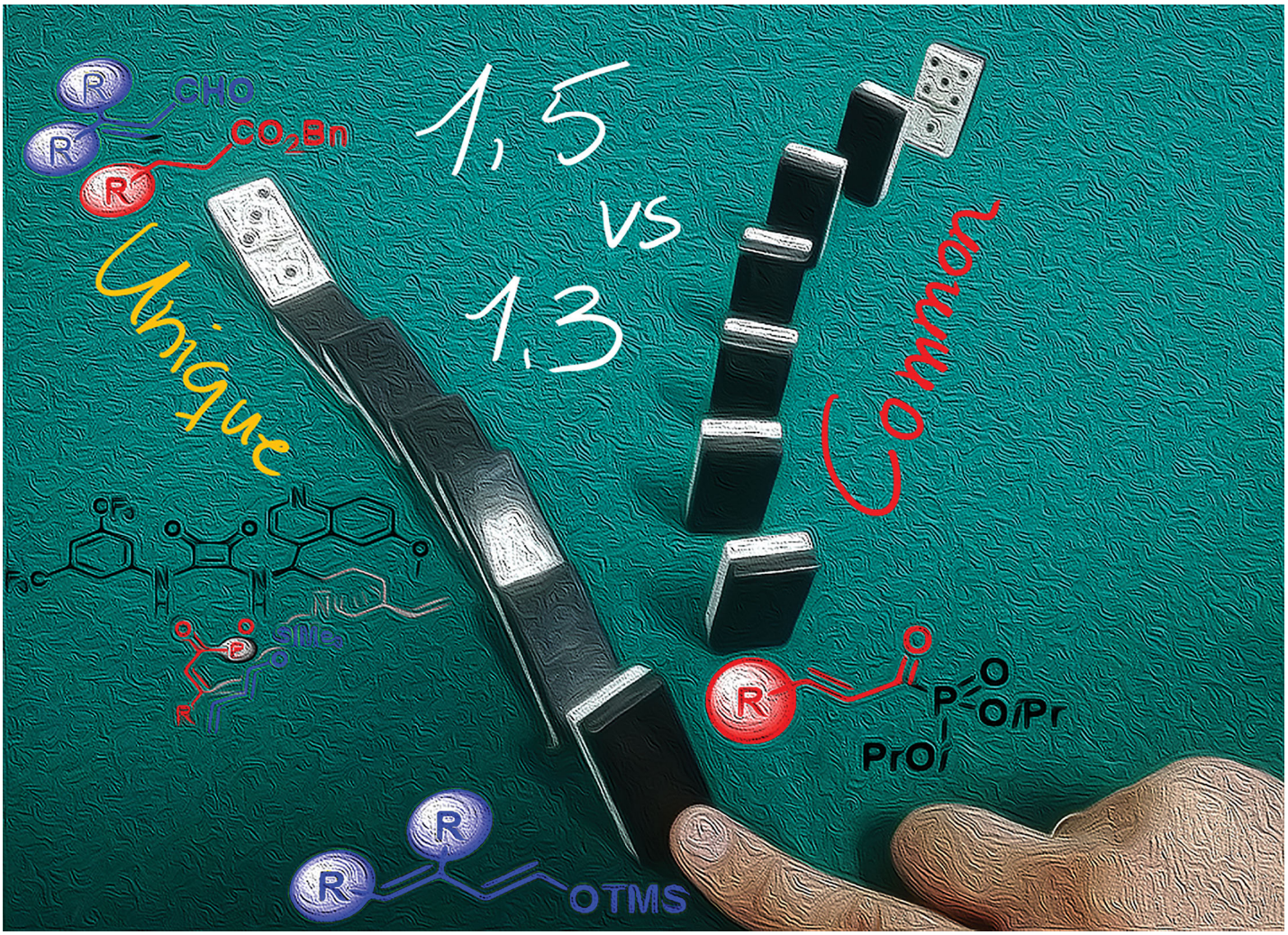


Showcasing research from Jose Aleman's group at Universidad Autonoma de Madrid, Spain.

Asymmetric synthesis of Rauhut–Currier-type esters *via* Mukaiyama–Michael reaction to acylphosphonates under bifunctional catalysis

As well as the domino effect making the chips fall on the domino token 1,3, the bifunctional organocatalyst triggers the reaction through the less reactive 1,3 position of the silyl dienol ether in a highly enantioselective Mukaiyama–Michael reaction to acylphosphonates.

As featured in:

See Jose A. Fernández-Salas, José Alemán *et al.*, *Chem. Commun.*, 2018, **54**, 13941.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

Registered charity number: 207890

ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Chem. Commun.*, 2018, **54**, 13941

Received 18th September 2018,
Accepted 22nd October 2018

DOI: 10.1039/c8cc07561a

rsc.li/chemcomm

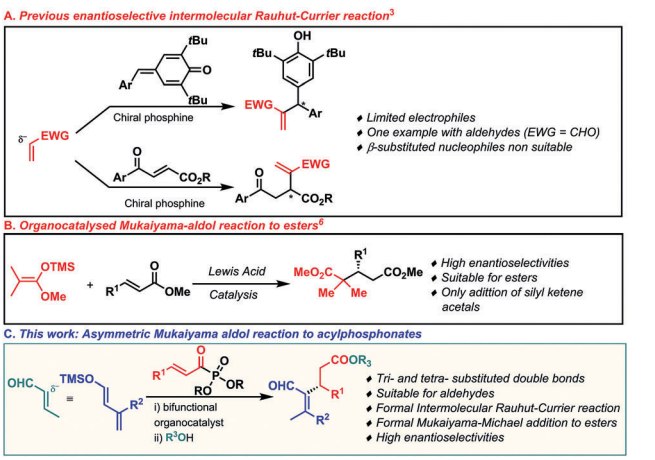
Asymmetric synthesis of Rauhut–Currier-type esters *via* Mukaiyama–Michael reaction to acylphosphonates under bifunctional catalysis†

Víctor Laina-Martín,[a] Roberto del Río-Rodríguez,[a] Sergio Díaz-Tendero,[bcd] Jose A. Fernández-Salas*[a] and José Alemán*[ab]

A highly enantioselective organocatalytic Mukaiyama–Michael reaction of silyloxy dienes and α,β-unsaturated acyl phosphonates under bifunctional organocatalysis is presented. The new reactivity triggered by the catalyst conducted to Rauhut–Currier type esters, *via* a formal conjugate addition to α,β-unsaturated esters. This protocol proceeds under mild conditions with complete regioselectivity and excellent enantiocontrol.

The development of efficient and practical strategies for the stereoselective construction of C–C bonds is an ongoing objective and still holds a preferred position in organic chemistry research.[1] In this field, the Rauhut–Currier reaction has been widely developed over the years, becoming a powerful tool for the construction of valuable compounds from two structurally diverse olefins.[2] In particular, asymmetric intramolecular Rauhut–Currier processes have been extensively explored and reported during the last few years.[2a] Different groups have focused their attention on developing chiral catalysts based on different nucleophilic species able to trigger the reaction.[2,3] However, the intermolecular cross-asymmetric version is still underdeveloped and only a few groups have described efficient methodologies (Scheme 1, eqn (a)).[3] In pursuit of this challenging objective, these research groups have described the use of well-designed multifunctional chiral phosphine-based catalysts, which have only allowed the efficient α-functionalization of 3-aroyl acrylates and *para*-quinone methides mainly with vinyl ketones.[3b,e–h] Despite these particular achievements, the enantioselective intermolecular cross Rauhut–Currier reaction has been applied successfully in the presence of certain electrophiles. Indeed, only very specific and reactive substrates such as terminal vinylic carbonyl compounds have shown sufficient reactivity. However, mono- and *gem*-disubstituted double bonds are more challenging electrophiles for this transformation.

The catalytic Mukaiyama-aldol (MA) reaction has become a powerful tool for the enantioselective construction of C–C bonds.[4] Despite the great efforts made in the development of MA reactions, the conjugate addition to α,β-unsaturated esters, which are difficult substrates to activate,[5] still stands as an outstanding objective in asymmetric organocatalysis. Indeed, only one example has recently been reported by List and coworkers in which a silylium imidodiphosphorimidate Lewis acid has been shown to be a very efficient catalyst in the asymmetric Mukaiyama–Michael reaction to α,β-unsaturated esters (Scheme 1, eqn (b)).[6] Similarly, the organocatalysed vinylogous Mukaiyama-aldol (VMA) reaction has been widely developed and has become the preferred method for the stereoselective synthesis of vinylogous aldol type products.[4e,7] The orbital coefficients provoke the observed 1,5-nucleophilic attack,[8] while the reactivity through the less reactive 3 position of the



Scheme 1 Previous works (A and B) and the present work (C).

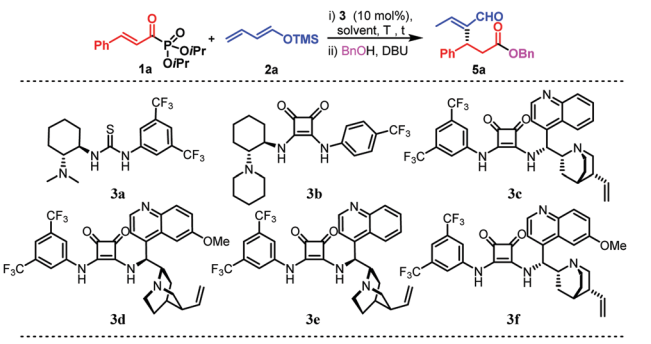
[a] *Departamento de Química Orgánica (Módulo 1), Facultad de Ciencias, Universidad Autónoma de Madrid, 28049-Madrid, Spain. E-mail: jose.aleman@uam.es; Web: www.uam.es/jose.aleman*
[b] *Institute for Advanced Research in Chemical Sciences (IAdChem), Universidad Autónoma de Madrid, 28049 Madrid, Spain*
[c] *Condensed Matter Physics Center (IFIMAC), Facultad de Ciencias, Universidad Autónoma de Madrid, 28049 Madrid, Spain*
[d] *Departamento de Química (Módulo 13), Facultad de Ciencias, Universidad Autónoma de Madrid, 28049-Madrid, Spain*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c8cc07561a

dienolate has been practically unexplored (Scheme 1, eqn (c)). Taking into account the challenge of expanding the asymmetric intermolecular Rauhut–Currier reaction,[9] we envisioned that the addition of silyl dienol ethers to acylphosphonates,[10] followed by an *in situ* acyl substitution, could potentially lead to Rauhut–Currier type esters. In order to achieve this objective, the nucleophilic addition to the conjugated system (1,4-addition) would need to take place through the less reactive position (1,3) of the silyl dienol ether. Herein, we describe a Mukaiyama–Michael process of silyl dienol ethers to α,β-unsaturated acyl phosphonates catalysed by a bifunctional organocatalyst.[11] The special and unusual reactivity shown by these dienolates when activated by the bifunctional organocatalyst and the use of acylphosphonates as ester surrogates have allowed us to develop the formal synthesis of Rauhut–Currier-type esters, not easy to access otherwise. In addition, very challenging β-mono and β-disubstituted formal acrolein adducts have been addressed using this methodology. Based on our experience in bifunctional catalysis,[9,12] we began our investigations by studying the reaction of acylphosphonate **1a** as a model substrate with a trimethyl silyl dienolate derivative **2a** and different thiourea and squaramide bifunctional organocatalysts (Table 1). Firstly, we examined catalysts **3a** and **3b** which led, after *in situ* treatment with BnOH and DBU, to the desired Rauhut–Currier type ester with moderate enantioselectivities (entries 1 and 2). Taking into account these preliminary results, the squaramide-quinine catalyst **3d** was tested and it clearly enhanced the selectivity of the process (90% ee) (entry 3). All four squaramides bearing a member of the quinine family (**3c–f**) led to similar yields and enantioselectivities of the desired Rauhut–Currier ester (entries 4–7). Different solvents were then studied taking **3d** as the optimised catalyst (entries 8–11). *p*-Xylene was considered as the optimum solvent (entry 9) as it led to higher enantioselectivity. A lower concentration and a higher catalyst loading boosted the efficiency of the reaction and yielded the desired product **5a** with a 57% yield and 97% enantiomeric excess (entry 14).

Once the reaction conditions had been optimised (entry 14, Table 1), we studied the scope of the reaction considering differently substituted α,β-unsaturated acyl phosphonates (Table 2). The Mukaiyama–Michael reaction embraced a variety of aromatics with complete regioselectivity observed in all cases. The reaction proceeded smoothly with the *p*-tolyl substituted double bond (**5b**) with an excellent enantioselectivity (96% ee). Acyl phosphonates bearing a poor aromatic ring (**5c**) led to the desired Rauhut–Currier product with excellent enantioselectivity, retaining the efficiency of the reaction. Differently substituted halogenated phosphonates at either the *ortho*, *meta* or the *para* position were very well tolerated, conducting to the β-substituted esters with excellent enantioselectivities (**5d–h**). The protocol enabled access to the corresponding ester in the presence of conjugated heterocyclic acylphosphonate with excellent enantioselectivities and moderate yield (**5i**). In the same manner, silyl dienolate reacted with an aliphatic conjugated system, affording **5j** with complete enantiocontrol albeit with a slightly lower yield. Other silyl dienolates were also studied.

Table 1 Screening of reaction conditions for the addition of **2a** to **1a** in the presence of different catalysts **3**[a]



Entry	3	Solvent	*t* (h)	Yield **5a** (%)[c]	ee[d]
1[b]	**3a**	THF	36	36	59
2[b]	**3b**	THF	36	51	66
3[b]	**3d**	THF	36	32	90
4	**3d**	THF	36	40	91
5	**3e**	THF	36	34	89
6	**3f**	THF	36	36	−88
7	**3c**	THF	36	42	−82
8	**3d**	DCM	36	36	94
9	**3d**	*p*-Xylene	36	36	96
10	**3d**	MeCN	36	35	90
11	**3d**	DME	36	30	93
12[e]	**3d**	THF	36	59	90
13[e]	**3d**	DCM	48	30	93
14[e]	**3d**	***p*-Xylene**	**36**	**57**	**97**

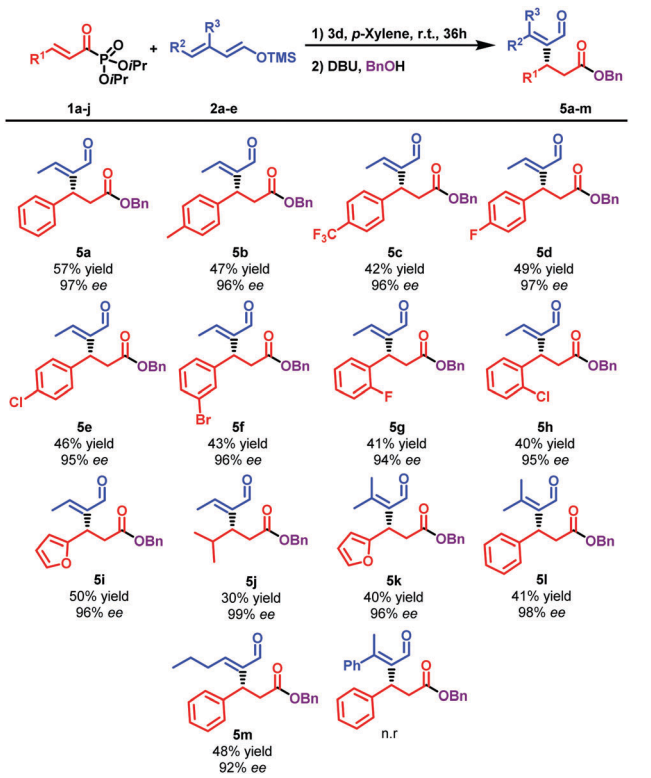
[a] All the reactions were performed on a 0.1 mmol scale in the presence of **3** (10 mol%) in 0.3 mL of solvent. [b] 3 equiv. of water was added. [c] Isolated yield. [d] Determined by SFC chromatography. [e] **3d** (20 mol%) and 0.6 mL of solvent (0.17 M).

While a silyl dienol ether bearing a longer aliphatic chain was well tolerated (**5m**), the presence of a phenyl group as a substituent did not conduct to the desired product. To our delight, when a 4-substituted silyloxy diene (**2b**) was tested, challenging β,β-disubstituted Rauhut–Currier adducts (**5k–5l**) were obtained with excellent enantioselectivities.

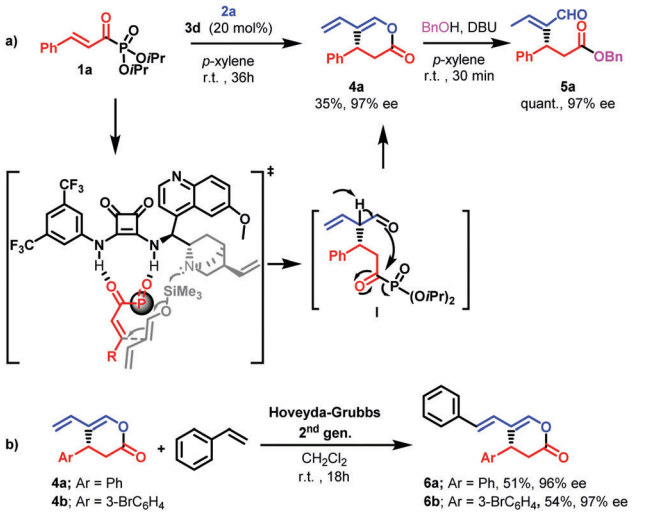
Interestingly, when the *in situ* acyl substitution was not performed under the optimised reaction conditions, the reaction conducted to the formation of the dihydropyranone derivative **4a** after an *in situ* lactonization through intermediate **I**. Subsequent lactone opening in the presence of BnOH and DBU led to the desired Rauhut–Currier type ester as a unique product in quantitative yield (Scheme 2, eqn (a)). These control experiments suggested that the moderate yields obtained might come from the intrinsic instability of **4a** under the reaction conditions during the long reaction times.[13] Considering the whole process, which involves conjugate addition of the dienolate, cyclisation and lactone opening, the functionalised esters are obtained in synthetically useful yields. In order to explain the observed configuration, a stereochemical proposal is shown in Scheme 2. We propose that the nitrogen of the quinine moiety directly triggers the Mukaiyama–Michael reaction from the *si*-face of the acyl phosphonate and the silyloxy diene reacts through its carbon 3 due to the close proximity.

Lactone rings are structural motifs very often present in natural products. Among naturally occurring lactones, the

Table 2 Scope of reaction for the addition of **2** to **1** in the presence of **3d**[a]



[a] All the reactions were performed on a 0.1 mmol scale in 0.6 mL of *p*-xylene. Enantiomeric excess was determined by SFC chromatography.



Scheme 2 (a) Control experiment and isolation of intermediate **4a**. Proposed coordination model. (b) Derivatization of dihydropyranone derivatives **4** to compounds **6a** and **6b**.

5,6-dihydropyran-2-one moiety is of considerable interest from a chemical and pharmacological perspectives.[14] Taking advantage of the enantioselective formation of lactone **4a**, 4,5-disubstituted dihydropyranones **6a** and **6b** were obtained with excellent enantioselectivities *via* simple alkene metathesis with styrene (Scheme 2, eqn (b)). The absolute configuration of the Rauhut–Currier type products series was assigned by the correlation with a known compound in the literature (**6a**) and by circular dichroism. It was determined as *R*, assuming the same stereochemical outcome for all the compounds **4**, **5** and **6** (see the ESI†).

In conclusion, we have described an asymmetric Mukaiyama–Michael reaction of silyl dienolates to α,β-unsaturated acyl phosphonates as ester surrogates. The employed bifunctional organocatalyst orchestrated the approach of the silyloxy diene to the Michael acceptor, leading to the formation of Rauhut–Currier type esters. The reaction proceeded under mild conditions with complete regioselectivity, excellent enantiocontrol and a reasonably high range of α,β-unsaturated phosphonates. In addition, the methodology led to tri- and tetra-substituted Rauhut–Currier type esters.

We are grateful to the Spanish Government (CTQ2015-64561-R and CTQ2016-76061-P) and the European Research Council (ERC-CG-UNBICAT, contract number: 647550). J. A. F.-S. and V. L.-M. thank the Spanish Government for a Juan de la Cierva Contract and the Universidad Autónoma de Madrid for a predoctoral fellowship (FPI-UAM), respectively. Financial support from the Spanish Ministry of Economy and Competitiveness, through the "Maria de Maeztu" Program of Excellence in R&D (MDM-2014-0377), is also acknowledged. We acknowledge the generous allocation of computing time at the CCC (UAM).

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) V. Farina, J. T. Reeves, C. H. Senanayake and J. J. Song, *Chem. Rev.*, 2006, **106**, 2734–2793; (*b*) M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Keßeler, R. Stürmer and T. Zelinski, *Angew. Chem., Int. Ed.*, 2004, **43**, 788–824.

2 For selected general reviews on the R–C reaction, see: (*a*) K. Chandra Bharadwaj, *RSC Adv.*, 2015, **5**, 75923–75946; (*b*) P. Xie and Y. Huang, *Eur. J. Org. Chem.*, 2013, 6213–6226; (*c*) J. L. Methot and W. R. Roush, *Adv. Synth. Catal.*, 2004, **346**, 1035–1050; (*d*) C. E. Aroyan, A. Dermenci and S. J. Miller, *Tetrahedron*, 2009, **65**, 4069–4084; (*e*) D. K. Nair, T. Kumar and I. N. N. Namboothiri, *Synlett*, 2016, 2425–2442; (*f*) A. M. Wensley, N. T. McDougal and S. E. Schaus, in *Lewis Base Catalysis in Organic Synthesis*, ed. E. Vedejs and S. E. Denmark, Wiley-VCH, 2016, pp. 655–714. For selected recent examples on the R–C reaction, see; (*g*) X. Su, W. Zhou, Y. Li and J. Zhang, *Angew. Chem., Int. Ed.*, 2015, **54**, 6874–6877; (*h*) S. Takizawa, T. M.-N. Nguyen, A. Grossmann, D. Enders and H. Sasai, *Angew. Chem., Int. Ed.*, 2012, **51**, 5423–5426.

3 (*a*) Q. Zhao, C. Pei, X. Guan and M. Shi, *Adv. Synth. Catal.*, 2011, **353**, 1973–1979; (*b*) S. Li, Y. Liu, B. Huang, T. Zhou, H. Tao, Y. Xiao, L. Liu and J. Zhang, *ACS Catal.*, 2017, **7**, 2805–2809; (*c*) W. Zhou, P. Chen, M. Tao, X. Su, Q. Zhao and J. Zhang, *Chem. Commun.*, 2016, **52**, 7612–7615; (*d*) C. Qin, Y. Liu, Y. Yu, Y. Fu, H. Li and W. Wang, *Org. Lett.*, 2018, **20**, 1304–1307; (*e*) H. Wang, K. Wang, Y. Man, X. Gao, L. Yang, Y. Ren, N. Li, B. Tang and G. Zhao, *Adv. Synth. Catal.*, 2017, **359**, 3934–3939; (*f*) T.-C. Kang, L.-P. Wu, Q.-W. Yu and X.-Y. Wu, *Chem. – Eur. J.*, 2017, **23**, 6509–6513; (*g*) X. Dong, L. Liang, E. Li and Y. Huang, *Angew. Chem., Int. Ed.*, 2015, **54**, 1621–1624; (*h*) W. Zhou, X. Su, M. Tao, C. Zhu, Q. Zhao and J. Zhang, *Angew. Chem., Int. Ed.*, 2015, **54**, 14853–14857.

4 For selected reviews, see: (*a*) S. B. J. Kan, Kenneth K.-H. Ng and I. Paterson, *Angew. Chem., Int. Ed.*, 2013, **52**, 9097–9108; (*b*) J.-i. Matsuo and M. Murakami, *Angew. Chem., Int. Ed.*, 2013, **52**, 9109–9118; (*c*) S. Hosokawa, *Tetrahedron Lett.*, 2018, **59**, 77–88;

(*d*) S. V. Pansare and E. K. Paul, *Chem. – Eur. J.*, 2011, **17**, 8770–8779; (*e*) M. Frías, W. Cieślik, A. Fraile, A. Rosado-Abón, A. F. Garrido-Castro, F. Yuste and J. Alemán, *Chem. – Eur. J.*, 2018, **24**, 10906–10933.

5 For selected examples of conjugate addition of various nucleophiles to α,β-unsaturated esters, see: (*a*) J. Y. Kang and R. G. Carter, *Org. Lett.*, 2012, **14**, 3178–3181; (*b*) Y. Kobayashi, Y. Taniguchi, N. Hayama, T. Inokuma and Y. Takemoto, *Angew. Chem., Int. Ed.*, 2013, **52**, 11114–11118; (*c*) A. J. M. Farley, C. Sandford and D. J. Dixon, *J. Am. Chem. Soc.*, 2015, **137**, 15992–15995; (*d*) J. Yang, A. J. M. Farley and D. J. Dixon, *Chem. Sci.*, 2017, **8**, 606–610; (*e*) E. Canales and E. J. Corey, *J. Am. Chem. Soc.*, 2007, **129**, 12686–12687.

6 T. Gatzenmeier, P. S. J. Kaib, J. B. Lingnau, R. Goddard and B. List, *Angew. Chem., Int. Ed.*, 2018, **57**, 2464–2468.

7 For a review, see: (*a*) S. V. Pansare and E. K. Paul, *Chem. – Eur. J.*, 2011, **17**, 8770–8779; (*b*) M. Kalesse, M. Cordes, G. Symkenberga and H.-H. Lu, *Nat. Prod. Rep.*, 2014, **31**, 563–594; (*c*) S. Hosokawa, *Tetrahedron Lett.*, 2018, **59**, 77–88. For selected examples, see: (*d*) R. P. Singh, B. M. Foxman and L. Deng, *J. Am. Chem. Soc.*, 2010, **132**, 9558–9560; (*e*) N. Zhu, B.-C. Ma, Y. Zhang and W. Wang, *Adv. Synth. Catal.*, 2010, **352**, 1291–1295; (*f*) V. Bhasker, M. Gravel and V. H. Rawal, *Org. Lett.*, 2005, **7**, 5657–5660; (*g*) S. E. Denmark and G. L. Beutner, *J. Am. Chem. Soc.*, 2003, **125**, 7800–7801; (*h*) M. Sickert and C. Schneider, *Angew. Chem., Int. Ed.*, 2008, **47**, 3631–3634; (*i*) L. Ratjen, P. García-García, F. Lay, M. E. Beck and B. List, *Angew. Chem., Int. Ed.*, 2011, **50**, 754–758.

8 S. E. Denmark, J. R. Heemstra and G. L. Beutner, *Angew. Chem., Int. Ed.*, 2005, **44**, 4682–4698.

9 M. Frías, R. Mas-Ballesté, S. Arias, C. Alvarado and J. Alemán, *J. Am. Chem. Soc.*, 2017, **139**, 672–679.

10 Acylphosphonates have been proven to be efficient ester surrogates. For a general review, see: (*a*) H. Jiang, M. W. Paixao, D. Monge and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2017, **132**, 2775–2783. For selected recent examples, see: (*b*) D. Kowalczyk and Ł. Albrecht, *J. Org. Chem.*, 2016, **81**, 6800–6807; (*c*) A.-D. Steinkamp, M. Frings, I. Thomé, I. Schiffers and C. Bolm, *Chem. – Eur. J.*, 2015, **21**, 7705–7708; (*d*) H.-Li Ma, L. Xie, Z. Zhang, J.-Q. Li, Z.-H. Qin and B. Fu, *Adv. Synth. Catal.*, 2016, **358**, 1011–1016.

11 For selected reviews on bifunctional organocatalysis and hydrogen bond activation, see: (*a*) W.-Y. Siau and J. Wang, *Catal. Sci. Technol.*, 2011, **1**, 1298–1310; (*b*) P. R. Schreiner, *Chem. Soc. Rev.*, 2003, **32**, 289–296; (*c*) A. G. Doyle and E. N. Jacobsen, *Chem. Rev.*, 2007, **107**, 5713–5743.

12 (*a*) A. Parra, R. Alfaro, L. Marzo, A. Moreno-Carrasco, J. L. García Ruano and J. Alemán, *Chem. Commun.*, 2012, **48**, 9759–9761; (*b*) V. Marcos, J. Alemán, J. L. García Ruano, F. Marini and M. Tiecco, *Org. Lett.*, 2011, **13**, 3052–3055; (*c*) F. Esteban, W. Cieślik, E. M. Arpa, A. Guerrero-Corella, S. Díaz-Tendero, J. Perles, J. A. Fernández-Salas, A. Fraile and J. Alemán, *ACS Catal.*, 2018, **8**, 1884–1890; (*d*) V. Laina-Martín, J. Humbrías-Martín, J. A. Fernández-Salas and J. Alemán, *Chem. Commun.*, 2018, **54**, 2781–2784; (*e*) T. Rigotti, A. Casado-Sánchez, S. Cabrera, R. Pérez-Ruiz, M. Liras, V. de la Peña O'Shea and J. Alemán, *ACS Catal.*, 2018, **8**, 5928.

13 The lower yield observed for cyclic product **4a** might also be due to its instability during the isolation process.

14 J. A. Marco, M. Carda, J. Murga and E. Falomir, *Tetrahedron*, 2007, **63**, 2929–2958.