Synthetic Methods

DOI: 10.1002/anie.200901333

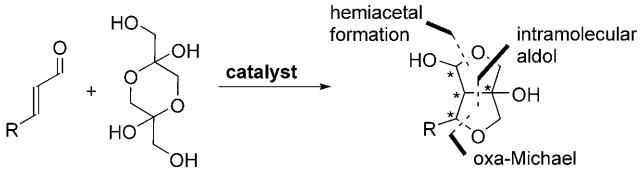
Enantioselective Organocatalytic Domino Oxa-Michael/Aldol/Hemiacetalization: Synthesis of Polysubstituted Furofuranes Containing Four Stereocenters**

Efraím Reyes, Garazi Talavera, Jose L. Vicario, Dolores Badía, and Luisa Carrillo*

The discovery of new methodologies for the synthesis of complex molecules in the shortest and most efficient way is a key field of research. In this context, domino or cascade reactions represent an advantage for the straightforward construction of biologically relevant compounds because they allow construction of complex molecules in an efficient way, thereby minimizing the number of laboratory operations and the generation of waste chemicals.[1] Additionally, when stereochemistry is a fundamental parameter to be controlled, domino processes arise as an effective approach for constructing the target molecule with good stereoselectivity. Among the different methodologies described in the chemical literature, organocatalytic enantioselective domino reactions represent a useful and competitive tool for the generation of molecular complexity from readily available and cheap starting materials, as well as displays exceptional performance with regard to stereochemical control.[2] More advantages of this methodology are related to the fact that organocatalysts are very often commercially available, environmentally friendly, water compatible, air stable, and robust reagents. Additional benefits are associated with the tolerance of the catalysts and the reactive intermediates to the presence of moisture or air in the reaction medium, which leads to an advantage in operational simplicity when carrying out the reaction.[3]

A particularly interesting situation is the use of chiral amines as catalysts in domino processes which are initiated by Michael-type reactions.[4] Chiral amines can activate α,β-unsaturated aldehydes or ketones by the reversible formation of an iminium ion which, after the conjugate addition step, delivers in intermediate enamine ready to participate in a subsequent reaction, therefore providing an opportunity for a domino process to occur. Related to this topic, several stereoselective amine-catalyzed cascade reactions initiated by conjugate additions have been reported, most of them involving a C–C bond formation in the cascade-initiating Michael reaction step and also some examples can be found in which a hetero-Michael reaction has been employed to start the process. Importantly, it has to be pointed out that oxa-Michael-initiated domino reactions have received little attention, just as the organocatalytic oxa-Michael reaction, which still remains a rather unexplored transformation. This lack of attention is mainly a result of the reversibility of the conjugate addition process,[4] which very often makes the oxa-Michael addition products configurationally unstable. An additional difficulty associated with this reaction is related to the low nucleophilicity of the alcohol functionality, which therefore requires a prior deprotonation step to activate it as an alkoxide ion. As a consequence of this the scope of the alcohols suitable candidates to be used as oxygen nucleophiles in oxa-Michael reactions is restricted to compounds of enhanced acidity.[5] In fact, literature examples are exclusively limited to the use of functionalized phenols as nucleophiles (in oxa-Michael-initiated cascade reactions or intramolecular versions)[6] and also a couple of elegant procedures have been reported by Jørgensen and co-workers[7] for the β-hydroxylation of α,β-unsaturated aldehydes and by List and co-workers[8] for the β-hydroxylation of enones using oximes and hydroperoxides, respectively, as O nucleophiles.

In this context, and in connection with our ongoing efforts to develop new organocatalytic reactions, we report herein a novel amine-promoted asymmetric domino reaction between dihydroxyacetone dimer and α,β-unsaturated aldehydes, which leads to the enantioselective formation of hexahydrofuro[3,4-*c*]furanes in a single step (Scheme 1). This transformation consists of an initial oxa-Michael reaction, a subsequent intramolecular aldol reaction, and lastly a hemiacetalization step, and it proceeds with the generation of four new stereocenters. Remarkably, the intramolecular aldol reaction step involves the participation of a ketone as internal electrophile, therefore generating a quaternary stereocenter. This reaction is in contrast with the other reported organo-



Scheme 1. One-step synthesis of hexahydrofuro[3,4-*c*]furanes by an oxa-Michael/aldol/hemiacetalization domino process.

[*] Prof. E. Reyes, G. Talavera, Prof. J. L. Vicario, Prof. Dr. D. Badía, Prof. L. Carrillo
Departamento de Química Orgánica II
Facultad de Ciencia y Tecnología
Universidad del País Vasco/Euskal Herriko Unibertsitatea
P.O. Box 644, 48080 Bilbao (Spain)
E-mail: joseluis.vicario@ehu.es
Homepage: http://www.ehu.es/GSA

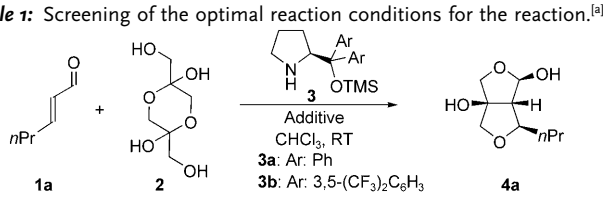
[**] This work was supported by the University of the Basque Country (GIU07/06), the Spanish MICINN (CTQ2008-00136/BQU), the Diputación Foral de Bizkaia (DIPE08/03), and the Basque Government (a fellowship to G.T.).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200901333.

catalytic cascade oxa-Michael/aldol processes in which an aldehyde moiety is chosen as a more reactive internal electrophile.[6] Notably, and to the best of our knowledge, this is the first example of a highly enantioselective direct β-alkoxylation of α,β-unsaturated aldehydes catalyzed by a chiral amine,[9] showing that even an aliphatic alcohol having a low pK_a value, such as dihydroxyacetone dimer, is able to participate as an oxygen nucleophile in a conjugate addition reaction under iminium activation.

Our studies began with the identification of the best catalyst and reaction conditions for this transformation using (*E*)-2-hexenal as a model substrate (Table 1). We started

Table 1: Screening of the optimal reaction conditions for the reaction.[a]



1a 2 4a

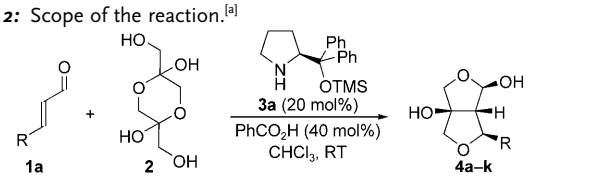
Entry	Catalyst	Additive	Conv. [%][b]	d.r.[c]	*ee* [%][d]
1	**3a**	–	<10	–	–
2	**3a**	$PhCO_2H$ (10 mol%)	50	>10:1	n.d.
3	**3a**	$PhCO_2H$ (20 mol%)	99 (93)[e]	>10:1	99
4	**3a**	$PhCO_2H$ (100 mol%)	99 (96)[e]	>10:1	97
5	**3a**	DABCO (10 mol%)	<10	–	–
6	**3a**	Et_3N (10 mol%)	<10	–	–
7	**3a**	NaOAc (10 mol%)	20	n.d.	n.d.
8[f]	**3b**	$PhCO_2H$ (10 mol%)	<10	–	–
9[f]	**3b**	$PhCO_2H$ (100 mol%)	50	>10:1	98
10[f]	**3b**	$PhCO_2H$ (200 mol%)	99	>10:1	98

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.2 mmol), and catalyst **3** (10 mol%) in $CHCl_3$ (5.0 mL) with stirring at RT for 16 h. [b] Conversion determined from ^{1}H NMR analysis of crude aliquots. [c] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d] Determined by HPLC analysis after conversion into the diacetylated product (see the Supporting Information). [e] Yield of the isolated product given within the parentheses. [f] The reaction was stirred for 5 days. n.d. = not determined, TMS = trimethylsilyl, DABCO = 1,4-diazabicyclo[2.2.2]-octane.

using *O*-trimethylsilyldiphenylprolinol (**3a**) as the catalyst, and after some experiments we concluded that chloroform was the best solvent for the reaction. We also found that a Brønsted acid co-catalyst was also required for the reaction to proceed to completion (Table 1, entry 1 versus entries 2–4). The amount of an acid additive used had an important influence on the reaction: after reacting for 16 hours the reaction proceeded with complete conversion when 20 mol% of $PhCO_2H$ or more was used (Table 1, entries 2–4). The possibility of using a base as an additive was also evaluated, but with negative results (Table 1, entries 5–7). We also evaluated the modified catalyst **3b**, but the reactions proceeded more slowly compared to those reactions using the catalyst **3a**, and they required the addition of two equivalents of benzoic acid, as an additive to undergo full conversion, as well as much longer reaction times (Table 1, entries 8–10).

Having established the best protocol for the reaction, we decided to extend this methodology to α,β-unsaturated aldehydes having different substituents. As shown in Table 2, the reaction protocol had to be slightly modified to obtain similar results to those obtained in the screening experiments, with respect to the yield and stereoselectivity, by

Table 2: Scope of the reaction.[a]



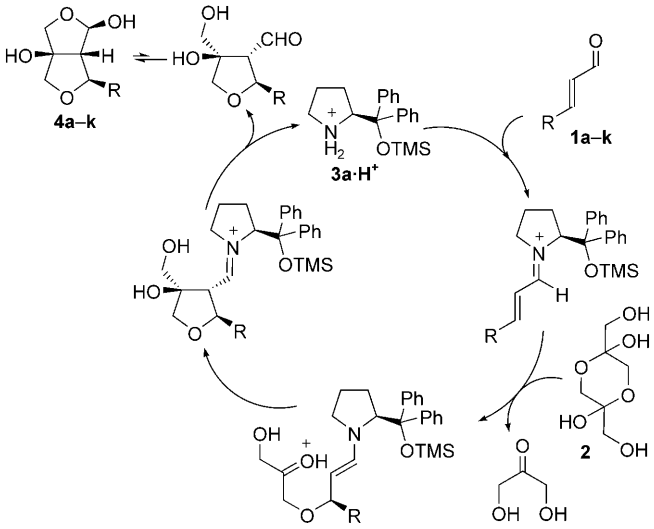
1a 2 4a–k

Entry	**1** (R)	Yield of **4** [%][b]	d.r.[c]	*ee* [%][d]
1	**1a** (*n*Pr)	96	>10:1	99
2	**1b** (Me)	89	7:1	92
3	**1c** (Et)	86	7:1	95
4	**1d** (*n*Bu)	89	>10:1	97
5	**1e** (nC_5H_{11})	92	>10:1	96
6	**1f** (nC_6H_{13})	78	>10:1	95
7	**1g** (*Z*-EtCH=$CHCH_2CH_2$)	83	>10:1	94
8	**1h** (nC_8H_{17})	76	>10:1	98
9	**1i** (Ph)	76	>10:1	98
10	**1j** (*o*-$MeOC_6H_4$)	71	>10:1	90
11	**1k** ((3-MeO)(4-AcO)C_6H_3)	67	>10:1	94
12[e]	**1d** (*n*Bu)	90	>10:1	98
13[e]	**1h** (nC_8H_{17})	74	>10:1	97
14[e]	**1i** (Ph)	77	>10:1	98
15[f]	**1d** (*n*Bu)	98	>10:1	97
16[f]	**1h** (nC_8H_{17})	96	>10:1	98
17[f]	**1i** (Ph)	80	>10:1	98

[a] Reaction conditions: **2** (0.2 mmol), **1** (0.3 mmol), **3a** (20 mol%), and $PhCO_2H$ (40 mol%) in $CHCl_3$ (2.0 mL). [b] Yield of isolated **4**. [c] Determined by NMR analysis of the crude reaction mixture. [d] Determined by HPLC analysis (see the Supporting Information). [e] Reaction conditions: **2** (1.0 mmol), **1** (1.5 mmol), **3a** (20 mol%) $PhCO_2H$ (40 mol%) in $CHCl_3$ (10 mL). [f] Reaction conditions: **2** (1.0 mmol), **1** (10 mmol), **3a** (20 mol%), $PhCO_2H$ (40 mol%) in $CHCl_3$ (50 mL).

increasing the amount of the catalyst to 20 mol%. Under these conditions, a wide variety of differently substituted hexahydrofuro[3,4-*c*]furanes **4a–k** were obtained with excellent yields and remarkably, as single diastereoisomers in almost all cases (Table 2, entries 1–11).[10] Additionally, the reaction proceeded with excellent enantioselectivity for all the substrates tested, furnishing the final heterocycles **4a–k** as highly enantioenriched compounds. The reaction could be carried out on larger scale (Table 2, entries 12–14), resulting in similar yields and stereoselectivities. Slightly higher yields of the final products **4** were obtained under more dilute reaction conditions and in the presence of a large excess of the enal reagent, while also maintaining a high diastereo- and enantioselectivity (Table 2, entries 15–17).

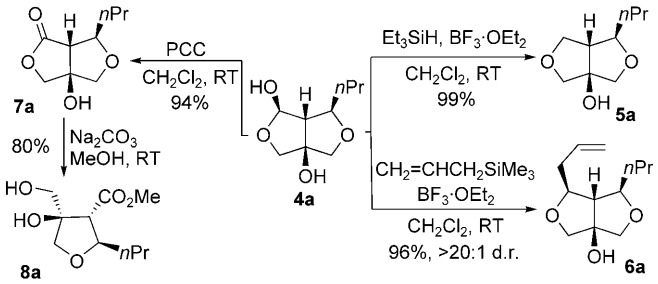
A plausible mechanistic proposal for this transformation is given in Scheme 2. The reaction could start with the conjugate addition of **2**[11] to the enal under iminium activation and then the intermediate enamine would undergo intramolecular aldol reaction delivering the final adducts **4** after releasing the catalyst by hydrolysis and undergoing a final internal hemiacetal-formation step. We believe that the high stereochemical control obtained in the overall process



Scheme 2. A plausible reaction pathway for the reaction.

relies on the irreversible intramolecular C–C bond-formation step, taking into account the known reversibility of oxa-Michael addition reactions.[7a,9] In this context, the efficiency of the catalyst **3a** to control the two stereocenters formed in the intramolecular aldol reactions is well documented.[2a,6] In contrast, with regard to the stereocontrol at the stereogenic center formed in the oxa-Michael step, two possibilities might explain the high selectivity observed: 1) a catalyst-controlled oxa-Michael reaction and a subsequent fast intramolecular aldol reaction which avoids the retro-oxa-Michael process, or 2) a dynamic kinetic resolution process, in which the chiral catalyst accelerates the aldol reaction for one diastereoisomer over the other, the later epimerizing because of the reversibility of the oxa-Michael reaction. We have been unable to detect the formation of or isolate the intermediate oxa-Michael product by using NMR analyses of aliquots of the reaction mixture or by carrying out the reaction under stoichiometric conditions; this lack of identification is suggestive of the first possible explanation discussed above. However, this experiment is not definitive proof for completely ruling out the dynamic kinetic resolution pathway. Finally, the last hydrolysis/hemiacetalization reaction should take place under thermodynamic control, furnishing the most stable diastereoisomer at the anomeric carbon center. Nevertheless, control experiments using a modified substrate indicate that the hemiacetal formation is also important to attaining full conversion.[12] We interpret this latter finding as efficient product scavenging from the catalytic cycle by the formation of a more stable bicyclic compound such as **4**. Regarding the role played by the additive, it is proposed that $PhCO_2H$ participates in the reaction not only by assisting in the formation of the iminium ion but also by activating the ketone moiety in the intramolecular aldol addition step through protonation.

We also decided to survey the reactivity of the obtained adducts **4** to illustrate their potential applications as chiral building blocks in organic synthesis (Scheme 3). All these transformations proceeded without epimerization at any of the stereogenic centers present in the starting materials.



Scheme 3. Survey of transformations carried out on the adduct **4a**. PCC = pyridinium chlorochromate.

Remarkably, the allylation reaction leading to **6a** proceeded in a fully diastereoselective fashion.

In conclusion, we have developed a very efficient domino process which leads to the synthesis of hexahydrofuro[3,4-*c*]furanes in excellent yields and diastereo- and enantioselectivities starting from readily available starting materials. Remarkably, this sequence involves the consecutive formation of two C–O and one C–C bonds and the fully stereocontrolled generation of four stereocenters, one of them being a quaternary center. Notably, this is also the first example of a highly enantioselective β-alkoxylation of α,β-unsaturated aldehydes catalyzed by a secondary amine. The fact that a high pK_a oxygen nucleophile is employed as a Michael donor to initiate the conjugate addition process, and the subsequent intramolecular aldol reaction takes place with a less electrophilic ketone moiety are unique features associated with this transformation. Moreover, the possibility of the selective manipulation of the different functionalities present within the obtained adducts allows the preparation of a wide range of different compounds which demonstrates the potential of this methodology for the enantioselective synthesis of useful chiral building blocks.

Received: March 10, 2009
Revised: May 18, 2009
Published online: June 25, 2009

Keywords: asymmetric catalysis · domino reactions · heterocycles · organocatalysis · oxa-Michael reaction

[1] For some selected reviews, see: a) N. Ismabery, R. Lavila, *Chem. Eur. J.* **2008**, *14*, 8444; b) C. J. Chapman, C. G. Frost, *Synthesis* **2007**, 1; c) H. Miyabe, Y. Takemoto, *Chem. Eur. J.* **2007**, *13*, 7280; d) N. T. Patil, Y. Yamamoto, *Synlett* **2007**, 1994; e) *Multicomponent Reactions* (Eds.: J. Zhu, H. Bienayme), Wiley-VCH, Weinheim, **2005**; f) D. Tejedor, F. Garcia-Tellado, *Chem. Soc. Rev.* **2007**, *36*, 484; g) L. F. Tietze, G. Brasche, K. Gerike, *Domino Reactions in Organic Chemistry*, Wiley-VCH, Weinheim, **2006**; h) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134; i) A. Dömling, *Chem. Rev.* **2006**, *106*, 17; j) H.-C. Guo, J.-A. Ma, *Angew. Chem.* **2006**, *118*, 362; *Angew. Chem. Int. Ed.* **2006**, *45*, 354; k) D. J. Ramón, M. Yus, *Angew. Chem.* **2005**, *117*, 1628; *Angew. Chem. Int. Ed.* **2005**, *44*, 1602.

[2] For two pioneering reports, see: a) M. Marigo, T. Schulte, J. Franzén, K. A. Jorgensen, *J. Am. Chem. Soc.* **2005**, *127*, 15710; b) Y. Huang, A. M. Walji, C. H. Larsen, D. W. C. MacMillan, *J.*

Am. Chem. Soc. **2005**, *127*, 15051. For general reviews on organocatalytic cascade reactions, see: c) X. Yu, W. Wang, *Org. Biomol. Chem.* **2008**, *6*, 2037; d) D. Enders, C. Grondal, M. R. M. Huettl, *Angew. Chem.* **2007**, *119*, 1590; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; e) G. Guillena, D. J. Ramon, M. Yus, *Tetrahedron: Asymmetry* **2007**, *18*, 693.

[3] For some selected general reviews on asymmetric organocatalysis, see: a) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem.* **2008**, *120*, 6232; *Angew. Chem. Int. Ed.* **2008**, *47*, 6138; b) A. Dondoni, A. Massi, *Angew. Chem.* **2008**, *120*, 4716; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; c) special issue on organocatalysis *Chem. Rev.* **2007**, *107*(12); d) B. List, J.-W. Yang, *Science* **2006**, *313*, 1584.

[4] a) J. L. Vicario, D. Badía, L. Carrillo, *Synthesis* **2007**, 2065; b) D. Almaçi, D. A. Alonso, C. Najera, *Tetrahedron: Asymmetry* **2007**, *18*, 299; c) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701; d) S. Sulzer-Mossé, A. Alexakis, *Chem. Commun.* **2007**, 3123.

[5] It has suggested that there is a pK_a barrier for nucleophile activation in conjugate additions proceeding by iminium activation, and this barrier lies between the pK_a values of 16 and 17: D. A. Alonso, S. Kitagaki, N. Utsumi, C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 4664; *Angew. Chem. Int. Ed.* **2008**, *47*, 4588.

[6] a) T. Govender, L. Hojabri, F. M. Moghaddam, P. I. Arvidsson, *Tetrahedron: Asymmetry* **2006**, *17*, 1763; b) H. Sunden, I. Ibrahem, G.-L. Zhao, L. Eriksson, A. Cordova, *Chem. Eur. J.* **2007**, *13*, 574; c) A. Merschaert, P. Delbeke, D. Daloze, G. Dive, *Tetrahedron Lett.* **2004**, *45*, 4697; d) H. Li, J. Wang, T. E-Nunu, L. Zu, W. Jiang, S. Wei, W. Wang, *Chem. Commun.* **2007**, 507; e) M. M. Biddle, M. Lin, K. A. Scheidt, *J. Am. Chem. Soc.* **2007**, *129*, 3830. See also f) D. R. Li, A. Murugan, J. R. Falck, *J. Am. Chem. Soc.* **2008**, *130*, 46; g) T. Tanaka, T. Kumamoto, T. Ishikawa, *Tetrahedron: Asymmetry* **2000**, *11*, 4633.

[7] a) S. Bertelsen, P. Diner, R. L. Johansen, K. A. Jorgensen, *J. Am. Chem. Soc.* **2007**, *129*, 1536. For a similar reaction using enones as Michael acceptors, see: b) A. Carlone, G. Bartoli, M. Bosco, F. Pesciaioli, P. Ricci, L. Sambri, P. Melchiorre, *Eur. J. Org. Chem.* **2007**, 5492.

[8] a) C. M. Reisinger, X. Wang, B. List, *Angew. Chem.* **2008**, *120*, 8232; *Angew. Chem. Int. Ed.* **2008**, *47*, 8112; b) X. Lu, Y. Liu, B. Sun, B. Cindric, L. Deng, *J. Am. Chem. Soc.* **2008**, *130*, 8134.

[9] For an earlier example of an attempted amine-catalyzed conjugate addition of alcohols to enals furnishing low levels of enantioselection, see: a) D. Díez, M. G. Nuñez, A. Benéitez, R. F. Moro, I. S. Marcos, P. Basabe, H. B. Broughton, J. G. Urones, *Synlett* **2009**, 390; b) T. Kano, Y. Tanaka, K. Maruoka, *Tetrahedron* **2007**, *63*, 8658.

[10] The absolute configuration of the compounds **4** was assigned by analogy from the X-ray analysis of the corresponding *O*-acetyl *p*-chlorobenzoyl derivative of **4b** (see the Supporting Information). CCDC 723339 contains 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.

[11] We also think that it is the dihydroxyacetone dimer **2** itself which acts as the oxygen nucleophile because reactions in solvents having the ability to retrodimerize **2**, such as MeOH or THF, proceeded with very low conversions.

[12] The reaction of crotonaldehyde with hydroxyacetophenone under the optimized reaction conditions did not furnish any product; only unmodified starting materials were recovered.

