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Highly enantioselective organocascade intermolecular iminium/enamine Michael addition on enals†

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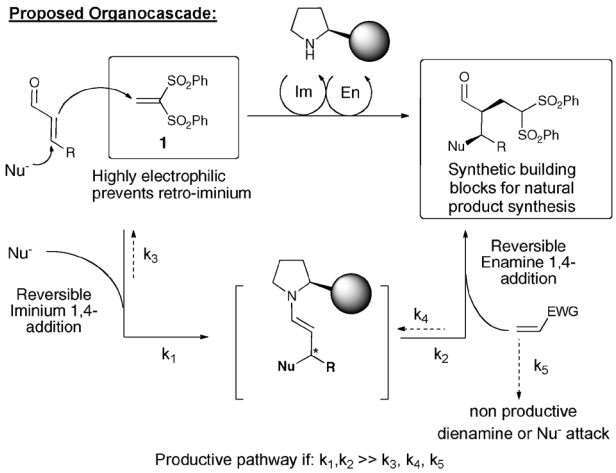
An unprecedented intermolecular iminium/enamine Michael addition on enals has been developed by taking advantage of the high reactivity of vinyl sulfones. This powerful organocascade allows for the rapid construction of attractive synthons in high enantioselectivities (typically 99% ee).

Multicomponent catalytic cascade reactions such as organocascades, mimicking the efficiency of biocatalytic processes, have recently appeared as methods of choice for the rapid construction of complex molecular structures.[1] These reactions are highly attractive given the industrial requirements for environmentally friendly reactions limiting the overall waste and time consuming operations. Among these multicomponent processes, aminocatalysis, unique because of its ability to promote multiple activation modes using a single catalyst, has come out to be a method of choice as soon as carbonyl groups are involved.[2] Notably, the combination of iminium/enamine catalysis on enals affords acyclic α,β-chiral aldehydes that are essential building blocks for natural products synthesis. In our ongoing research for the rapid construction of such challenging molecules, we were surprised by the lack of general approach for the generation of acyclic α,β-chiral aldehydes containing an alkyl group in the α-position.[3] Indeed, even though many organocascade iminium/enamine processes are able to perform an enamine C–C bond trapping in an intramolecular way, most of the corresponding acyclic methods only afford C-heteroatom bond formation.[1,4]

The lack of organocascade process creating this essential backbone by C–C bond forming reactions arises from several critical issues associated with the reactivity of most carbon bond forming electrophiles notably Michael acceptors. This challenging reaction was unsolved until now due to all the inherent problems of aminocatalyzed Michael additions depicted in Scheme 1.[5]

To obtain a powerful nucleophile—carbon addition through an olefin *via* iminium–enamine organocascade, one must first solve the compatibility issues between both steps (solvent, co-catalyst, reactant, turnover...). Probably the most problematic aspect: the iminium addition adduct should react faster with the electrophile before a possible retro-Michael addition (the entering iminium nucleophile acting as a leaving group); retro-addition that would considerably reduce the overall selectivity/efficiency of the process. Given the usual low reactivity of most Michael acceptors in enamine catalysis, this reversibility of the iminium step seems detrimental for the development of the proposed process. Other crucial point: Michael acceptors should selectively react with the intermediate aldehyde and not with the starting enal by dienamine catalysis or with the iminium nucleophile. Consequently, the control of the kinetics of the different pathways is the key for the development of the expected cascade reactions.



Scheme 1 Hypothesis and limiting issues for the development of an iminium/enamine Michael addition through an olefin.

Finally, we recently disclosed the important observation that if two sterically different groups are present in the β-position of an aldehyde there were conflicting interactions between the incoming Michael acceptor, the substrate and the catalyst leading to decrease in both reactivity and enantioselectivities (substrate *vs.* catalyst control).[6] This particular behaviour could render such reaction, where bulky groups are entered in the β-position, even harder to perform and to control.

Vinyl sulfones introduced recently in our group for enamine catalysis present several interesting key features.[7] Compared to most Michael acceptors, they appear to be highly reactive in many different conditions (1–2 hour reactions) using only a

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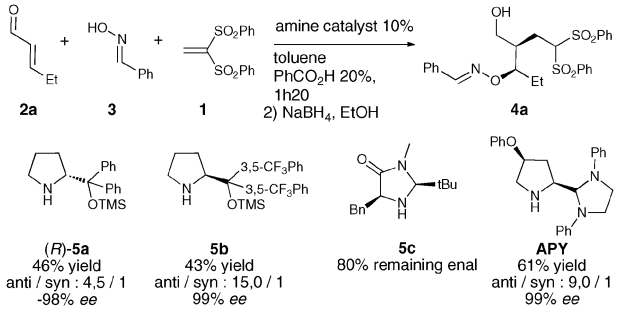
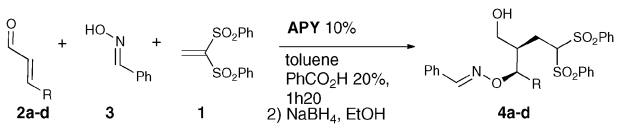


Scheme 2 Catalysts screening for the hydro-alkylation of enals.

slight excess of aldehyde (1.1 eq). In addition, this sulfonyl group can easily be used as a formal alkyl chain in further transformations rendering it highly useful for its future application in total synthesis or in Diversity Oriented Synthesis.[8] We thus postulated that the exceptional reactivity of bis-vinyl sulfone **1** would allow us to overcome the problem associated with other Michael acceptors. The transient aldehyde should react irreversibly and rapidly under kinetic control with the sulfone avoiding any detrimental epimerization. Herein we describe an unprecedented organocascade intermolecular iminium/enamine Michael addition through an olefin leading to the synthesis of highly attractive synthons for further synthetic applications.

To validate our hypothesis we first focused our attention on the hydro-alkylation of pentenal **2a** using benzaldoxime **3** as nucleophile (Scheme 2).[9] This reaction would lead to highly attractive chiral 1,3 diols. Gratifyingly, performing the domino reaction (all the reactant/catalyst added all at once), the expected cascade product was obtained in moderate to good yields depending on the catalyst (MacMillan imidazolidinone was the only catalyst inefficient here). The best result was obtained using only 10 mol% of aminal pyrrolidine (**APY**) with a good 61% yield together with good stereoselectivities (9/1 dr, 99% ee).[7c,7h] This demonstrates the high potential of **APY** for organocascade reactions where both iminium and enamine catalysis are involved. The observed high yield, perfect enantioselectivity and short reaction time confirm our initial hypothesis of global reaction rate acceleration by the entering electrophile. Decreasing the temperature to 0 °C slightly reduced the yield (52% yield) while not increasing the stereoselectivities (result not shown). This is probably due to the fact that reduced temperature disfavours the kinetic differences between productive and unproductive pathways.

Table 1 Scope of the hydro-alkylation of enals



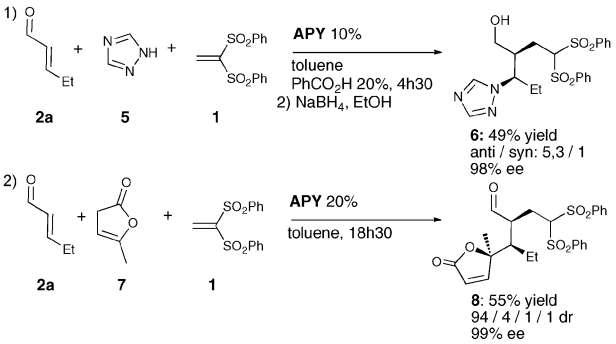
Entry	R	Yield[a] (%)	dr (anti/syn)[b]	ee[c] (%)
1	Me	**4b** : 58	9/1	99
2	Et	**4a** : 61	9/1	99
3	nC_7H_{15}	**4c** : 58	11,5/1	99
4	*i*Pr	**4d** : 30[d]	nd	nd

[a] Yield of the isolated product. [b] Determined by ^{1}H NMR analysis on the crude material. [c] Determined by chiral Supercritical Fluid Chromatography for the major diastereoisomer. [d] NMR yield determined by ^{1}H NMR.

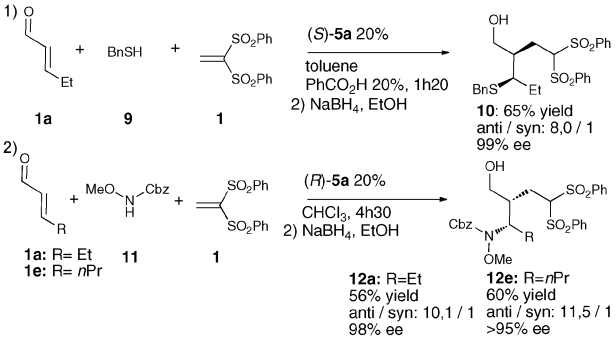
To fully explore this remarkable transformation, we continued investigating the scope by testing the hydroxy-alkylation to a small family of enals (Table 1). Different linear chains from methyl to C_7H_{15} could be used in this process without any influence on the overall selectivity of the reaction (58–61% yield, 9 : 1 to 11,5 : 1 dr, 99% ee). When increasing the steric requirement of the R functionality with an *i*Pr, a dramatic loss in reactivity was observed leading to an inseparable mixture of products while cinnamaldehyde did not react at all.

Despite the creation of 1,3 diols, we screened a variety of diverse nucleophiles that would render this approach even more attractive. As a general trend the organocascade tolerated a wide variety of heteroatoms or carbon nucleophiles. These nucleophiles can be divided into three groups. First of all, triazole **5** and Angelica lactone **7** did react in the **APY** catalyzed process leading efficiently to the cascade product in perfect enantioselectivities (98–99% ee, Scheme 3).[10] Remarkably, the product of addition of Angelica lactone containing three contiguous stereocenters one being tetra substituted was obtained almost as a single diastereoisomer (eqn (2)).

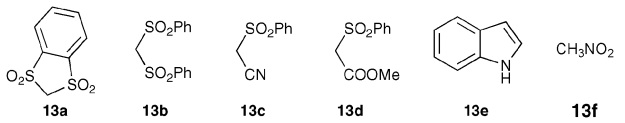
The second class of nucleophiles consists of thiol and nitrogen nucleophiles that failed to react using **APY** (Scheme 4).[11] Indeed, under these conditions, the only product observed was the one arising from the addition of the iminium nucleophile to the vinyl sulfone. This indicates that **APY** does not catalyze the required iminium reaction. Fortunately, turning to diphenyl prolinol silyl ether **5a** and adding the electrophile after a short iminium reaction time, the efficiency



Scheme 3 Organocascade triazole-alkylation and double alkylation of enals.



Scheme 4 Organocascade sulfa-alkylation and amino-alkylation.



Scheme 5 Class 3 nucleophiles: no organocascade.

of the organocascade was recovered. Good to excellent enantioselectivities (95–99% ee) were obtained in this process giving rise to highly valuable synthons such as **12e**, a 1,3 amino alcohol that should be applied as a precursor of indolizidine.[12]

Finally, several carbon nucleophiles failed to give organocascade products and are classified in class 3 (Scheme 5).[13] They all have the same particularity of giving slow conversion in the iminium catalysis. This can explain the bad results observed in organocascade. Indeed, if the iminium reaction is rather slow, it is possible that the retro-Michael occurs faster than the electrophilic trapping. This reduces the amount of enamine present in the mixture and increases potential side reactions. Furthermore, increasing the steric hindrance notably with compounds **13a–13e** probably slows down the enamine reaction.

This hypothesis of fast retro-Michael compared to electrophilic trapping was confirmed when performing a two-pot reaction with compounds **13b–13d**. Even though the electrophile was added after isolation of the transient aldehyde, an unidentified mixture of compounds was obtained, probably arising from initial retro-iminium and subsequent product decompositions. The importance of the kinetic stability of the transient iminium adduct was further confirmed when performing the enamine trapping with racemic iminium adducts derived from Angelica lactone where a resolution of the aldehyde was observed.[14]

In conclusion we have developed an unprecedented intermolecular iminium/enamine Michael addition on enals taking advantage of the high reactivity of vinyl sulfones. This powerful organocascade allows for the rapid construction of highly attractive synthons in high enantioselectivities (typically 99% ee). The described study has allowed for a clear understanding of both reactivity and selectivity issues. We are convinced that it will find further applications in total synthesis and in the development of other organocascade reactions.

Notes and references

1 For selected review on organocascade reactions see: (*a*) A. M. Walji and D. W. C. MacMillan, *Synlett*, 2007, 1477; (*b*) D. Enders, C. Grondal and M. R. M. Hüttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570; (*c*) G. Guillena, D. J. Ramon and M. Yus, *Tetrahedron: Asymmetry*, 2007, **18**, 693; (*d*) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, 2010, **2**, 167.

2 Selected reviews on aminocatalysis: (*a*) S. Bertelsen and K. A. Jørgensen, *Chem. Soc. Rev.*, 2009, **38**, 2178; (*b*) D. W. C. MacMillan, *Nature*, 2008, **455**, 304; (*c*) P. Melchiorre, M. Marigo, A. Carlone and G. Bartoli, *Angew. Chem., Int. Ed.*, 2008, **47**, 6138; (*d*) P. I. Dalko, *Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, 2007; (*e*) A. Erkkilae, I. Majander and P. M. Pihko, *Chem. Rev.*, 2007, **107**, 5416.

3 For recently appeared examples without incorporation of heteroatoms (without potential leaving groups) see: (*a*) Y. Chi, S. T. Scroggins and J. M. J. Fréchet, *J. Am. Chem. Soc.*, 2008, **130**, 6322; (*b*) M. Rueping, K. L. Haack, W. Ieawsuwan, H. Sùnden, M. Blanco and F. R. Schoepke, *Chem. Commun.*, 2011, **47**, 3828; (*c*) S.-K. Xiang, B. Zhang, L.-H. Zhang, Y. Cui and N. Jiao, *Chem. Commun.*, 2011, **47**, 5007.

4 Intermolecular iminium/enamine cascade reactions on enals: (*a*) Y. Huang, A. M. Walji, C. H. Larsen and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2005, **127**, 15051; (*b*) M. Marigo, T. Schulte, J. Franzen and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2005, **127**, 15710; (*c*) J. Yang, W. M. T. Hechavarria Fonseca and B. List, *J. Am. Chem. Soc.*, 2005, **127**, 15036; (*d*) H. Jiang, J. B. Nielsen, M. Nielsen and K. A. Jørgensen, *Chem.–Eur. J.*, 2007, **13**, 9068; (*e*) P. Galzerano, F. Pesciaioli, A. Mazzanti, G. Bartoli and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2009, **48**, 7892; (*f*) B. Simmons, A. M. Walji and D. W. C. MacMillan, *Angew. Chem., Int. Ed.*, 2009, **48**, 4349; (*g*) C. Appayee and S. E. Brenner-Moyer, *Org. Lett.*, 2010, **12**, 3356.

5 Selected reviews on aminocatalyzed 1,4 addition: (*a*) S. Sulzer-Mossé and A. Alexakis, *Chem. Commun.*, 2007, 3123; (*b*) D. Almasi, D. A. Alonso and C. Najera, *Tetrahedron: Asymmetry*, 2007, **18**, 299; (*c*) S. B. Tsogoeva, *Eur. J. Org. Chem.*, 2007, 1701; (*d*) D. Roca-Lopez, D. Sadaba, I. Delso, R. P. Herrera, T. Tejero and P. Merino, *Tetrahedron: Asymmetry*, 2010, **21**, 2561.

6 A. Quintard, A. Alexakis and C. Mazet, *Angew. Chem., Int. Ed.*, 2011, **50**, 2354.

7 (*a*) S. Mossé and A. Alexakis, *Org. Lett.*, 2005, **7**, 4361; (*b*) Q. Zhu and Y. Lu, *Org. Lett.*, 2008, **10**, 4803; (*c*) A. Quintard, C. Bournaud and A. Alexakis, *Chem.–Eur. J.*, 2008, **14**, 7504; (*d*) Q. Zhu, L. Cheng and Y. Lu, *Chem. Commun.*, 2008, 6315; (*e*) A. Landa, M. Maestro, C. Masdeu, A. Puente, S. Vera, M. Oiarbide and C. Palomo, *Chem.–Eur. J.*, 2009, **15**, 1562; (*f*) A. Quintard and A. Alexakis, *Chem.–Eur. J.*, 2009, **15**, 11109; (*g*) S. Sulzer-Mossé, A. Alexakis, J. Mareda, G. Bollot, G. Bernardinelli and Y. Filinchuk, *Chem.–Eur. J.*, 2009, **15**, 3204; (*h*) A. Quintard, S. Belot, E. Marchal and A. Alexakis, *Eur. J. Org. Chem.*, 2010, 927; (*i*) A. Quintard and A. Alexakis, *Chem. Commun.*, 2010, **46**, 4085; (*j*) Q. Zhu and Y. Lu, *Chem. Commun.*, 2010, **46**, 2235; (*k*) A. Quintard and A. Alexakis, *Adv. Synth. Catal.*, 2010, **352**, 1856; (*l*) C. Bournaud, E. Marchal, A. Quintard, S. Sulzer-Mossé and A. Alexakis, *Tetrahedron: Asymmetry*, 2010, **21**, 1666; (*m*) J. Xiao, Y.-L. Liu and T.-P. Loh, *Synlett*, 2010, 2029; (*n*) P. J. Chua, B. Tan, L. Yang, X. Zeng, D. Zhu and G. Zhong, *Chem. Commun.*, 2010, **46**, 7611; (*o*) S. A. Moteki, S. Xu, S. Arimitsu and K. Maruoka, *J. Am. Chem. Soc.*, 2010, **132**, 17074; (*p*) A. Quintard and A. Alexakis, *Org. Biomol. Chem.*, 2011, **9**, 1407; (*q*) J. Xiao, Y.-P. Lu, Y.-L. Liu, P.-S. Wong and T.-P. Loh, *Org. Lett.*, 2011, **13**, 876.

8 Recent reviews on the use of sulfones in organocatalysis: (*a*) M. Nielsen, C. B. Jacobsen, N. Holub, M. W. Paixao and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2010, **49**, 2668; (*b*) Q. Zhu and Y. Lu, *Aust. J. Chem.*, 2009, **62**, 951; (*c*) A.-N. R. Alba, X. Companyo and R. Rios, *Chem. Soc. Rev.*, 2010, **39**, 2018.

9 (*a*) S. Bertelsen, P. Dinér, R. L. Johansen and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2007, **129**, 1536; (*b*) N. R. Andersen, S. G. Hansen, S. Bertelsen and K. A. Jørgensen, *Adv. Synth. Catal.*, 2009, **351**, 3193.

10 For the iminium catalyzed addition of triazole: (*a*) P. Dinér, M. Nielsen, M. Marigo and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2007, **46**, 1983; For the iminium catalyzed addition of Angelica lactone: (*b*) A. Quintard, A. Lefranc and A. Alexakis, *Org. Lett.*, 2011, **13**, 1540.

11 For the iminium catalyzed addition of thiol: ref. 4(*b*); for the iminium catalyzed addition of **11**: (*a*) Y. K. Chen, M. Yoshida and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2006, **128**, 9328.

12 X. Pu and D. Ma, *J. Org. Chem.*, 2003, **68**, 4400.

13 For pioneering iminium addition of **13a**: (*a*) A. Landa, A. Puente, J. I. Santos, S. Vera, M. Oiarbide and C. Palomo, *Chem.–Eur. J.*, 2009, **15**, 11954; **13b**: (*b*) J. L. Garcia Ruano, V. Marcos and J. Aleman, *Chem. Commun.*, 2009, 4435; (*c*) A.-N. Alba, X. Companyo, A. Moyano and R. Rios, *Chem.–Eur. J.*, 2009, **15**, 11095; **13e**: (*d*) J. F. Austin and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2002, **124**, 1172; **13f**: (*e*) N. Halland, R. G. Hazell and K. A. Jørgensen, *J. Org. Chem.*, 2002, **67**, 8331. The addition of **13c** and **13d** was precedently unreported in the literature.

14 See ESI† for details.