CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200900894

One-Pot Synthesis of Pentasubstituted Cyclohexanes by a Michael Addition Followed by a Tandem Inter–Intra Double Henry Reaction

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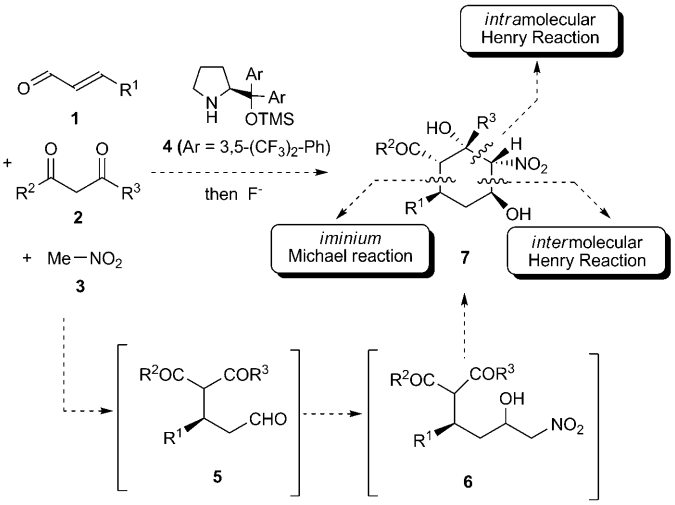
The rapid construction of structurally complex molecules from simple starting materials, aimed at the development of cascade, tandem, or multicomponent reactions,[1] is a new direction in organocatalysis.[2] These one-pot reactions[3] minimize cost, waste, and manual efforts. A large number of attractive organocatalytic cascade reactions, in which the different steps involved are promoted by the same catalyst, have been reported in the last two years.[4] The cornerstone in this field is the cascade reaction developed by Enders with aldehydes, α,β-unsaturated aldehydes, and nitroalkenes that react following an enamine–iminium–enamine sequential activation with silyl prolinol ether derivatives.[4a,b] Other attractive examples involving similar catalysts are the iminium–iminium–enamine triple activation of α,β-unsaturated aldehydes in the presence of activated methylene compounds,[4c] the tandem Michael/Henry reaction of pentane-1,5-dial and nitroalkenes,[4d] and the tandem Michael/Morita–Baylis–Hillman reaction[4e] of the Nazarov reagent with α,β-unsaturated aldehydes. This strategy has been widely applied for the synthesis of six-membered rings, which is the case for reactions of 1,3-dinitroalkanes with α,β-unsaturated aldehydes (Michael/Henry processes)[4f] and also those of aliphatic aldehydes and α,β-unsaturated aldehydes with doubly activated alkenes[4g] (Michael/Michael aldol). The creation of up to five chiral centers in a one-pot reaction confers a large synthetic relevance to these processes even though their diastereomeric excesses are usually not too high.

Multicatalytic processes that combine organocatalysts with metal catalysts have been reported,[5a–i] however, multi-organocatalytic processes remain scarce[5j] despite their presumed advantages for combining reactions of different nature. Therefore, the search for two organocatalysts that could be used in a one-pot multistep process is a question of crucial importance. Herein, we present our results regarding the synthesis of cyclohexanes with five chiral centers in one pot by using two organocatalytic species. According to the synthetic sequence shown in Scheme 1, this could be realized by the combination of proline-type organocatalysts (facilitating the iminium activation of the unsaturated aldehyde) with fluoride-type organocatalysts (promoting the double addition of nitromethane) and initiating a Michael addition of dicarbonyl compounds **2** to α,β-unsaturated aldehydes **1** followed by a tandem inter–intra double Henry reaction with nitromethane.



Scheme 1. Synthesis of pentasubstituted cyclohexanes.

To check the efficiency of the fluoride-containing promoters that give the double Henry reaction,[6] we initially studied the reaction of simple dicarbonyl compounds with nitroalkanes and a catalytic amount of TBAF as the promoter.[7] The reaction of 2,4-hexanedione did not proceed, which was

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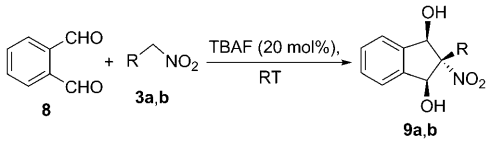
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200900894.

not unexpected due to the lower reactivity of ketones in these processes. Fortunately, treatment of dialdehyde **8** with nitromethane under neat conditions and catalyzed by 20 mol% of TBAF led to exclusive formation of **9a** in 66% isolated yield (Scheme 2). The complete stereocontrol



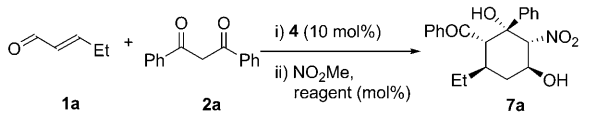
Scheme 2. Inter–intramolecular double Henry reaction. Compound **3a**: R=H; compound **3b**: R=Me; compound **9a**: R=H, yield 66%, d.r.>98:2; compound **9b**: R=Me, yield 78%, d.r.>98:2.

shown in this reaction was maintained from nitroethane. In this case, **9b** was exclusively obtained in 78% yield (Scheme 2).

On the basis of these results we reasoned that reactions of enantiomerically pure nonsymmetrical dicarbonyl compounds (thus precluding the formation of *meso* compounds) could provide optically enriched carbocycles with highly controlled diastereoselectivity. One of the best organocatalytic methods for generating this type of precursor is the Michael addition of 1,3-diketones to α,β-unsaturated aldehydes, promoted by iminium activation.[8] When the organocatalysts used in the first step were not compatible with the fluoride source required for the double Henry reaction, it would necessary to increase the amount of fluoride source in order to make possible a one-pot synthesis of highly substituted cyclohexanes (Scheme 1).

We first studied the treatment of 1,3-diphenyl-1,3-propanedione (**2a**) with (*E*)-2-pentenal (**1a**) and nitromethane by using (*S*)-2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilyloxymethyl]pyrrolidine **4**[9] as the catalyst for iminium activation and different bases for the promotion of the Henry additions (Table 1). To avoid addition of nitromethane to the α,β-unsaturated aldehyde,[10] the reaction was carried out in one pot but the nitromethane and the base were added after the Michael addition was finished. Therefore, we studied the effect of different bases on the reaction course. No reaction was observed with DABCO (Table 1, entry 1). KF, CsF, KF/alumina, and TMAF gave **7a** in low yield as a single diastereoisomer (Table 1, entries 2–5) with moderate to good enantioselectivity (58–92% enantiomeric excess (*ee*)). The use of TBAF[11] provided the best results, allowing the formation of **7a** as a single diastereoisomer in 45% yield and with almost complete enantioselectivity (99% *ee*; Table 1, entry 6). In all these cases, purification was made on neutralized silica gel. The use of other purification methods, such as Iatrobeads or Fluorisil (Table 1, entries 7 and 8), gave lower yields and the products could not be separated from the starting material. Despite a yield of only 45% for **7a**, it is worth noting some useful features of this reaction: high optical purity, simple conditions, and the molecular complexity of the resulting five-chiral-center-containing compounds.[12]

Table 1. Screening results for the reaction of aldehyde (**1a**) with 1,3-dione (**2a**).[a]



1a 2a 7a

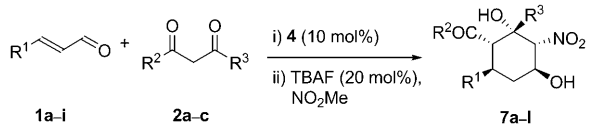
	Reagent (mol%)	d.r.[b]	Yield [%]	*ee*[c] [%]
1	DABCO (40)	–	n.r.[d]	–
2	KF (40)	>98:2	28	74
3	KF/aluminia (40)	>98:2	32	92
4	CsF (40)	>98:2	40	59
5	TMAF (20)	>98:2	17	74
6	TBAF (20)	>98:2	45	99
7	TBAF (20)	>98:2	–[e]	–
8	TBAF (20)	>98:2	–[f]	–

[a] All reactions were performed on a 0.2 mmol scale in 0.2 mL of solvent at RT for 4 h for the Michael reaction and 18 h for the inter–intramolecular Henry reaction. Abbreviations used: DABCO=1,4-diazabicyclo-[2.2.2]octane, TMAF=tetramethylammonium fluoride, TBAF=tetrabutylammonium fluoride. [b] Diastereoisomeric ratio determined by ^{1}H NMR spectroscopic analysis of the crude mixture. [c] Determined by HPLC (see the Supporting Information). [d] No reaction. [e] Purification performed with Fluorisil (see text). [f] Purification performed with silanized silica gel 60 (see text).

We then applied these optimized conditions to the reactions of nitromethane with different α,β-unsaturated aldehydes (**1a–i**)[13] and 1,3-diketones (**2a–c**). These results are summarized in Table 2. The best results for diketone **2a** ($R^2=R^3=$Ph) were obtained with **1b** ($R^1=$Me), which gave enantiomerically pure **7b** in 55% yield as a single diastereoisomer (Table 2, entry 2). A similar result was obtained when the reaction was scaled up to 2.0 mmol (Table 2, entry 2, results in parentheses). On the other hand, the enantiomer of **7b** (*ent*-**7b**) was obtained under similar conditions by using (*R*)-**4** as the catalyst (Table 2, entry 3). Alkyl-substituted α,β-unsaturated aldehydes **1c–g** with longer aliphatic chains also afforded compounds **7c–g** as single diastereoisomers in good to excellent enantioselectivities (Table 2, entries 4–8). Conditions were compatible with the presence of double bonds or aromatic groups in the aliphatic chain (Table 2, entries 9 and 10). Symmetrical dione **2b** ($R^2=R^3=$PMP) also reacted with **1b** to give **7j** with good enantio- and diastereoselectivity but in a slightly lower yield (Table 2, entry 11). Interesting results were also obtained for the reactions of nonsymmetrical diketone **2c** ($R^2=$Ph, $R^3=$Me) with crotonaldehyde **1b** and pentenaldehyde **1a**. They afforded **7k** and **7l**, respectively, which exhibited high levels of regio- and stereoselectivity (Table 2, entries 12 and 13). This indicates that the methylcarbonyl group is much more reactive than the phenylcarbonyl group towards the intramolecular attack of the α-nitro anion. Unfortunately, no reaction was observed for aromatic α,β-unsaturated aldehydes (Table 2, entry 14).

The absolute configuration of cyclohexane **7b** was unequivocally established as (1*S*,2*R*,3*R*,4*S*,6*R*) by X-ray diffrac-

Table 2. Results obtained from treatment of aldehydes (**1a–i**) with 1,3-diones (**2a–c**) and nitromethane.[a]



	R^1	R^2	R^3	Product	d.r.[b]	Yield [%]	*ee* [%][b]
1	Et	Ph	Ph	**7a**	>98:2	45	99
2	Me	Ph	Ph	**7b**	>98:2	55 (47)[d]	>99 (99)[d]
3	Me	Ph	Ph	*ent*-**7b**	>98:2	57	>99[e]
4	*n*-propyl	Ph	Ph	**7c**	>98:2	46	92
5	*n*-pentyl	Ph	Ph	**7d**	>98:2	40	>99
6	*n*-nonyl	Ph	Ph	**7e**	>98:2	40	92
7	*n*-butyl	Ph	Ph	**7f**	>98:2	43	92
8	*n*-hexyl	Ph	Ph	**7g**	>98:2	42	>99
9	(*Z*)-*n*-hex-3-enyl	Ph	Ph	**7h**	>98:2	42	94
10	$PhCH_2CH_2$	Ph	Ph	**7i**	>98:2	46	>99
11	Me	PMP	PMP	**7j**	>98:2	35	98
12	Me	Ph	Me	**7k**	>98:2	44	98
13	Et	Ph	Me	**7l**	>98:2	47	94
14	Ph	Ph	Ph	–	–	n.r.[e]	–

[a] All reactions were performed with (*S*)-**4** on a 0.2 mmol scale in 0.2 mL of solvent at 0°C (RT for entries 1 and 2) for 12 h (4 h for entries 1 and 2) for the first step and at RT for 48 h (18 h for entries 1 and 2) for the second step. PMP = *p*-methoxyphenyl. [b] Diastereoisomeric ratio determined by ^1H NMR spectroscopic analysis of the crude mixture. [c] Determined by HPLC (see the Supporting Information). [d] Reaction performed on a 2.0 mmol scale. [e] Compound (*R*)-**4** was used as the catalyst. [e] No reaction.

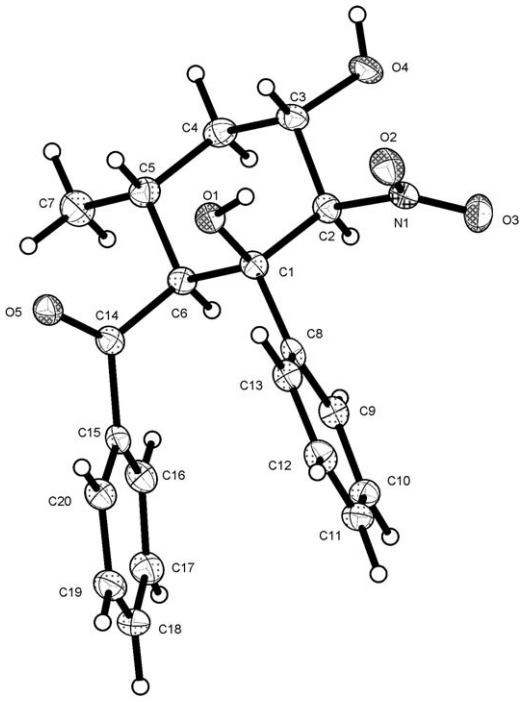
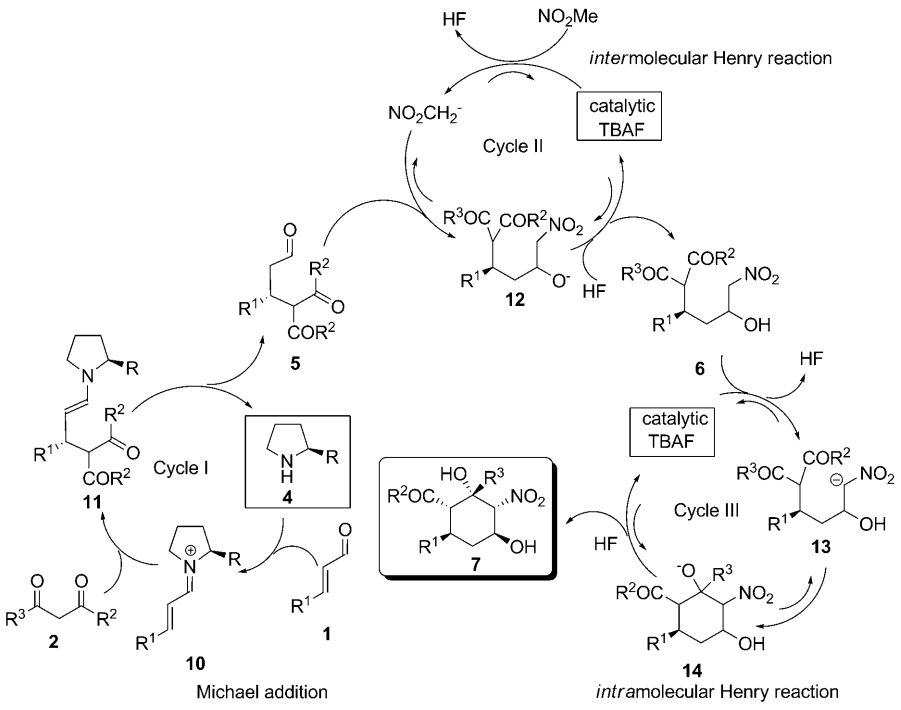


Figure 1. X-ray structure of compound **7b**.

tion studies (Figure 1).[14] The most relevant aspect of this structure is the equatorial arrangement of all substituents except for the hydroxyl group at C1, which is intramolecularly associated to the nitro group (2.06 Å). The equatorial arrangement of the bulkier substituents of the five chiral centers suggests that the formed diastereoisomer is the most stable one of all possible isomers with the same substitution pattern. Similar reaction courses and spectroscopic similarities for the rest of compounds **7** in Table 2 were observed, which suggests that they all have the same configuration and spatial arrangement of substituents.

The proposed mechanism for the reaction course of this transformation is summarized in Scheme 3. The course of the first cycle (Cycle I), that is, the Michael addition of nucleophile **2** to α,β-unsaturated aldehyde **1** activated by catalyst **4**, is well established.[8,9] The resulting adduct, **5**, reacts with the anion of nitromethane (generated by the fluoride anion) according to an intermolecular Henry reaction in Cycle II to give nitroalcohol **6**,



Scheme 3. Proposed mechanism for the one-pot reaction.

which undergoes a subsequent intramolecular Henry reaction catalyzed by the fluoride anion in Cycle III to give **7** as the final cyclohexane (Scheme 3). According to previously reported models,[8,9] the stereochemistry of the chiral center created in the first step is controlled by the configuration of catalyst **4** (in Scheme 3 the attack of nucleophile **2** on the *Re* face of planar iminium ion **10** is favored on steric grounds). Although configurational control at the four chiral centers created in the last two steps (Henry reactions) could be exerted by the chiral center created in the first step (Michael addition), the way in which such control is achieved is not evident from Scheme 3. Taking into account that the diastereoselectivity of these reactions is almost complete (>98:2 d.r.) and the structure of compounds **7** correspond to the most stable diastereoisomer (see above), we propose that the Henry reactions are not kinetically controlled and, therefore, give mixtures of all possible diastereoisomers. The complete stereoselectivity observed in these reactions must be a consequence of the reversibility of Cycles II and III in Scheme 3, which results in the formation of the thermodynamically favored product.[15] According to this explanation, the lower *ee* observed with fluoride sources other than TBAF (Table 1, entries 2–5) suggests that these sources are inducing the retro-Michael addition to a higher degree and thus decreasing the enantioselectivity.[16]

According to this mechanistic proposal, the enantioselectivity is defined in the first cycle of the one-pot reaction and, therefore, the *ee* is based on the temperature of the Michael addition. To confirm this hypothesis, the first step of the reactions shown in Table 2 were performed at room temperature (instead of 0°C), which resulted in lower enantiomeric excesses in all cases (see the Supporting Information for more details).

In conclusion, we have shown that a one-pot process that combines diarylprolinol ether **4** and TBAF results in an effective synthesis of cyclohexanes with five chiral centers from α,β-unsaturated aldehydes, β-dicarbonyl compounds, and nitromethane. This process involves a Michael addition followed by tandem inter–intramolecular Henry reactions that proceed with high enantio- and diastereoselectivity for a wide range of substrates. We are now studying the scope of the double Henry reaction of dicarbonyl compounds in an effort to prepare optically pure cycles of different sizes.

Acknowledgements

Financial support of this work by the Ministerio de Educación y Ciencia (CTQ2006-06741/BQU) is gratefully acknowledged. V.M. and J.A. thank the Ministerio de Ciencia e Innovación for a predoctoral fellowship and a "Juan de la Cierva contract", respectively. L.M. thanks the Ministerio de Educación, Política Social y Deporte for a undergraduate fellowship.

Keywords: carbocycles · diarylprolinol ethers · homogeneous catalysis · one-pot reactions · organocatalysis

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[11] These reactions required the use of 20 mol% of fluoride source because a 10 mol% was consumed by the silyl prolinol ether **4**.

[12] Lower yields were obtained if the reaction was performed in two consecutive reactions. Under these conditions, the Michael adduct was obtained in 80% yield, which suggests an average yield of around 75% for each one of the Henry reactions involved in the one-pot process.

[13] We have tried aromatic α,β-unsaturated aldehydes under different conditions and catalysts without any conversion.

[14] CCDC-718713 (**7b**) 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.

[15] Reactions with nitroethane afforded mixtures of diastereoisomers, which is expected because the presence of an additional methyl group on the ring distorts the ideal all-*trans* relationship achieved for all substituents in compounds **7**, indicating that several diastereoisomers have a similar stability.

[16] To confirm this suggestion, samples of Michael adduct **5a** (94% *ee*), which was isolated in the first step, were exposed to 40 mol% CsF. After 18 h we recovered the compound in 62% *ee*, demonstrating that the catalyst (CsF) initiated the retro-Michael reaction.

Received: April 3, 2009
Published online: June 2, 2009

Please note: Minor changes have been made to this publication in Chemistry–A European Journal Early View. The Editor.

