Organocatalytic synthesis of spiro compounds *via* a cascade Michael–Michael-aldol reaction†

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Received 21st May 2010, Accepted 3rd August 2010
DOI: 10.1039/c0cc01522a

The synthesis of spiro compounds *via* a Michael–Michael-aldol reaction is reported. The reaction affords spirooxindole derivatives in good yields and in almost diastereo- and enantiopure form. Moreover, the reaction works with several heterocycles such as oxindoles, benzofuranones, pyrazolones or azlactones rendering the final spiro compounds in good yields and excellent stereoselectivities.

Natural compounds present sometimes very complex scaffolds with a well defined three-dimensional structure. This complexity is generally correlated with stereospecificity in their biological properties. One of the most common goals for organic chemists is the development of new methodologies to build very complex structures in a stereocontrolled fashion and, if possible, a catalytic way. One of the great challenges in natural product synthesis is the construction of spiro compounds in an enantioselective fashion. Several natural products have this motif in their structure: gelsemine, spirotryprostatin B, marcfortine B, phalarine, coerulescine, horsfiline, pseurotin, agarospirol, *etc.*[1] For this reason, the quest for new synthetic methodologies that allow the construction of spiro compounds is a common goal for many chemists.

Organocatalytic domino or cascade reactions[2] are one of the common approaches that satisfy the criteria of economic and effective processes and follow the rules of green and sustainable chemistry.[3]

In 2006, Enders and co-workers showed the potential of organocatalysis for the synthesis of complex structures with a triple cascade organocatalytic reaction, which led to the synthesis of cyclohexanes with four stereocenters with exceptional degrees of enantioselectivity and moderate to good diastereoselectivities.[4]

In 2007, Jørgensen and co-workers reported a powerful triple domino asymmetric reaction between malononitrile and unsaturated aldehydes, consisting in a Michael–Michael-aldol reaction that built a cyclohexene in excellent yields and enantioselectivities, but in moderate to good diastereoselectivities.[5] In 2009, Enders and co-workers employed the same concept starting from nitromethane and unsaturated aldehydes, with similar results.[6]

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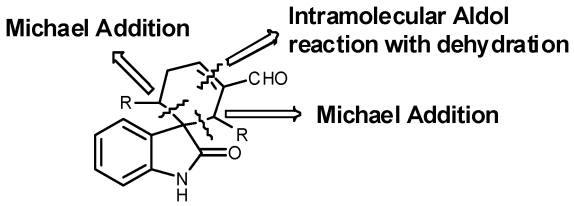
† Electronic supplementary information (ESI) available: Experimental procedures and spectral data. See DOI: 10.1039/c0cc01522a



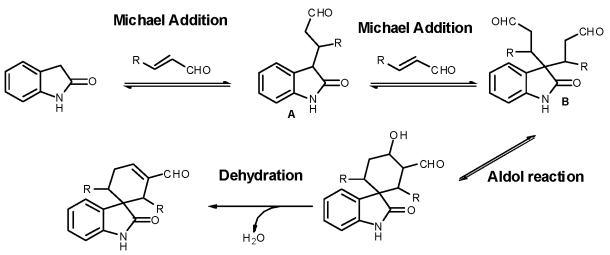
Scheme 1 Proposed reaction.

In this context, Melchiorre and Gong reported in 2009 an extremely elegant synthesis of spirooxindoles *via* an organocascade reaction with excellent yields and enantioselectivities and moderate to good diastereoselectivities.[7]

Based on these previous reports and on our previous experience working with oxindoles,[8] we disclosed that oxindoles could react with unsaturated aldehydes *via* a Michael–Michael-aldol reaction to furnish the desired spirocyclic compounds (Scheme 1).

In any case, important challenges had to be addressed. In our previous report, we disclosed that the addition of 2-substituted oxindoles to unsaturated aldehydes catalyzed by diphenylprolinol derivatives afforded the desired adducts in excellent enantioselectivities but with poor diastereoselectivities. These adducts epimerized slowly in solution, probably due to a retro-Michael reaction. These findings opened our eyes to an easy and straightforward access to spiro compounds. We envisioned that oxindole could react with unsaturated aldehydes to lead to compounds A or B. These additions would work in good enantioselectivities but probably in poor diastereoselectivities in the first step. However, the quaternary carbon formed in compound B would be non-stereogenic, and this compound would be desymmetrized by the last irreversible dehydration after the aldol reaction (Scheme 2).

To our delight, when oxindole was treated with cinnamaldehyde in the presence of catalyst **I** (20%) and benzoic acid (20%) in toluene, the reaction rendered only one product, in diastereo- and enantiopure form. It should be noticed that the use of benzoic acid is crucial for the formation of these spiro

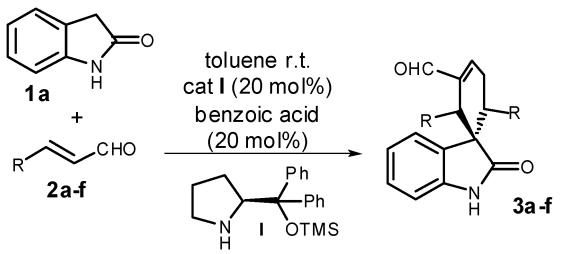


Scheme 2 Possible reaction pathway.

compounds. Without the addition of acid the reaction did not work, probably because of retro-Michael reactions previously reported. We think that the role of benzoic acid is to promote the irreversible dehydration step. The reaction worked in other solvents such as $CHCl_3$ and AcOEt, albeit with lower conversions and diastereoselectivities (see ESI†).

Then, we decided to study the scope of the reaction with a variety of α,β-unsaturated aldehydes, realizing that the reaction worked with aliphatic and aromatic unsaturated aldehydes with excellent yields (entries 1–3, Table 1). Aromatic enals rendered the final spiro compounds with excellent diastereo- and enantioselectivities. On the other hand, aliphatic enals gave lower diastereoselectivities. The reaction tolerated several functional groups like CN, NO_2 or halogens (entries 4–6; Table 1) without any loss of diastereo- or enantioselectivity.

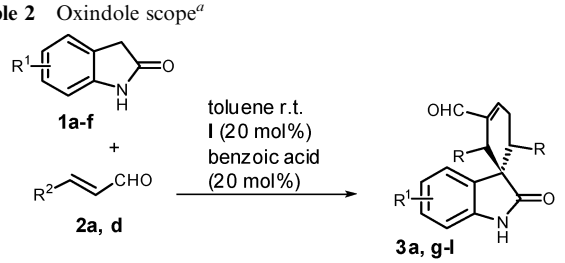
Table 1 Reaction scope[a]



Entry	R	Product	Yield[b] (%)	d.r.[c]	ee[d] (%)
1	Ph	**3a**	71	> 25 : 1	> 99
2	Me	**3b**	65	7 : 1	99
3	CO_2Et	**3c**	58	> 25 : 1	> 99
4	*p*-NO_2Ph	**3d**	82	> 25 : 1	> 99
5	*p*-CNPh	**3e**	77	> 25 : 1	> 99
6	*o*-BrPh	**3f**	53	> 25 : 1	99

[a] In a small vial, oxindole **1a** (0.25 mmol) and aldehyde **2a–g** (0.75 mmol) were stirred in the presence of catalyst **I** (20 mol%, 0.05 mmol) and benzoic acid (20 mol%, 0.05 mmol) at room temperature overnight. [b] Isolated yield after column chromatography. [c] Determined by ^{1}H-NMR of the crude mixture. [d] Determined by chiral HPLC.

Table 2 Oxindole scope[a]



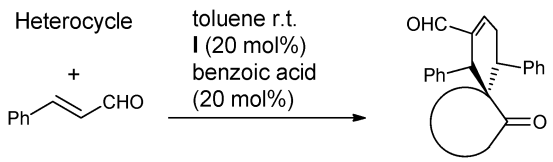
Entry	R^1	R^2	Product	Yield[b] (%)	d.r.[c]	ee[d] (%)
1	H	Ph	**3a**	71	> 25 : 1	> 99
2	5-NO_2	Ph	**3g**	62	> 25 : 1	> 99
3	5-NO_2	*p*-NO_2Ph	**3h**	90	> 25 : 1	97
4	6-Cl	Ph	**3i**	82	> 25 : 1	> 99
5	7-Cl	Ph	**3j**	90	> 25 : 1	> 99
6	1-Me	Ph	**3k**	62	15 : 1	83
7	5-Cl	Ph	**3l**	73	> 25 : 1	> 99

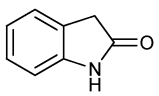
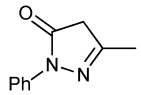
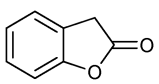
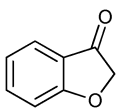
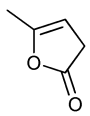
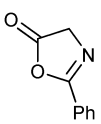
[a] In a small vial, oxindole **1a–f** (0.25 mmol) and aldehyde **2** (0.75 mmol) were stirred in the presence of catalyst **I** (20 mol%, 0.05 mmol) and benzoic acid (20 mol%, 0.05 mmol) at room temperature overnight. [b] Isolated yield after column chromatography. [c] Determined by ^{1}H-NMR of the crude mixture. [d] Determined by chiral HPLC.

Next, we decided to study the reaction with different oxindoles. To our delight, the reaction afforded in all the examples the final spirooxindole in diastereo- and enantiopure form. Only when *N*-methyl substituted oxindole was used, the enantioselectivity and diastereoselectivity decreased, showing the importance of this hydrogen in the reactivity (entry 6; Table 2). It is noteworthy that the reaction also tolerated several functional groups such as nitro (entries 2 and 3; Table 2) and halogens in different positions of the oxindole ring (entries 4, 5 and 7; Table 2).

The relative configuration was determined by means of NOE and NOESY NMR experiments (see ESI†), and the absolute configuration was assigned by means of TD-DFT calculations of the electronic circular dichroism (ECD) spectra.[9] As shown in Fig. 1 (ESI†), the spectra calculated for **3a**, assuming 1*S*, 2*S*, 6*R* configuration, match with the experimental spectra (using (*R*)-**I** as catalyst). Both relative and absolute configurations are in agreement with related aminocatalytic conjugate additions promoted by catalyst **I**.[5]

Table 3 Heterocycle scope[a]



Entry	Heterocycle	Product	Yield[b] (%)	d.r.[c]	ee[d] (%)
1		**3a**	71	> 25 : 1	> 99
2[e]		**4a**	55	> 25 : 1	> 99
3[f]		**5a**	85	> 25 : 1	93
4[f,g]		**6a**	50	6 : 1	> 99
5		**7a**	85[h]	1.2 : 1	n.d.
6[f]		**8a**	59	1.2 : 1	> 99/ > 99

[a] In a small vial, heterocycle **3–8** (0.25 mmol) and aldehyde **2a** (0.75 mmol) were stirred in the presence of catalyst **I** (20 mol%, 0.05 mmol) and benzoic acid (20 mol%, 0.05 mmol) at room temperature overnight. [b] Isolated yield after column chromatography. [c] Determined by ^{1}H-NMR of the crude mixture. [d] Determined by chiral HPLC. [e] Absolute configuration was determined with the same method as that for **3a**. [f] The relative configuration of phenyls of the compound was *trans* by means of NOE analysis. [g] Reaction run in AcOEt. [h] Only mono addition product was isolated (see ESI†).

Finally, in order to show the broad utility of this procedure we performed the reaction with several heterocyclic compounds. In all the examples, the reaction furnished the spirocompounds in good yields and enantioselectivities, with diastereoselectivities ranging from moderate (only two of the four possible diastereomers were detected in all cases) to excellent. The reaction could be performed with pyrazolones (**4a**), benzofuran-2(3*H*)-ones (**5a**), benzofuran-3(2*H*)-ones (**6a**) or even azlactones (**8a**). In all the examples the products have a *trans* relative stereochemistry between both Ph groups (NMR studies) even in **8a** where both isolated products are epimers at C1. The absolute configuration of compound **4a** was 5*S*, 6*S*, 10*R* when *S*-catalyst was used (see ESI†). This allows us to build spiro derivatives from different heterocycles giving this reaction a very broad scope in terms of applicability. It should be noticed that, when α-angelica lactone was used, only the mono addition product was isolated (entry 5; Table 3).

In conclusion, we have developed a new methodology for the construction of spirocompounds based on organocatalysis. The final products were obtained in good yields and in a total stereocontrolled fashion in most of the examples. Further studies of the scope of this new reaction with different heterocycles are ongoing in our laboratories.

We thank the Spanish Ministry of Science and Innovation (MICINN) for financial support (Project AYA2009-13920-C02-02). A.-N. R. Alba and X. Companyó are also grateful to MICINN and to the Generalitat de Catalunya, respectively, for their pre-doctoral fellowships. A. Mazzanti thanks the University of Bologna (RFO funds 2008).

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