COMMUNICATION

DOI: 10.1002/chem.200((will be filled in by the editorial staff))

Synergistic Catalysis: Enantioselective Ring Expansion of Vinyl Cyclopropanes combining four catalytic cycles. Synthesis of Highly substituted spiro-cyclopentanes bearing up to four stereocenters

Marta Meazza and Ramon Rios\*[a]

[a] Dr. Marta Meazza, Dr. Ramon Rios  
School of Chemistry  
University of Southampton  
E-mail: rrt1f11@soton.ac.uk  
Homepage ((optional)): [www.riosresearchgroup.com](http://www.riosresearchgroup.com)

Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.))

This paper is dedicated to Professor Dieter Enders for his 70th birthday. He has always been a source of inspiration to develop new cascade reactions.

The art of creating new molecules has become one of the greatest achievements for organic chemists due to the necessity of pharma and agrochemical industries to test original structures for the development of new drugs, pesticides or agrochemicals.

As Mother Nature does, chemists try to emulate biosynthetic pathways through the development of new cascade reactions. More than a decade ago the major part of catalytic cascade reactions was ruled by organometallic chemistry. Metal complexes were able to activate starting materials and build, in a stereoselective fashion, new 3D scaffolds. However, some issues associated with organometallic chemistry need to be addressed, such as the use of inert atmosphere, expensive ligands, etc… that makes difficult to apply the reactions on a large scale or to face the topics related to green chemistry.[1] After the breakthrough of organocatalysis, a plethora of new organocascade reactions, showing exceptional levels of stereoinduction and using very soft conditions were developed.[2] However, despite this advantages, some issues must still be considered such as the poor chemical diversity or the use of highly activated nucleophiles or electrophiles.

At the end of the last decade, the two words (organometallic and organocatalysis) converged in the development of new methodologies merging the advantages of both and achieving the synthesis of very complex structures. For example Córdova, Alexakis, Jørgensen, List, MacMillan, etc. joined organocatalytic and organometallic activation with excellent results.[3]

Merging transition metal complexes with organocatalysts obviously enriches the chemical diversity thus allowing the use of some starting materials that cannot be used as such. This new approach based on synergistic catalysis (where the concurrent activation of both reactants allows the use of both unreactive substrates to form a new C-C bond), presents several advantages with respect to other type of multicatalysis, such as the easy optimization of each catalyst as well as no need of using expensive ligands.[4]

Inspired by these achievements and by Nature, we started a vigorous research plan in synergistic catalysis merging transition metal chemistry and organocatalysis. We want to merge the rich chemistry of the transition metals with the cheap and easy stereoselective prediction of the organocatalysts. In 2014, we developed the addition of benzoxazoles to MBH carbonates and enals combining metal Lewis acid and organocatalysts with good results.[5] Spurred by these initials results, we successfully proved that this synergistic concept could be expanded to the development of cascade reactions by joining three catalytic cycles (metal Lewis acid, iminium chemistry and enamine chemistry) for the synthesis of cyclopropanes in high yields and stereoselectivities.[6]

Due to our interest in the enantioselective synthesis of carbocycles, we focused our attention in the development of a methodology based on synergistic catalysis for the synthesis of cyclopentanes. Opposite to their brother cyclohexanes that could be easily accessed by Diels-Alder reactions, the cyclopentane moiety represents a superior challenge as few methodologies are available for its synthesis. To cite a few examples: Pauson-Khand reaction,[7] Nazarov cyclization[8] or Au catalysed cyclization,[9] however, hardly any of them are enantioselective. With the advent of organocatalysis, several Michael initiated ring closure have been developed by Córdova,[10] Wang[11] and others,[12] however the need to use highly activated nucleophiles in the first step limited somehow the scope of these approaches. Córdova and coworkers in 2013 circumvented some of these limitations by using a different synergistic approach. The use of carbon pronucleophiles bearing an allyl acetate activated by Pd, with enals activated by secondary amines, opened a new gate in terms of access to cyclopentanes.[13] The requirement to use a strong pronucleophile is still limiting the scope of these reactions. Moreover, the syntheses of the starting materials are quite tedious, requiring the use of protecting groups and, in definitive, limiting their practical usefulness. In order to circumvent all the limitations and, at the same time, to develop a more atom economic process by avoiding the use of leaving groups, we thought that the use of vinyl cyclopropanes[14] could allow us to synthesize vinyl-cyclopentanes in a highly stereoselective fashion (Scheme 1).[15]



***Scheme 1.*** Previous works and our work.

Several research groups have been working on the synthesis of cyclopentanes using vinyl cyclopropanes as starting materials.[16] For example Trost in 2011 reported a Pd catalyzed vinylcyclopropane addition to alkylidene azalactones, using chiral diphosphine ligands with excellent results.[17] Very recently Liu and coworkers reported the addition of vinylcyclopropanes to nitroolefines using chiral bis (*tert*-amine)ligands.[18]

Mindful of this, we conceived a simple one-pot cascade reaction for the synthesis of cyclopentanes. We envisioned that the use of vinylcyclopropanes (easily synthesized in one step from commercially available starting materials) that could be opened “in situ” in combination with enals, represents an excellent platform for the synthesis of cyclopentanes. In order to achieve this, we planned to use **four catalytic cycles in a double synergistic cascade reaction**. **For the first time, two different synergistic reactions will be coupled in a cascade fashion without the need of inert atmosphere nor additional ligands**.

Firstly, Pd will activate the opening of the cyclopropane to generate “in situ” the pronucleophile by an oxidative addition. This will lead to the formation of the zwitterion, followed by an organocatalyzed Michael addition. Next, the enamine intermediate will react with the allyl complex to generate the cyclopentane (Figure 1). The challenges that we must face are considerable. First, the possible autoquench of both catalysts (transition metal catalyst and organocatalysts) or the dual role of both catalysts to generate four different catalytic cycles.



***Figure 1.*** Proposed catalytic cycles

As a proof of concept of this new double synergistic cascade reaction, we decided to use 1,3-indanedione derivative **6**, that will show a good nucleophilicity and will lead to the synthesis of spiro compounds.[19] Moreover, indanones and their derivatives containing spirocyclopentane are common building blocks in biologically active compounds, drugs and in functional materials.[20] Probably the most important compound containing this motif is Fredericamycin A[21] which exhibits potent cytotoxicity and represents a novel anticancer drug lead. For these reasons a methodology that will deliver these structural motifs in a highly stereoselective fashion and in a single step is of great interest.

Based on our previous experience in synergistic catalysis and organocatalysis[22] we started the study of the reaction employing compound **6** with cinnamaldehyde and testing several metals, solvents and temperatures. To our delight the reaction renders the final product with reasonable stereoselectivities and yields when CH3CN is used as the solvent and the reaction is run at 40 °C.

Next we decided to explore the use of ligands in order to improve the stereoselectivity of the reaction. The use of phosphine ligands like dppe or PPh3 or the use of nitrogen ligands such as phenanthroline did not give any positive outcome in the reaction (entries 2-4; Table 1). Next we decided to study the effect of the solvent. Toluene, EtOAc and THF rendered the final products with improved diastereoselectivities and enantioselectivities while DMSO gave only complex mixtures (entries 5-8, Table 1). Further screening of the reaction conditions allowed us to find the optimized conditions by using EtOAc at room temperature. Toluene and CH3CN at room temperature allowed us to obtain the final products in good yields, with moderate diastereoselectivities and good enantioselectivities and when EtOAc was used, we got excellent conversions, diastereoselectivity and enantioselectivities (entries 9-11, Table 1). The reaction works at room temperature, in 14 hours, without the need of neither inert atmosphere nor additional ligands.

***Table 1.*** Screening [a]

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Entry | Ligand | Solvent | Temp | Conversion [b] | d.r.[c] | Ee(%)[d] |
| 1 | - | CH3CN | 40oC | 100% | 1:1 | nd/99 |
| 2e | dppe | CH3CN | 40oC | 20% | 1.7:1 | 78/99 |
| 3f | phe | CH3CN | 40oC | 77% | 1:1.2 | 53/99 |
| 4g | PPh3 | CH3CN | 40oC | 20% | 1.2:1 | 41/99 |
| 5 | - | Toluene | 40oC | 68% | 4.3:1 | 88/98 |
| 6 | - | THF | 40oC | 40% | 3.1:1 | 87/99 |
| 7 | - | DMSO | 40oC | c.m.[h] | - | - |
| 8 | - | EtOAc | 40oC | 70% | 4.3:1 | 92/99 |
| 9 | - | CH3CN | r.t. | 86% | 3.4:1 | 32/99 |
| 10 | - | Toluene | r.t. | 46% | 5.6:1 | 93/99 |
| 11 | - | EtOAc | r.t. | 100% | 7:1 | 99/n.d.[i] |

[a] In a small vial, 1 equiv of **3a**,1.2 equiv of **6,** 5 mol% of Pd2(dba)3 and 20 mol% of **I** were added in 1 mL solvent at the temperature reported in the table [b] Determined by 1H NMR analysis of the crude mixture after 14h [c] Determined by 1H NMR analysis of the crude mixture [d] Determined by HPLC analysis of the crude mixture [e] 12 mol% [f] “phe” = phenanthroline (12 mol%) [g] 20 mol% [h] c.m. = complex mixture [i] n.d. = not determined

With the best conditions on hands, we decided to study the scope of the reaction in terms of the enals. To our delight the results were excellent in almost all the cases. The reaction with simple cinnamaldehyde renders the final product **7a** in good yields and excellent stereoselectivities (87% yield, 7:1 d.r. and 99% ee). The reaction tolerates several functional electronwithdrawing groups in the aromatic ring, like *p*-CN (**4b**), *p*-NO2 (**4d**) or *m*-NO2 (**4g**), giving the final cyclopentanes in excellent yields (90-93%) and only slightly worse stereoselectivities (10-8:1 d.r. and 99-87% ee). Remarkably, the reaction tolerates the presence of halogens in the aromatic ring such as *p*-Br (**4c**), *o*-Br (**4f**) or *p*-F (**4e**) giving excellent yields, diastereo- and enantioselectivities. Only in the case of the *m*-Br the diastereoselectivity of the reaction is reduced (2.5:1) probably due to steric interactions. Aliphatic aldehydes such as Me (**4i**), Et (**4j**), Pr (**4l**), or heptyl (**4k**) gave the final cyclopentanes in excellent yields and stereoselectivities, the only substrate that has a different behavior is dienal **4m**. The first surprise is that the dienal reacts by the second conjugated double bond exclusively instead of the middle double bond as previously reported in other organocascade reactions.[23] This makes that the conformation of the iminium transition state will not be as fixed as in the other cases, leading to the loss of facial discrimination and rendering the final product with low enantioselectivity (**7m**). However, as far as we are aware, **this is the first example of a total regioselective reaction with dienal by the second conjugated double bond.**





***Scheme 2.*** Scope of the reaction

We propose a plausible mechanism as shown in Figure 2: in the presence of palladium complex the vinylcyclopropane **6** is cleaved by oxidative addition of the palladium[24] and the corresponding zwitterionic -allylpalladium intermediate **9** is generated. On the other hand, the enal reacts with the chiral secondary amine **I** to form the iminium intermediate **10**. The carbon anion of the dipole acts as a nucleophile through a Michael addition to the iminium intermediate leading to an enolate intermediate **11** (first synergistic catalytic cycle). Next the enamine intermediate reacts intramolecularly with the previously generated allylic palladium via a 5-*exo*-*trig* cyclization furnishing, after protonation and reductive elimination of the Pd complex and hydrolysis of the iminium intermediate, the final cyclopentane compound **7** with the release of the catalysts, thus completing the catalytic cycle. Remarkably, the stereoselectivity of the reaction is perfectly controlled by the chiral secondary amine that blocks one of the faces of the iminium and enamine intermediates. The proposed mechanism is in agreement with the previously reported ones in similar organocascade reactions.



***Figure 2.*** Proposed mechanism

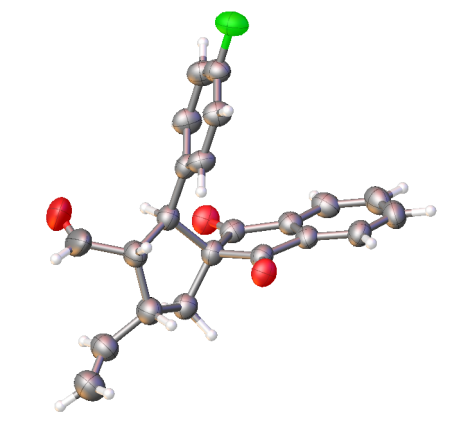
The *cis* configuration between the allyl group and the aldehyde can be explained by the cyclic transition state proposed in Figure 2. In order to avoid steric interaction, the Pd of the allyl complex will be located on the opposite face respect to the enamine substituent. Next, the irreversible stereoselective intermolecular nucleophilic *Si*-facial attack, by the chiral enamine, will lead to the final *cis* configuration observed.





***Figure 3.*** Proposed Transition State

The final (*2S,3S,4R*) configuration is in agreement with the mechanism proposed and with the previous works done with this type of catalysts, where the stereochemistry at the -position of the enal is perfectly controlled by the catalyst (**I**).[13]



***Figure 4*** X-ray structure of compound **7e.** The displacement ellipsoids are drawn at the 50% probability level.[25]

Next we decided to expand the scope of the reaction by using interesting heterocycles, cyano esters or meldrum acid derivatives as starting materials. As it is depicted in Scheme 3, first we focused our attention on the synthesis of spiro heterocycles such as oxindoles and benzofuranones. Spirooxindoles and spirobenzofuranones are common motifs in many natural products such as gelsemine, spirotryprostatin B or marcfortine B among others. When vinyl cyclopropanes oxindoles or benzofuranones are used, the reaction renders the final spiro products in moderate yields, low to good diastereoselectivities and moderate to good enantioselectivities (**12a**, **13a**). Next we decided to study the reaction using diester and cyanoester derivatives that could be excellent precursors for cyclic β-amino acids after amide conversion of one of the esters or by reduction of the cyano group. Surprisingly, the reaction with malonate derivatives did not give any conversion, probably for their low nucleophilicity. For this reason, we turned our attention to a more nucleophilic diester like Meldrum’s acid derivative. In this case we obtained the final product in good yields but moderate enantioselectivities and diastereoselectivities (**14a**). Finally, we tested the reaction with cyanoester derivatives, obtaining the final cyclopentane derivatives in excellent yields and stereoselectivities (**15a, 15b**). Remarkably, in this last two examples we break 1 C-C bond and form 2 C-C bond with 4 consecutive stereocenters (1 quaternary) with total enantiocontrol and with excellent yields, showing that this approach could be a valid platform not only for the synthesis of spiro compounds but also for cyclic -amino acid derivatives. Unfortunately, when the reaction was tested with malonate derivatives (**16**) or ketoesters (**17**) the reaction did not render the final compounds.

***Scheme 3.*** Scope of the reaction

In summary, we reported for the first time a double synergistic cascade reaction for the synthesis of cyclopentane derivatives. The reaction is simply catalyzed by the combination of Pd(0) complexes and chiral secondary amines giving the final products in excellent yields and stereoselectivities. We not only prove the viability of this approach for the synthesis of spiroindanones but also for the synthesis of spirooxindoles, spirobenzofuranones and β-amino acid precursors. Mechanistic studies and the expansion of the present methodology to other interesting scaffolds such as vinyl aziridines, epoxides, carbamates or carbonates are ongoing in our research laboratory and will be reported in due course.[26]

Experimental Section

**General Procedure**: In a closed vial were added in this sequence: the organic catalyst 2-(diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine (20 mol% equiv), α,β-unsaturated aldehyde (1 equiv), vinyl-cyclopropane (1.2 equiv, 0.2 mmol), Pd2(dba)3 (5 mol% equiv) and EtOAc (1 mL). The reaction mixture was stirred at room temperature overnight. The crude was purified by flash column chromatography (*n*-hexane/EtOAc) to obtain the desired product.

Acknowledgements ((optional))

M.M. and R.R. are grateful for EPSRC Core Capability Funding (EP/ K039466/1).

**Keywords:** Cyclopentanation **·** Synergistic catalysis **·** enantioselective **·** allyl palladium **·** cascade reaction

[1] R. A. Sheldon, I. W. C. E. Arends, U. Hanefeld, Green Chemistry and Catalysis, Wiley-VCH Verlag GmbH & Co. KGaA, **2007**.

[2] For reviews on organocascade reactions, see: a) A. Moyano, R. Rios, *Chem. Rev.* **2011**, *111*, 4703–4832; b) A.-N. Alba, X. Companyó, M. Viciano, R. Rios, *Curr. Org. Chem.* **2009**, *13*, 1432–1474; c) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590–1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581.

[3] For reviews merging transition metals with organocatalysis see: a) M. Meazza, R. Rios, *Synthesis* **2016**, *48*, 960-973; for selected examples see: (a) Q. Ding and J. Wu, J. *Org. Lett*. **2007**, *9*, 4959-4962; b) A. E. Allen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2010**, *132*, 4986-4987; c) M. Ikeda, Y. Miyake, Y. Nishibayashi, *Angew. Chem., Int. Ed.* **2010**, *49*, 7289-7393; (d) A. Yoshida, M. Ikeda, G. Hattori, Y. Miyake, Y. Nishibayashi, *Org. Lett.* **2011**, *13*, 592-595; e) M. P. Sibi, M. Hasegawa, *J. Am. Chem. Soc.* **2007**, *129*, 4124-4125; f) A. E. Allen, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 4260-4263; g) D. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77-80; h) I. Ibrahem, P. Breistein, A. Cordova, *Angew. Chem. Int. Ed*. **2011**, *50*, 12036-12041; i) I. Ibrahem, G. Ma, S. Afewerki, A. Cordova, *Angew. Chem. Int. Ed.* **2013**, *52*, 878-882; j) I. Ibrahem, S. Santoro, F. Himo, A. Cordova, *Adv. Synth. Catal.* **2011**, *353*, 245-252; k) G. Jiang and B. List, *Angew. Chem. Int. Ed.* **2011**, *50*, 9471-9474; i) G. Jiang, R. Halder, Y. Fang, and B. List *Angew. Chem. Int. Ed.* **2011**, *50*, 9752-9755; j) S. Mukherjee, B. List, *J. Am. Chem. Soc*. **2007**, *129*, 11336-11337; k) S. Liao, B. List, *Angew. Chem. Int. Ed.* **2010**, *49*, 638-641; l) G. Jiang, B. List, *Adv. Synth. Catal*. **2011**, *353*, 1667-1670; m) G. Jiang, B. List, *Chem. Commun.* **2011**, *47*, 10022-10024.

[4] For an excellent review on synergistic catalysis see: A. E Allen, D. W. C. MacMillan, *Chem. Sci.* **2012**, *3*, 633–658.

[5] (a) V. Ceban, P. Putaj, M. Meazza, M. B. Pitak, S. J. Coles, J. Vesely, R. Rios, *Chem. Commun*. **2014**, *50*, 7447-7450; b) M. Meazza, V. Ceban, M. B. Pitak, S. J. Coles, R. Rios, *Chem. Eur. J.* **2014**, *20*, 16853-16857.

[6] M. Meazza, M. E. Light, A. Mazzanti, R. Rios, *Chem. Sci.* **2016**, *7*, 984-988.

[7] The Pauson-​Khand Reaction: Scope, Variations and Applications. Ed. Ramon Rios John Wiley & Sons Ltd., **2012**.

[8] For a review: D. R. Wenz, J. Read de Alaniz, *Eur. J. Org. Chem*. **2015**, 23-37.

[9] For a recent example, see: Y. Tokimizu, M. Wieteck, M. Rudolph, S. Oishi, N. Fujii, A. S. K. Hashmi, H. Ohno, *Org. Lett.* **2015**, *17*, 604-607.

[10] a) I. Ibrahem, G.-L. Zhao, R. Rios, J. Vesely, H. Sunden, P. Dziedzic, A. Cordova, *Chem. Eur. J*. **2008**, *14*, 7867-7879, b) R. Rios, J. Vesely, H. Sunden, I. Ibrahem, G.-L. Zhao, A. Cordova, *Tetrahedron Lett.* **2007**, *48*, 5835-5839.

[11] J. Wang, H. Li, H. Xie, L. Zu, X. Shen, W. Wang, *Angew. Chem. Int. Ed.* **2007**, *46*, 9050-9053.

[12] for example: a) D. Enders, C. Wang, J.W. Bats, *Angew. Chem. Int. Ed.* **2008**, *47*, 7539-7542.

[13] a) G. Ma, S. Afewerki, L. Deiana, C. Palo-Nieto, L. Liu, J. Sun, I. Ibrahem, A. Cordova, *Angew. Chem. Int. Ed*. **2013**, *52*, 6050–6054; b) S. Afewerki, G. Ma, I. Ibrahem, L. Liu, J. Sun, A. Cordova, *ACS Catal*. **2015**, *5*, 1266–1272.

[14] a) T. Hudickly, J. W. Reed, *Angew. Chem. Int. Ed*. **2010**, *49*, 4864-4876; b) J. E. Baldwin, *Chem. Rev.* **2003**, *103*, 1197-1212.

[15] This work was presented, for the first time, in the RSC Organic Division South-West Regional Meeting, UK, **January 13th,** **2016.**

[16] a) I. Shimizu, Y. Ohashi, J. Tsuji, *Tetrahedron Lett.* **1985**, *26*, 3825–3828; b) A. F. G. Goldberg, B. M. Stoltz, *Org. Lett*. **2011**, *13*, 4474–4476; c) L.-y. Mei, Y. Wei, Q. Xu, M. Shi, *Organometallics* **2012**, *31*, 7591–7599.

[17] a) B. M. Trost, P. J. Morris, *Angew. Chem. Int. Ed*. **2011**, *50*, 6167-6170; For a similar reaction with enones see: b) B. M. Trost, P. J. Morris, S. J. Sprague*, J. Am. Chem. Soc*. **2012**, *134*, 17823–17831.

[18] F. Wei, C.-L. Ren, D. Wang, L. Liu, *Chem. Eur. J.* **2015**, *21*, 2335-2338.

[19] For a review regarding the enantioselective synthesis of spiro compounds see, R. Rios, *Chem. Soc. Rev.* **2012**, *41*, 1060-1074.

[20] a) G. Feuer in Progress in Medicinal Chemistry, Vol. 10 (Eds.: G. P. Ellis, G. B. West), Elsevier, **1974**, pp. 85–158; b) D. Leblois, S. Piessard, G. Le Baut, P. Kumar, J.-D. Brion, L. Sparfel, R.-Y. Sanchez, M. Juge, J.-Y. Petit, L. Welin, *Eur. J. Med. Chem*. **1987**, *22*, 229–238; c) K. A. Bello, L. Cheng, J. Griffiths, J. Chem. Soc. Perkin Trans. 2 **1987**, 815–818; d) D. B. Hansen, M. M. Joullie, *Chem. Soc. Rev.* **2005**, *34*, 408–417.

[21] a) Y. Chen, Y. Lun, J. Ju, E. W. Pienkowski, S. R. Rajski, B. Shen; *J. Nat. Prod.* **2008**, *71*, 431-437; b) D. L. Boger, O. Heuter, K. Mbiya, M. Zhang, *J. Am. Chem. Soc.* **1995**, *117*, 11839-11849.

[22] For examples of our previous works in organocatalysis: (a) X. Companyo, A. Moyano, A. Mazzanti, A. Janecka, R. Rios, *Chem. Commun*. **2013**, *49*, 1184-1186.

[23] For example: R. Rios, H. Sunden, J. Vesely, G.-L. Zhao, P. Dziedzic, A.Córdova, *Adv. Synth. Catal.* **2007**, *349*, 1028-1032.

[24] S. C. Wang, D. M. Troast, M. Conda-Sheridan, G. Zuo, D. LaGarde, J. Louie, D. J. Tantillo, *J. Org. Chem*. **2009**, *74*, 7822-7833.

[25] A suitable crystal was selected and mounted on a dtrek-CrysAlisPro-abstract goniometer imported rigaku-d\*trek images diffractometer. The crystal was kept at T = 100(2) K during data collection. Using Olex2 (O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K Howard, H. Puschmann, *J. Appl. Cryst.* **2009**, *42*, 339-341.), the structure was solved with the ShelXT (G.M. Sheldrick, *Acta Cryst.* **2015**, *A71*, 3-8.) structure solution program, using the Direct Methods solution method and refined with the ShelXL (G.M. Sheldrick, *Acta Cryst.* 2015, *C71*, 3-8) refinement package using Least Squares minimisation. Crystal Data for C22H17FO3 (M =348.35 g/mol): monoclinic, space group P21 (no. 4), a = 12.28394(19) Å, b = 9.25225(14) Å, c = 15.6776(2) Å, β = 90.6893(12)°, V = 1781.69(4) Å3, Z = 4, T = 100(2) K, μ(CuKα) = 0.763 mm-1, Dcalc = 1.299 g/cm3, 35672 reflections measured (5.638° ≤ 2Θ ≤ 140.746°), 6464 unique (Rint = 0.0272, Rsigma = 0.0149) which were used in all calculations. The final R1 was 0.0403 (I > 2σ(I)) and wR2 was 0.1112 (all data). Crystallographic data (excluding structure factors) for the structure **7e** have been deposited with the Cambridge Crystallographic Data Centre with CCDC number 1442949. Copies of the data can be obtained, free of charge, on application to Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk))

[26] After the initial submission of this work, two groups independently reported similar vinylcyclopropane cycloadditions with enals: a) M. Laugeois, S. Ponra, V. Ratovelomanana-Vidal, V. Michelet, M. R. Vitale, *Chem. Commun*. **2016**, *52*, 5332-5335; b) K. S. Halskov, L. Naesborg, F. Tur, K. A. Jorgensen, *Org. Lett.* **2016**, *16*, 2220-2223.

Received: ((will be filled in by the editorial staff))  
Revised: ((will be filled in by the editorial staff))  
Published online: ((will be filled in by the editorial staff))

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

Layout 1:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Synergistic Catalysis −−−−−−−−−−−−− |  |  |  | **Double make it easy**: For first time a double synergistic cascade reaction is reported merging transition metal and amine catalysis. The reaction between vinyl cyclopropanes and enals render the final cyclopentane derivatives in excellent yields and stereoselectivities |
| M. Meazza, R. Rios\*)) ………… Page – Page  Synergistic Catalysis: Enantioselective Ring Expansion of Vinyl Cyclopropanes Combining Four Catalytic Cycles. Synthesis of Highly Substituted Cyclopentanes Bearing up to Four Stereocenters |