Organocatalytic Domino Mannich Aza-Michael Reactions towards the Stereoselective Synthesis of Highly Substituted Pipecolic Esters

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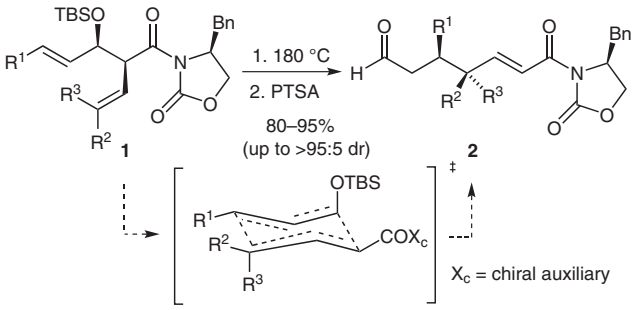
Abstract: Readily available chiral 7-oxo-2-enimides have been converted into highly substituted pipecolic esters in moderate yields and excellent stereocontrol through a proline-catalyzed domino Mannich aza-Michael reaction.

Key words: aza-Michael reaction, Cope rearrangement, domino reaction, Mannich reaction, organocatalysis, pipecolic ester

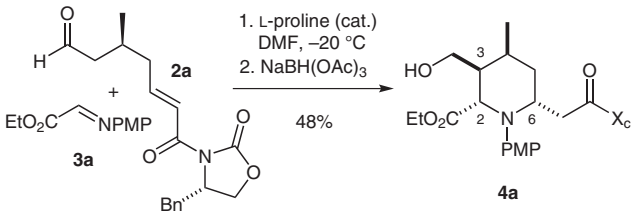
In recent years we have investigated the silyloxy-Cope rearrangement of 1,5-hexadienes **1** embedded in a *syn*-aldol structure giving rise to chiral 7-oxo-2-enimides **2** in good yields and typically excellent diastereoselectivity (Scheme 1).[1] On the basis of their unique functional group pattern we have successfully employed these products for the stereoselective preparation of a broad range of diverse structural motifs such as heterocycles, carbocycles, terpenes, and polyol chains.[2]



Scheme 1

With the advent of asymmetric organoenamine catalysis that allows for the highly enantioselective α-functionalization of aldehydes we wondered whether we could employ the Cope products as substrates in organocatalytic C–C bond-forming reactions.[3] We now wish to report that chiral 7-oxo-2-enimides **2** containing an aldehyde moiety tethered to an α,β-unsaturated imide undergo proline-catalyzed domino Mannich aza-Michael reactions[4] with glyoxyl imines **3** furnishing highly substituted pipecolic esters **4** in moderate yields and typically excellent stereocontrol.

Barbas and co-workers had established that proline-catalyzed Mannich reactions of aldehydes and glyoxyl imines furnished α-amino esters with high degrees of diastereo- as well as enantiocontrol.[5] Building on this precedence we treated Cope product **2a** with *N*-PMP-imino ethyl glyoxylate (**3a**) and L-proline (20 mol%) in DMF for 20 hours at –20 °C and obtained after subsequent aldehyde reduction 48% of pipecolic ester **4a** as a single stereoisomer (Scheme 2).[6] This domino-type[7] reaction comprised an initial proline-catalyzed Mannich reaction followed by a subsequent aza-Michael addition of the in situ formed amine onto the α,β-unsaturated imide moiety. Small amounts (<5%) of the corresponding uncyclized Mannich product were also isolated.



Scheme 2

For the unambiguous assignment of product configuration **4a** was converted into the corresponding acetate **5a** which gave crystals suitable for crystallographic analysis[8] proving the 2,3-*trans* and 2,6-*cis* configuration within the piperidine ring (Figure 1). This analysis corresponds to the expected highly *syn*-selective Mannich reaction[5] and an aza-Michael reaction onto a preaxially oriented conjugate double bond as had been found in other aza-Michael

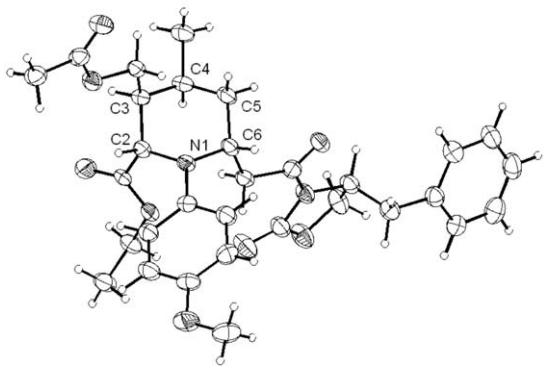


Figure 1 X-ray crystal structure of acetate **5a** (50% ellipsoids)

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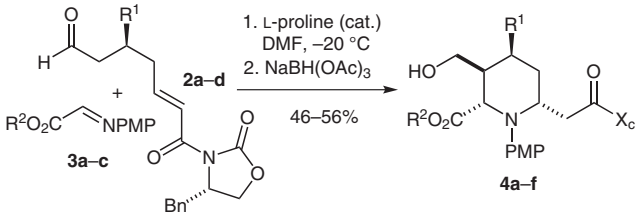
additions with these substrates previously.[2d] Interestingly, the piperidine ring accommodates the 2- and 6-substituents in pseudoaxial positions which are bent away from each other in order to avoid significant 1,3-diaxial interactions.

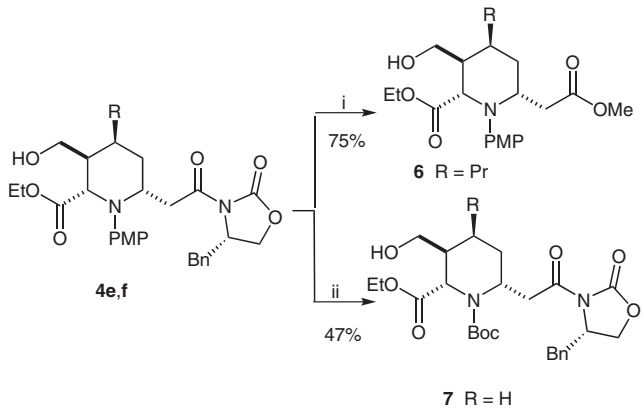
In order to determine the scope and limitations of this new domino process we subsequently reacted various 7-oxo-2-enimides **2a–d** with glyoxyl imines **3a–c** according to this protocol and obtained the desired highly substituted pipecolic esters **4a–f** (Scheme 3) in generally moderate yields and mostly as single stereoisomers (Table 1). In select cases small amounts (<5%) of the corresponding 6-epimers were additionally formed but could be readily removed by chromatography. Less reactive imines failed to furnish the piperidines according to this scheme because the initial Mannich reaction did not proceed.



Scheme 3

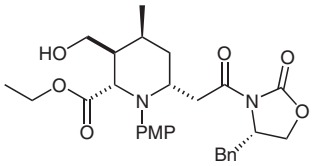
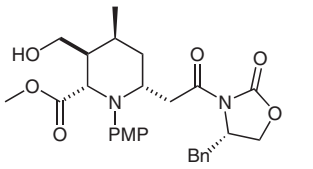
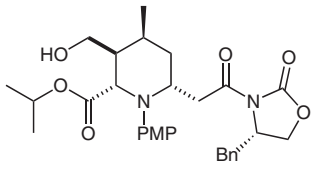
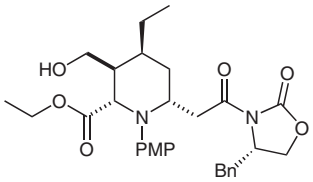
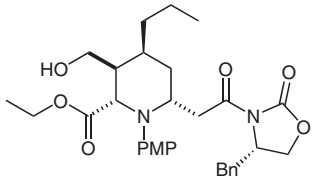
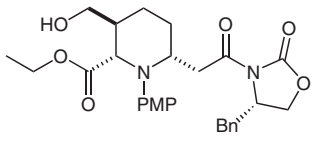
When the reaction of **2a** and **3a** was repeated with D-proline as organocatalyst a 2:1-mixture of diastereomers with respect to the 6-position was obtained. Both of the diastereomers shared the opposite configuration at the 2- and 3-position within the piperidine ring (relative to the L-proline-catalyzed reaction) indicating that the initial Mannich reaction is a catalyst-controlled event whereas the subsequent aza-Michael addition apparently proceeds under substrate control.

The chiral auxiliary may be readily cleaved off with magnesium methoxide as was demonstrated for pipecolic ester **4e** giving rise to methyl ester **6** in good yield (Scheme 4). Likewise the PMP group in **4f** was exchanged for a Boc group through an oxidative cleavage with CAN followed by an in situ Boc protection to yield pipecolic ester **7** (Scheme 4).



Scheme 4 *Reagents and conditions*: (i) MeMgCl, MeOH, CH_2Cl_2, 0 °C; (ii) (a) CAN, H_2O–MeCN, 0 °C to r.t.; (b) Boc_2O, DMAP.

Table 1 L-Proline-Catalyzed Domino Mannich Aza-Michael Reactions towards Pipecolic Esters **4a–f**[a]

Entry	Product	Yield (%)[b]
1	 **4a**	48
2	 **4b**	56
3	 **4c**	54
4	 **4d**	49
5	 **4e**	51
6	 **4f**	46

[a] Reagents and conditions: 7-oxo-2-enimide **2** (1 equiv), imine **3** (1.5 equiv), 0.3 M in DMF, –20 °C, 20 h; then $NaBH(OAc)_3$ (3.0 equiv) in EtOAc, 0 °C, 15 min.
[b] Isolated yield of purified product.

In conclusion, we have established a novel organocatalytic domino process for the rapid synthesis of highly substituted pipecolic esters in just one step. Two new σ bonds and three new stereogenic centers are formed with excellent stereocontrol. Further work along these lines will be reported in due course.

Acknowledgment

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Libya). Wacker AG and Evonik AG are thanked for the generous donation of chemicals.

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(6) **Typical Experimental Procedure**: To a stirred solution of *N*-PMP-protected α-imino ethyl glyoxalate (**3a**; 47 mg, 0.228 mmol) and L-proline (3.5 mg, 20 mol%) in DMF (0.5 mL) at –20 °C was added aldehyde **2b** (R^1 = Et; 50 mg, 0.152 mmol) and the stirring was continued for 20 h at –20 °C. The reaction mixture was then diluted with EtOAc (1 mL) and added to a solution of sodium triacetoxyborohydride (3 equiv) in EtOAc at 0 °C. After the reaction mixture had been stirred for further 15 min, the reaction was quenched with phosphate buffer (pH 7) and the crude product was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by flash column chromatography (PE–EtOAc, 1:2 → 1:1) to afford the product **4d** (40 mg, 49%) as a viscous oil, which was recrystallized from EtOAc–PE; mp 50 °C; $[\alpha]_D^{21}$ +15.8° (*c* = 0.07, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.2 Hz, 3 H, Me), 1.14 (t, *J* = 7.2 Hz, 3 H, Me), 1.31–1.88 (m, 6 H, 4-CH, 5-CH_2, CH_2CH_3, OH), 2.43 (m, 1 H, 3-CH), 2.60 (dd, *J* = 13.5, 9.6 Hz, 1 H, CH-benzyl), 3.10 (dd, *J* = 17.7, 3.0 Hz, 1 H, CHCO), 3.21 (dd, *J* = 13.5, 3.0 Hz, 1 H, CH-benzyl), 3.53 (dd, *J* = 17.7, 10.0 Hz, 1 H, CHCO), 3.61–3.72 (m, 2 H, CH_2OH), 3.73 (s, 3 H, MeO), 4.09–4.14 (m, 4 H, OCH_2CH_3, 5″-CH_2), 4.40–4.46 (m, 1 H, 6-CH), 4.50 (d, *J* = 4.2 Hz, 1 H, 2-CH), 4.62 (m_c, 1 H, 4″-CH), 6.81 (d, *J* = 8.8 Hz, 2 H, phenyl-CH), 7.04 (d, *J* = 8.8 Hz, 2 H, phenyl-CH), 7.14 (d, *J* = 6.8 Hz, 2 H, phenyl-CH), 7.25–7.29 (m, 3 H, phenyl-CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.79 (Me), 14.22 (Me), 24.01 (CH_2CH_3), 27.03 (C_4), 31.71 (CH_2CO), 32.04 (C_5), 37.99 (benzyl-C), 42.55 (C_3), 49.59 (C_6), 55.24 (C''_4), 55.97 (OMe), 59.86 (C_2), 59.97 (CH_2CO), 61.06 (CH_2OH), 66.22 (C''_5), 114.5, 118.7, 127.4, 129.05, 129.4, 135.4, 142.3, 153.7 (phenyl-C), 153.2 (CO-urethane), 172.4 (CO-amide), 174.0 (CO-ester). IR (film): 3500 (OH), 3029, 2959, 2875, 2833 (CH), 1785 (CO-urethane), 1720 (CO-ester), 1695 (CO-amide), 1605, 1512, 1454, 1384, 1351 (Me, CH_2), 1244, 1180, 1087, 1043, 970, 941, 788, 702, 626 cm^{-1}. MS (ESI, Na): *m*/*z* = 539.2 $[M + H]^+$, 561.2 $[M + Na]^+$. Anal. Calcd for $C_{30}H_{38}N_2O_7$ (538.63): C, 66.90; H, 7.11; N, 5.20. Found: C, 66.46; H, 7.00; N, 5.19.

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(8) The structural data have been deposited with the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 686773, which contains the supplementary crystallographic data for this paper.