# Enantioselective Synthesis of Seven-Membered Carbo- and Heterocyles by Organocatalyzed Intramolecular Michael Addition.

**James O. Guevara-Pulido, José M. Andrés, Deisy P. Ávila and Rafael Pedrosa.***

Instituto CINQUIMA and Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Valladolid. Paseo de Belén 7. 47011-Valladolid. Spain

E-mail: pedrosa@qo.uva.es

Web: http://sintesisasimetrica.blogs.uva.es

**Abstract**.

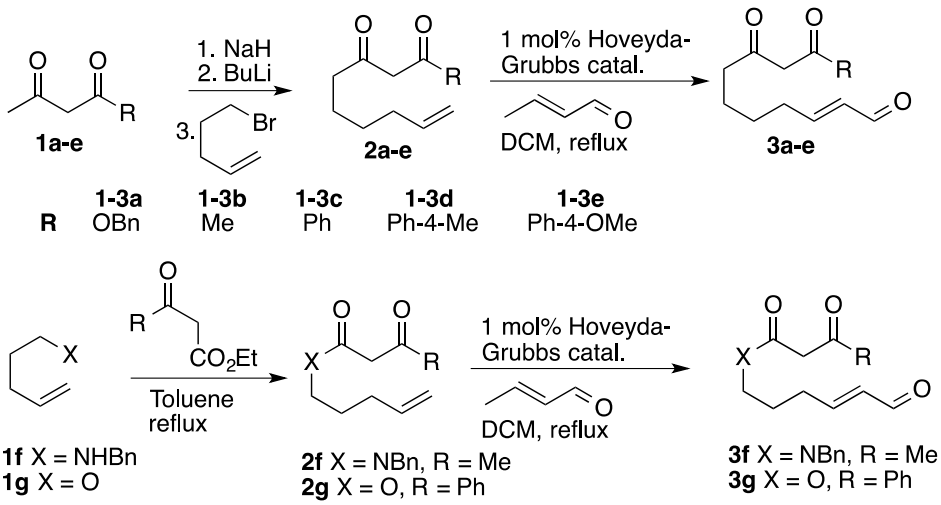
Unprecedented diastereo- and enantioselective synthesis of seven-membered rings has been achieved by organocatalyzed intramolecular Michael addition of enals bearing β-diketone functionality. The cyclization, leads to 2,3-disubstituted cycloheptanone derivatives in high yield and excellent stereoselectivity. The same organocatalyzed cyclization process has been used to prepare six-membered homologs, but with lower stereoselectivity.

Enantioselective organocatalyzed synthesis of five- and six-membered rings have been extensively studied in the last decade[1] but, in spite of their biological interest, the synthesis of both carbo- and heterocyclic seven-membered structures has been less developed, probably as a consequence of the difficult intramolecular reaction leading to cycles with seven members.[2] Thus, the search for the enantioselective synthesis of that kind of cycles is an active area of research, and recently both metal and organocatalyzed methodologies have been developed.[3]

In that way, organocatalytic [4 + 3][4] or [5 + 2][5] cycloaddtions lead to seven membered carbo- and heterocycles in good yield and stereoselection. Organocatalytic sequential [3 + 2] cycloadditions,[6] Michael-Frieldel Crafts reactions,[7] and Michael-aldol tandem processes followed by opening of the formed bicyclic intermediates[8] have been also applied to the enantioselective synthesis of cycloheptane derivatives. Additionally, chiral phosphoric acids are able to promote three components reactions to enantioenriched diazepine derivatives,[9] and chiral azepanes[10] have also been obtained by domino Michael-cyclization reaction catalyzed by prolinol derivatives.

Based on these antecedents and our previous experience on enantioselective organocatalyzed Michael additions,[11] we envisaged a way to synthesize seven-membered carbo- and heterocycles by iminium activation[12] of easily accessible enals bearing an enolizable methylene group in their structure.

Starting compounds **3a-g** were prepared[13] by cross-metathesis of the corresponding dicarbonyl compounds **2a-g** with crotonaldehyde in the presence of second generation Hoveyda-Grubbs catalyst in methylene chloride at reflux.[14] Keto ester **2a** and diketo olefins **2b-e** were obtained by alkylation of the corresponding dianions derived from benzyl acetoacetate **1a** or β-diketones **1b-e** with 5-bromo-1-pentene.[15] Amide **2f** was synthesized by aminolysis[16] of ethyl acetoacetate with benzyl 4-pentenyl amine **1f**, whereas **2g** was prepared by transesterification[17] of ethyl benzoylacetate with 4-penten-1-ol (Scheme 1).




**Scheme 1**. Synthesis of the starting enals **3a-f**.

In order to study the best catalyst and conditions for the intramolecular Michael reaction, we subjected β-ketoester **3a** to the cyclization process in DCM at rt in the presence of 10 mol% of three different catalysts and 20 mol% of *p*-nitrobenzoic acid (PNBA) as co-catalyst (Scheme 2). Quinidine-derived primary amine **A**[18] and (*S*)-1-(2-pyrrolidinylmethyl) pyrrolidine **B**[19] are very active, but a very complex mixture of products was formed in the reactions promoted by both catalysts. On the contrary, the monofunctional Jörgensen-Hayashi catalyst **C**[20] was able to promote the cyclization of **3a** to an unseparable equimolar mixture of *cis*- and *trans*- 2,3-disubstituted cycloheptanones **4a** in very good ee for *trans* diastereoisomer (entry 1 in Table 1). The yield was improved and the reaction time shortened, maintaining the stereoselection, by using ethereal solvents (entries 2, 3 in Table 1), but the best results were obtained in toluene as solvent (entries 4-7 in Table 1). In this solvent, no important variations in both the yield and ee were observed by modifying the concentration (entry 5), and the temperature (entry 6), but the ee dropped to 70% when the reaction was carried out in the absence of PNBA as co-catalyst (entry 7 in Table 1). The variation of stereoselection with the nature of the counterion, which is dependent on the acid used as co-catalyst is a very well known act in organocatalytic transformations.[21] The acid additive accelerates the formation of iminium ion, and in the present case the drop in the enantioselection could be attributed to the extension in which the uncatalyzed background cyclization occurs.

**Scheme 2**. Cyclization of **3a** promoted by catalyst **C**.

**Table 1**. Screening of conditions for the cyclization of **3a** promoted by 10 mol% of catalyst **C**.

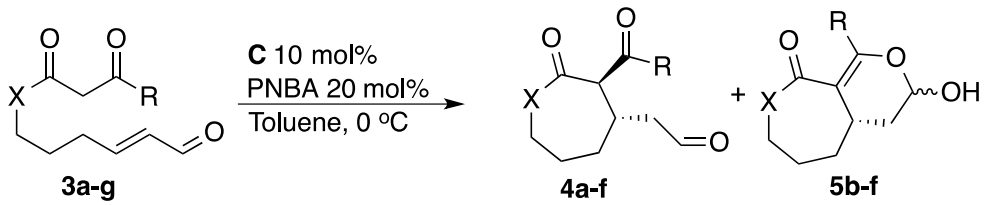
| Entry | Solvent | Conc [M] | T ($^{o}$C) | Time (h) | Yield (%)[a] | Ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 | DCM | 0.1 | 0 | 35 | 30 | 90 |
| 2 | THF | 0.1 | 0 | 26 | 37 | 92 |
| 3 | $Et_2O$ | 0.1 | 0 | 24 | 35 | 90 |
| 4 | Toluene | 0.1 | 0 | 24 | 45 | 93 |
| 5 | Toluene | 0.05 | 0 | 38 | 43 | 92 |
| 6 | Toluene | 0.1 | - 18 | 40 | 45 | 92 |
| 7 | Toluene | 0.1 | 0 | 25 | 45 | 70[c] |

[a] Isolated yields as a mixture (1:1) of cis and trans diastereoisomers. [b] Determined by chiral HPLC for the trans diastereoisomer. [c] Reaction without PNBA as co-catalyst.

The reaction in toluene at 0 $^{o}$C in the presence of 10 mol% of catalyst **C** and 20 mol% of PNBA as co-catalyst was selected as the best reaction conditions, and the reaction extended to different enals bearing β-diketones or β-ketoamides (**3b-f**) in their structure, and the results are summarized in Scheme 3 and Table 2.

Acetylacetone-derived enal **3b** (entry 2 in Table 2) cyclized in much better yield than ketoester **3a**, but leading to an unseparable equimolar mixture of *cis* and *trans*-cycloheptanone derivative **4b** and hemiacetal **5b** in a ratio 3:1. Fortunately, an important improvement in both yield and the diastereoselection was achieved for the cyclization of the enal derived from benzoyl acetone **3c**. The cyclization of **3c** gave the 2,3-disubstituted cyloheptanone in 77% yield, as a mixture (1:2.5) of hemiacetal **5c** and *trans*-**4c** as a single diastereoisomer in excellent enantioselectivity (90% ee) (entry 3 in Table 2). The behavior of *p*-tolyl substituted derivative **3d** was similar to that showed by **3c** (entry 4), whereas the *para*-methoxy substituted **3e** was less reactive increasing the reaction time to 30 h, but leading to the cyclization product in good yield (73%) and total diastereoselectivity and very good enantioselectivity (84% ee) (entry 5 in Table 2).

We then tried to extend the methodology to the preparation of heterocycles with one nitrogen or oxygen in their structure starting from amide **3f** or ester **3g**. Acetylacetamide derived enal **3f** easily cyclized to a mixture (1:2) of hemiacetal **5f** and *trans* α,β-disubstituted caprolactam **4f** as a single diastereoisomer in a total 78% yield and excellent enantioselectivity (92%) (entry 6). The ester derived from benzoylacetic acid **3g** also reacted in the presence of 10 mol% of catalyst **C**, but leading to a very complex mixture of products where it was not possible to isolate the cyclization products **4g** or **5g**.




| 3, 4, 5 | a | b | c | d | e | f | g |
|---|---|---|---|---|---|---|---|
| X | $CH_2$ | $CH_2$ | $CH_2$ | $CH_2$ | $CH_2$ | BnN | O |
| R | OBn | Me | Ph | Me-4-Ph | MeO-4-Ph | Me | Ph |

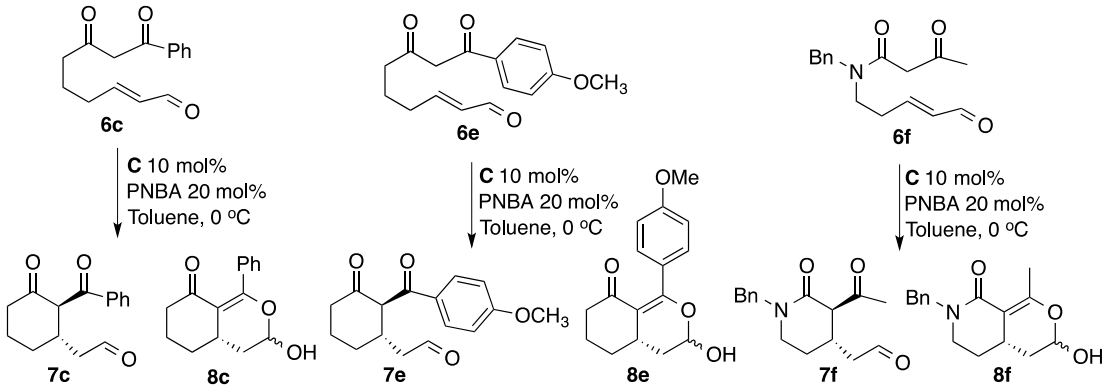
**Scheme 3.** Synthesis of seven-membered rings by intramolecular Michael addition.

**Table 2.** Synthesis of enantioenriched disubstituted seven-membered ring by intramolecular Michael reaction catalyzed by diphenyl prolinol derivative **C**.

| Entry | Reagent | T (h) | Yield [a] | Ratio (**4**/**5**)[b] | (cis-**4**/trans-**4**)[b] | Ee[c] |
|---|---|---|---|---|---|---|
| 1 | **3a** | 24 | 45 | - | 1:1 | 93 |
| 2 | **3b** | 24 | 80 | 3/1 | 1:1 | 88 |
| 3 | **3c** | 16 | 77 | 2.5/1 | >1:<99 | 90 |
| 4 | **3d** | 20 | 76 | 2.2/1 | >1:<99 | 93 |
| 5 | **3e** | 30 | 73 | 2/1 | >1:<99 | 84 |
| 6 | **3f** | 20 | 78 | 2/1 | >1:<99 | 92 |
| 7 | **3g** | 15 | -- | -- | -- | -- |

[a] Total yield of **4** and **5**. [b] Determined by HNMR of the reaction mixture. [c] The values were determined by chiral HPLC, and refer to the trans-isomer.

The good results obtained in the formation of cycloheptanone derivatives led us to explore the synthesis of six-membered rings from enals **6c**, **6e** and **6f** for comparative purposes. Starting compounds were prepared by sequential alkylation cross-metathesis as described above, and subjected to intramolecular Michael addition in the same conditions used for the cyclization of **3a-g** (Scheme 4 and Table 3).




**Scheme 4**. Intramolecular Michael addition leading to six-membered rings.

**Table 3.** Synthesis of enantioenriched disubstituted six-membered ring by intramolecular Michael reaction catalyzed by diphenyl prolinol derivative **C**.

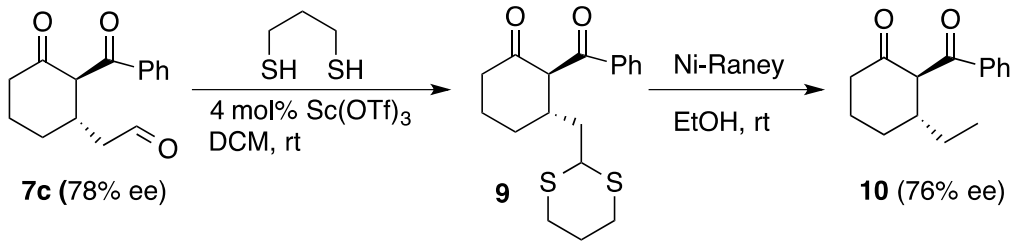
| Entry | Reagent | T (h) | Yield [a] | Ratio (**7**/**8**)[b] | (cis-**7**/trans-**7**)[b] | Ee[c] |
|---|---|---|---|---|---|---|
| 1 | **6c** | 23 | 80 | 3/1 | >1:<99 | 78 |
| 2 | **6e** | 50 | 83 | 4.5/1 | >1:<99 | 89 |
| 3 | **6f** | 17 | 50 | 1.5/1 | 1:3.5 | 64 |

[a] Total yield of **4** and **8**. [b] Determined by HNMR of the reaction mixture. [c] The values were determined by chiral HPLC, and refer to the trans-isomer.

The best result, in terms of yield and enantioselection, was obtained for diketone **6e**, leading to the cyclization product in 83% as a mixture (1:4.5) of hemiketal **8e** and *trans*-disubstituted cyclohexanone **7e** as a single diastereomer in very good 89% ee (entry 2 in Table 3). On the contrary, benzoylacetone-derived enal **6c** reacted faster than **6e**, leading to a mixture (1:3) of hemiketal **8c** and *trans*-**7c**, but in worse enantioselection (78% ee) than its homolog **3c** (compare entry 1 in Table 3 *versus* entry 3 in Table 2). In the same way, amide **6f** easily cyclized, in moderate yield, to a

mixture (1:1.5 ratio) **8f** and **7f** as a mixture (1:3.5) of *cis* and *trans* diastereoisomers, but the stereoselection dropped a lot with respect to the cyclization of **3f** to the seven-membered lactam **4f** (compare entry 3 in Table 3 *versus* entry 6 in Table 2).

The relative *trans* stereochemistry of the compounds was determined by COSY and NOESY experiments for compound **7e**,[13] and the absolute configuration was established by chemical correlation of **7c** with the known (*2S*,*3R*)-2-benzoyl-3-ethyl cyclohexanone (**10**),[22] and extended for all the compounds.




**Scheme 5**. Chemical correlation of **7c** with (*2S*,*3R*)-2-benzoyl-3-ethyl cyclohexanone.

In summary, we have described the unprecedented synthesis of enantioenriched seven-membered rings by stereoselective intramolecular Michael addition of dicarbonyl functionalized enals. The reaction worked very well by using the Jorgensen-Hayashi catalyst, leading to a mixture of *trans* 2,3-disubstituted cyclic derivatives and their corresponding hemiacetals, with good yields and excellent stereoselection. The same protocol can be used for the preparation of six-membered rings, but the cyclization occurred in lower diastereo- and enantioselectivities.

**Acknowledgements**

We acknowledge the financial support provided by the Spanish MINECO (Project CTQ2014-59870-P) and Junta de Castilla y León (Project, VA064U13). J. O. G.-P. thanks the Universidad de Valladolid for a predoctoral fellowship.

**Notes and References**.

1 For some recent reviews see: (a) S. Goudedranche, W. Raimondi, X. Bugaut, T. Constantieux, D. Bonne, J. Rodriguez, *Synthesis* 2013, **45**, 1909. (b) Y.-C. Xiao, Y.-C. Chen in *Comprehensive Enantioselective Organocatalysis: Catalysts, Reactions*,

*and Applications*. P. I. Dalko Ed. Vol. 3, Ch. 36, p. 1067. Wiley-VCH 2013. Weinheim. (c) A. Moyano, R. Rios, *Chem. Rev.* 2011, **111**, 4703. (d) M. G. Núñez, P. García, R. F. Moro, D. Díez, *Tetrahedron* 2010, **66**, 2089. (e) P. Merino, E. Marqués-López, T. Tejero, R. P. Herrera, *Synthesis* 2010, 1. (f) H. Yang, R. G. Carter, *Synlett* 2010, 2827. (g) X. Yu, W. Wang, *Org. Biomol. Chem.* 2008, **6**, 2037. (h) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem. Int. Ed.* 2007, **46**, 1570.

2 M. A. Casadei, C. Galli, L. Mandolini, *J. Am. Chem. Soc.* 1984, **106**, 1051.

3 For recent reviews see: (a) K. E. O. Ylijoki, J. M. Stryker, *Chem Rev.* 2013, **113**, 2244. (b) T. A. Reekie, M. E. Kavanagh, M. Longworth, M. Kassiou, *Synthesis* 2013, **45**, 3211. (c) H. Pellissier, *Adv. Synth. Catal.* 2011, **353**, 189. (d) M. A. Battiste, P. M. Pelphrey, D. L. Wright, *Chem. Eur. J.* 2006, **12**, 3438. (e) M. Harmata, *Adv. Synth. Catal.* 2006, **348**, 2297.

4 (a) J. Izquierdo, A. Orue, K. A. Scheidt, *J. Am. Chem. Soc.* 2013, **135**, 10634. (b) H. Lv, W.-Q. Jia, L.-H. Sun, S. Ye, *Angew. Chem. Int. Ed.* 2013, **52**, 8607. (c) M. Harmata, S. K. Ghosh, X. Hong, S. Wacharasindhu, P. Kirchhoefer, *J. Am. Chem. Soc.* 2003, **125**, 2058.

5 (a) A. Orue, U. Uria, E. Reyes, L. Carrillo, J. L. Vicario, *Angew. Chem. Int. Ed.* 2015, **54**, 3043. (b) M. R. Witten, E. N. Jacobsen, *Angew. Chem. Int. Ed.* 2014, **53**, 5912. (c) N. Z. Burns, M. R. Witten, E. N. Jacobsen, *J. Am. Chem. Soc.* 2011, **133**, 14578.

6 J. Vesely, R. Rios, I. Ibrahem, G.-L. Zhao, L. Eriksson, A. Córdova, *Chem. Eur. J.* 2008, **14**, 2693.

7 N. S. Dange, B.-C. Hong, C.-C. Lee, G.-H. Lee, *Org. Lett.* 2013, **15**, 3914.

8 M. Rueping, A. Kuenjel, F. Tato, J. W. Bats, *Angew. Chem. Int. Ed.* 2009, **48**, 3699.

9 Y. Wang, M.-S. Tu, F. Shi, S.-J. Tu, *Adv. Synth. Catal.* 2014, **356**, 2009.

10 S. Goudedranche, D. Pierrot, T. Constantieux, D. Bonne, J. Rodriguez, *Chem. Commun.* 2014, **50**, 15605.

11 (a) J. O. Guevara-Pulido, J. M. Andrés, R. Pedrosa, *J. Org. Chem.* 2014, **79**, 8638. (b) J. O. Guevara-Pulido, J. M. Andrés, R. Pedrosa, *Eur. J. Org. Chem.* 2014, 8072.

(c) R. Manzano, J. M. Andrés, R. Alvarez, M. D. Muruzábal, A. Rodríguez de Lera, R. Pedrosa, *Chemistry Eur. J.* 2011, **17**, 5931. (d) R. Manzano, J. M. Andrés, M. D. Muruzábal, R. Pedrosa, *Adv. Synth. Catal.* 2010, **352**, 3364.

12 A. Erkkilä, I. Majander, P. Pihko, *Chem. Rev.* 2007, **107**, 5416.

13 For details see ESI.

14 (a) B. Bradshaw, C. Parra, J. Bonjoch, *Org. Lett.* 2013, **15**, 2458. (b) J.-R. Chen, C.-F. Li, X.-L. An, J.-J. Zhang, X.-Y. Zu, W.-J. Xaiao, *Angew. Chem. Int. Ed.* 2008, **47**, 2489. (c) S. Fustero, D. Jiménez, J. Moscardó, S. Catalán, C. del Pozo, *Org. Lett.* 2007, **9**, 5283.

15 Y. Zhang, J. Jiao, R. A. Flowers, *J. Org. Chem.* 2006, **71**, 4516.

16 D. Yang, G.-Y. Lian, H.-F. Yang, J. D. Yu, D.-W. Zhang, X. Gao, *J. Org. Chem.* 2009, **74**, 8610.

17 J. S. Yadav, B. V. S. Reddy, A. D. Krishna, C. S. Reddy, A. V. Narsaiah, *J. Mol. Catal. A Chem.* 2007, **261**, 93.

18 H. Brunner, P. Schmidt, *Eur. J. Org. Chem.* 2000, 2119.

19 S. K. Hendrie, J. Leonard, *Tetrahedron* 1987, **43**, 3289.

20 (a) M. Marigo, T. C. Wabnitz, D. Fielenbach, K. A. Jörgensen, *Angew. Chem. Int. Ed.* 2005, **44**, 794. (b) Y. Hayashi, H. Gotoh, T. Hayashi, M. Shoji, *Angew. Chem. Int. Ed.* 2005, **44**, 4212.

21 For a very recent review see: L. Hong, W. Sun, D. Yang, G. Li, R. Wang, *Chem. Rev.* DOI: 10.1021/acs.chemrev.5b00676.

22 (a) X. Tang, A. J. Blake, W. Lewis, S. Woodward, *Tetrahedron: Asymmetry* 2009, **20**, 1881. (b) K. Agapiou, D. F. Cauble, M. J. Krische, *J. Am. Chem. Soc.* 2004, **126**, 4528. (c) B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos, A. H. M. de Vries, *Angew. Chem. Int. Ed.* 1997, **36**, 2620.