) and 1544708 (**9a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Entry for the Table of Contents (Please choose one layout)

COMMUNICATION



The first asymmetric formal [3+2] cycloaddition involving 2-isocyanato esters and electrophilic alkenes is reported. Diisopropyl 2-isocyanatomalonate reacts with α,β-unsaturated *N*-(*o*-anisidyl) imines in the presence of a $Mg(OTf)_2$-BOX complex to give highly substituted chiral pyrrolidinones with excellent yields and enantiomeric excesses up to 99%.

Miguel Espinosa, Gonzalo Blay, Luz Cardona, M. Carmen Muñoz, José R. Pedro**

Page No. – Page No.

Catalytic Asymmetric Formal [3+2] Cycloaddition of 2-Isocyanatomalonate Esters and Unsaturated Imines: Synthesis of Highly Substituted Chiral γ-Lactams