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ORIGINAL PAPER

Assessment of non-standard reaction conditions for asymmetric 1,3-dipolar organocatalytic cycloaddition of nitrone with α,β-unsaturated aldehydes

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Non-standard experimental conditions can often enhance organocatalytic reactions considerably. The current study explores the effectiveness of a range of non-standard reaction conditions for the asymmetric organocatalytic 1,3-dipolar cycloaddition of a nitrone with α,β-unsaturated aldehydes. The influence of ionic liquids, high-pressure conditions, ultrasound, microwave irradiation and ball-milling was tested as well as the flow process. Because of the low reactivity of the nitrone and unsaturated aldehydes in the 1,3-dipolar cycloaddition, cycloadducts were isolated in only moderate yields from the majority of experiments. However, high diastereo- and enantioselectivities were observed in ionic liquids under solvent-free conditions and in the flow reactor.

Keywords: dipolar cycloaddition, ball-milling, flow reactor, ionic liquids, microwave, ultrasound

Introduction

Dipolar cycloaddition is a powerful synthetic tool for the formation of many biologically active compounds (Kobayashi & Jörgensen, 2002). Azides, nitrones and azomethine ylides are some of the typical 1,3-dipoles for the synthesis of structures with biological relevance (Pellissier, 2007). 1,3-Dipolar cycloadditions of nitrones with alkenes lead to isoxazolidines with up to three new contiguous stereocentres. These compounds are useful building blocks for the synthesis of various biologically active compounds, such as amino acids, alkaloids, pharmaceuticals (inhibitors of HIV, HSV, HCV) (Najera & Sansano, 2009), agrochemicals and natural compounds, e.g. hobartine (Gribble & Barden, 1985) and anisomycin (Ballini et al., 1992).

Apart from the traditional Lewis acid-catalysed dipolar cycloadditions (Xing & Wang, 2012; Stanley & Sibi, 2008) a variety of organocatalysed cycloadditions has recently been developed (Pellissier, 2012). In the first example of stereoselective organocatalytic 1,3-dipolar cycloaddition, Jen et al. (2000) showed that chiral imidazolidinones activated α,β-unsaturated aldehydes through the formation of chiral iminium salts and these salts acted as dipolarophiles in the cycloaddition with nitrones. Imidazolidinones also catalyse several other variants of 1,3-dipolar cycloadditions (Selim et al., 2012). Puglisi et al. (2004) used a PEG-immobilised imidazolidinone as a catalyst in dipolar cycloadditions. Ionically-tagged MacMillan's imidazolidinone was also an effective catalyst for the cycloaddition of nitrones with crotonaldehyde. The catalyst was re-used in five reaction cycles without any deleterious effect on the reaction (Shen et al., 2012). Recycling was also possible with the imi-

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dazolidinone catalyst attached to magnetic nanoparticles (Pagoti et al., 2013). Apart from imidazolidinones, pyrrolidine derivatives also act as suitable catalysts for some dipolar cycloadditions. Nitrones underwent 1,3-dipolar cycloadditions with 1-cycloalkene-1-carboxaldehydes catalysed by a variety of pyrrolidinium salts to afford fused *exo*-bicyclic isoxazolidines (Karlsson & Högberg, 2002, 2003). Rios et al. (2007) described the dipolar cycloadditions of nitrones with α,β-unsaturated aldehydes catalysed by diphenylprolinol derivatives which provided moderate yields and high diastereo- and enantioselectivity. The pyrrolidine-derived, Jörgensen–Hayashi organocatalyst was also used in the regiospecific, highly chemo-, diastereo- and enantioselective one-pot cascade synthesis of tricyclic bis-oxazolidines (Vesely et al., 2008). The triflate salt of the Jörgensen–Hayashi catalyst provided the corresponding isoxazolidines with good yields and high diastereoselectivities and enantioselectivities (Chow et al., 2007).

Other organocatalysts were also useful. For instance, camphor-derived hydrazides catalysed the asymmetric cycloadditions of nitrones with α,β-unsaturated aldehydes, but the diastereoselectivities were lower than those achieved with MacMillan's imidazolidinones. On the other hand, the use of hydrazide catalysts afforded access to the *exo* cycloadduct, which was otherwise difficult to obtain from acyclic dipolarophiles (Lemay et al., 2007). The cycloadditions of nitrones with nitroolefins catalysed with chiral thiourea-derived catalysts proceeded with good yields, excellent diastereoselectivities and high enantioselectivities (Du et al., 2008). Chiral phosphoramide-catalysed 1,3-dipolar cycloadditions of diaryl nitrones with ethyl vinyl ether afforded the corresponding products with good yields (Jiao et al., 2008). An asymmetric formal [3 + 2] nitrone cycloaddition using *N*-Boc- and *N*-Cbz-protected *N*-hydroxy-α-amido sulphones as nitrone precursors with glutaconates was catalysed with cinchona alkaloid-derived ammonium salts (Gioia et al., 2009). A cinchona alkaloid-derived catalyst was used in a domino reaction of nitroolefins with 2-allyl malonates involving Michael addition and cyclisation (Raimondi et al., 2010). 1,3-dipolar cycloadditions of various nitrones to crotonaldehyde can also be catalysed by hybrid diamines obtained from (*S*)-BINAM and amino acids (Weseliński et al., 2009, 2011, 2012). Organocatalytic dipolar cycloadditions are also useful reaction steps in domino sequences (Zhu et al., 2009; Tan et al., 2010; Chua et al., 2010).

A considerable disadvantage of organocatalytic dipolar cycloadditions is the long reaction times needed to obtain products with reasonable yields. In particular, the reactions of nitrones often extend over several days. Almost all the 1,3-dipolar cycloadditions of nitrones described were carried out in organic solvents or in a mixture of organic solvents and H_2O. The use of ionic liquids, microwave irradiation or other non-standard experimental techniques can have a positive impact on organocatalytic reactions (Toma et al., 2011; Hernández & Juaristi, 2012; Chauhan & Chimni, 2012; Bruckmann et al., 2008). Accordingly, it was decided to examine the effects of several non-standard experimental conditions on organocatalysed dipolar cycloadditions. This paper details the results of the study of organocatalytic 1,3-dipolar cycloadditions of a prototypical nitrone to unsaturated aldehydes in ionic liquids. In addition, non-conventional activation methods such as high pressure, solvent-free conditions, microwave irradiation, ultrasound and flow techniques were evaluated.

Experimental

NMR spectra were recorded on a Varian NMR System 300 (USA) instrument (300 MHz for ^{1}H NMR, 75 MHz for ^{13}C NMR). Chemical shifts are given in δ relative to TMS. Flash chromatography (FC) was performed on silica gel 60 Å, 0.035–0.070 nm, from Fluka (Germany). Thin-layer chromatography (TLC) was performed on Merck (Germany) TLC-plates silica gel 60, F-254. Enantiomeric excesses were determined by HPLC on a Chiralcel AD-H (Daicel, USA) column using hexane/*i*-PrOH as a mobile phase and UV detection. Microwave reactions were performed in a Microwave Synthesis Reactor Monowave 300 (Anton Paar, Austria; IR sensor for temperature control, sealed vessel), the sonochemical reaction proceeded in an ultrasonic cleaning bath Kraintek 6 (Slovakia; 20 kHz) and a vibrational ball mill MM400 (Retsch, Germany; 20 Hz) was used for the solvent-free reactions. *N*-benzylidene-1-phenylmethanamine oxide (*I*) was prepared according to the procedure described in the literature (Mečiarová et al., 2013). Catalysts Cat-I, Cat-III, Cat-V–Cat-VIII were purchased from Sigma–Aldrich (USA). Cat-II and Cat-IV were prepared according to the literature (Chow et al., 2007; Jen et al., 2010).

Procedure for synthesis of (3R,4S,5R)-2-benzyl-4-formyl- sb5-methyl-3-phenylisoxazolidine (endo-IIIa)

Procedure for the reaction in CH_2Cl_2: the catalyst (0.05 mmol) was added to the stirred solution of nitrone *I* (53 mg; 0.25 mmol) in CH_2Cl_2. The mixture was cooled to 5 ℃ or heated to 40 ℃ then crotonaldehyde (*IIa*; 60 μL, 0.75 mmol) was added to the flask drop-wise. A further amount of *IIa* was added to the mixture at 0.5 h intervals (5 × 20 μL; 0.25 mmol). The mixture was stirred for the time given in Table 2, then concentrated under vacuum and the residue was analysed by ^{1}H NMR spectroscopy to establish the *endo*/*exo* ratio. The crude product was then purified by flash chromatography (SiO_2, hexane/AcOEt (φ_r = 7 : 3) to afford the product as an oil.

Table 1. Physical and spectral data of prepared compounds

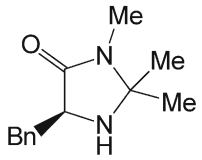
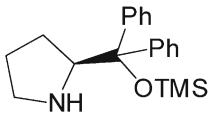
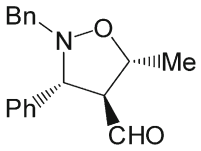
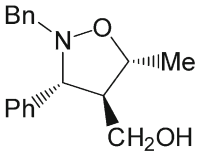
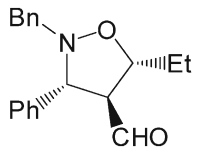
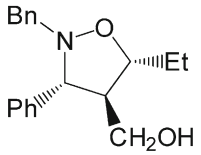
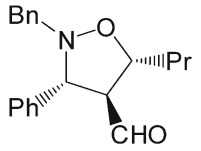
Compound	Physical and spectral data	Reference
 Cat-IV	m.p. 155–158 °C ^{1}H NMR (300 MHz, D_6-DMSO), δ: 7.39–7.29 (m, 5H, in Ph), 4.69 (m, 1H, COCH), 3.34 (dd, J = 15.2 Hz, J = 3.2 Hz, 1H, CH_2Ph), 2.98 (dd, J = 15.1 Hz, J = 10.7 Hz, 1H, CH_2Ph), 2.80 (s, 3H, CH_3NCO), 1.63 (s, 3H, CH_3), 1.49 (s, 3H, CH_3)	Jen et al. (2000)
 Cat-II	m.p. 148–150 °C ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.44 (bs, 1H), 7.39–7.33 (m, 10H, 2 × Ph), 6.47 (bs, 1H), 4.79 (bs, 1H, NHCH), 3.28–3.16 (m, 1H, CH_2), 2.67 (bs, 1H, CH_2), 2.37–2.25 (m, 1H, CH_2), 2.07–1.89 (m, 2H, CH_2), 1.61–1.45 (m, 1H, CH_2), –0.09 (s, 9H, Me_3Si)	Chow et al. (2007)
 *endo-IIIa*	^{1}H NMR (300 MHz, $CDCl_3$), δ: 9.79 (d, J = 2.4 Hz 1H, CH═O), 7.45–7.25 (m, 10H, Ph and CH_2Ph), 4.57 (dq, J = 12.0 Hz, J = 5.9 Hz, 1H, $CHCH_3$), 4.16 (d, J = 7.8 Hz, 1H, CHPh), 4.03 (d, J = 14.3 Hz, 1H, CH_2Ph), 3.84 (d, J = 14.3 Hz, 1H, CH_2P), 3.14 (m, 1H, CHCH═O), 1.51 (d, J = 6.2 Hz, 3H, CH_3)	Puglisi et al. (2004)
 *endo-IVa*	^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.44–7.19 (m, 10H, Ph and CH_2Ph), 4.22–4.09 (m, 1H, CHON), 3.99 (d, J = 14.4 Hz, 1H, CH_2Ph), 3.79 (d, J = 14.4 Hz, 1H, CH_2Ph), 3.74–3.69 (m, 2H, CH_2OH), 3.63 (d, J = 8.4 Hz 1H, CHPh), 2.38–2.29 (m, 1H, $CHCH_2$OH), 1.43 (d, J = 6.2 Hz, 3H, CH_3) HPLC (Chiralcel AD-H; hexane/EtOH (φ_r = 95 : 5); 0.8 mL min^{-1}, λ = 216 nm): t_R (major) = 20.10 min, t_R (minor) = 15.09 min	Puglisi et al. (2004)
 *endo-IIIb*	^{1}H NMR (300 MHz, $CDCl_3$), δ: 9.79 (d, J = 2.4 Hz, 1H, CH═O,), 7.43–7.20 (m, 10H, Ph and CH_2Ph), 4.26 (td, J = 7.5 Hz, J = 5.6 Hz, 1H, $CHCH_2CH_3$), 4.13 (d, J = 7.8 Hz, 1H, CHPh), 3.99 (d, J = 14.4 Hz, 1H, CH_2Ph), 3.79 (d, J = 14.4 Hz, 1H, CH_2Ph), 3.17–3.12 (m, 1H, CHCHO), 2.07–1.93 (m, 1H, CH_2CH_3), 1.79–1.65 (m, 1H, CH_2CH_3), 0.96 (t, J = 7.4 Hz, 3H, CH_2CH_3)	Shen et al. (2012)
 *endo-IVb*	^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.38–7.13 (m, 10H, Ph and CH_2Ph), 4.16–4.13 (m, 1H, CHON), 3.95 (d, J = 14.7 Hz, 1H, CH_2Ph), 3.84–3.79 (m, 1H, CH_2Ph), 3.71–3.62 (m, 2H, CH_2OH), 3.56 (d, J = 8.2 Hz, 1H, CHPh), 2.38–2.28 (m, 1H, $CHCH_2$OH), 1.64–1.57 (m, 2H, CH_2CH_3), 0.96 (t, J = 7.4 Hz, 3H, CH_2CH_3) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 139.6 (C_q in Ph), 138.1 (C_q in Ph), 128.7 (CH_{Ph}), 128.3 (CH_{Ph}), 128.0 (CH_{Ph}), 127.9 (CH_{Ph}), 127.8 (CH_{Ph}), 126.8 (CH_{Ph}), 81.4 (CHON), 73.9 (CHNO), 63.1 (CH_2Ph), 60.4 (CH_2OH), 59.7 ($CHCH_2$OH), 28.6 (CH_2CH_3), 10.4 (CH_2CH_3) HPLC (Chiralcel AD-H; hexane/IPA (φ_r = 97 : 3); 2 mL min^{-1}, λ = 213 nm): t_R (major) = 15.54 min, t_R (minor) = 11.33 min	Shen et al. (2012)
 *endo-IIIc*	^{1}H NMR (300 MHz, $CDCl_3$), δ: 9.78 (d, J = 2.5 Hz, 1H, CH═O), 7.43–7.23 (m, 10H, Ph a CH_2Ph), 4.38–4.32 (m, 1H, CHON), 4.13 (d, J = 7.8 Hz, 1H, CHPh), 3.99 (d, J = 14.4 Hz, 1H, CH_2Ph), 3.80 (d, J = 14.4 Hz, 1H, CH_2Ph), 3.17–3.11 (m, 1H, CHCH═O), 2.07–1.92 (m, 1H, $CH_2CH_2CH_3$), 1.70–1.58 (m, 1H, $CH_2CH_2CH_3$), 1.48–1.33 (m, 2H, $CH_2CH_2CH_3$), 0.93 (t, J = 7.4 Hz, 3H, $CH_2CH_2CH_3$) ^{13}C NMR (75 MHz, $CDCl_3$), δ: 198.8 (CH═O), 138.3 (C_q in Ph), 137.4 (C_q in Ph), 130.0 (CH_{Ph}), 128.9 (CH_{Ph}), 128.4 (CH_{Ph}), 128.1 (CH_{Ph}), 127.6 (CH_{Ph}), 127.0 (CH_{Ph}), 77.3 (CHON), 71.0 (CHNO), 70.4 (CHCH=O), 59.3 (CH_2Ph), 37.6 ($CH_2CH_2CH_3$), 19.2 ($CH_2CH_2CH_3$), 13.9 ($CH_2CH_2CH_3$)	Shen et al. (2012)

Table 1. (continued)

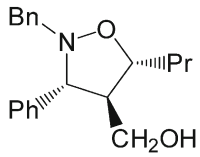
Compound	Physical and spectral data	Reference
 *endo-IVc*	^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.45–7.20 (m, 10H, Ph and CH_2Ph), 4.23–4.20 (m, 1H, CHON), 4.01–3.93 (m, 2H, CH_2Ph), 3.81–3.71 (m, 2H, CH_2OH), 3.56 (d, J = 8.2 Hz, 1H, CHPh), 2.45–2.36 (m, 1H, $CHCH_2OH$), 2.07–2.00 (m, 1H, $CH_2CH_2CH_3$), 1.97–1.85 (m, 1H, $CH_2CH_2CH_3$), 1.67–1.56 (m, 2H, $CH_2CH_2CH_3$), 0.93 (t, J = 7.3 Hz 3H, CH_2CH_3) HPLC (Chiralcel AD-H; hexane/IPA (φ_r = 97 : 3); 2 mL min^{-1}, λ = 217 nm): t_R (major) = 18.76 min, t_R (minor) = 12.92 min	Shen et al. (2012)

Table 2. Dipolar cycloaddition of nitrone *I* with aldehydes *IIa–IIc* in ionic liquids

Entry	Catalyst	Aldehyde	Reaction conditions	Yield/%	*Endo*/*exo* ratio[a]	Enantiomeric ratio of *endo-II*[b]
1	Cat-I	*IIa*	CH_2Cl_2, 5 °C, 4 d	45	62 : 38	55 : 45
2	Cat-I	*IIa*	IL-I, 5 °C, 4 d	47	80 : 20	51 : 49
3	Cat-IV · HOTf	*IIa*	IL-I, 5 °C, 5 d	20	92 : 8	56 : 44
4	Cat-IV · HCl	*IIa*	IL-I, 5 °C, 5 d	21	79 : 21	91 : 9
5	Cat-IV · HCl	*IIa*	IL-I, 40 °C, 3 d	48	64 : 36	69 : 31
6	Cat-IV · HCl	*IIb*	IL-I, H_2O, r.t., 3 d	32	69 : 31	54 : 46
7	Cat-IV · HCl	*IIb*	IL-II, H_2O, r.t., 3 d	24	63 : 37	52 : 48
8	Cat-IV · HCl	*IIb*	IL-III, H_2O, r.t., 3 d	17	69 : 31	56 : 44 (90 : 10)[c]
9	Cat-IV · HCl	*IIb*	IL-IV, H_2O, r.t., 3 d	47	83 : 17	75 : 25 (77 : 23)[c]
10	Cat-IV · HCl	*IIb*	IL-V, H_2O, r.t., 3 d	51	76 : 24	66 : 34 (85 : 15)[c]
11	Cat-II · HOTf	*IIb*	IL-V, H_2O, r.t., 3 d	35	83 : 17	n.d.
12	Cat-V	*IIb*	IL-V, H_2O, r.t., 3 d	30	72 : 28	73 : 27
13	Cat-VIII	*IIb*	IL-V, H_2O, r.t., 3 d	34	77 : 23	52 : 48
14	Cat-III	*IIb*	IL-V, H_2O, r.t., 3 d	30	50 : 50	83 : 17
15	Cat-VII	*IIb*	IL-V, H_2O, r.t., 3 d	40	77 : 23	77 : 23
16	Cat-IV · HCl	*IIb*	IL-VI, H_2O, r.t., 3 d	0	–	–
17	Cat-IV · HCl	*IIc*	IL-V, H_2O, r.t., 3 d	32	63 : 37	72 : 28

Reactions were carried out with 0.25 mmol of nitrone *I* and 0.05 mmol of organocatalyst. *a*) Determined by ^{1}H NMR of crude product; *b*) enantiomeric ratio was determined by HPLC on chiral stationary phase (aldehyde *III* was first converted into corresponding alcohol *IV*); *c*) enantiomeric purity of *exo-IIIb*; r.t. – ambient temperature.

Reaction in ILs: reactions were performed in the same way as in CH_2Cl_2. A small amount of H_2O (5 mL) was added to the mixture prior to the extraction with *t*-BuOMe. The organic layer was dried (Na_2SO_4), filtered, concentrated and the residue was analysed by ^{1}H NMR spectroscopy to establish the *endo*/*exo* ratio. The crude product was purified by flash chromatography as per the reaction in CH_2Cl_2.

Procedure for the microwave reaction: nitrone *I* (53 mg; 0.25 mmol), catalyst (0.05 mmol) and *IIa* (0.165 mL; 2 mmol) were dissolved in CH_2Cl_2 and irradiated in the MW reactor at 90 °C for 6 h. The mixture was concentrated under vacuum and the residue was analysed by ^{1}H NMR spectroscopy to establish the *endo*/*exo* ratio. The crude product was purified by flash chromatography, as per the reaction in CH_2Cl_2.

Procedure for the reaction in high pressure reactor: nitrone *I* (53 mg; 0.25 mmol), catalyst (0.05 mmol) and *IIa* (0.165 mL; 2 mmol) were dissolved in CH_2Cl_2 in a special tube, then placed in a high-pressure reactor at 13 MPa for the time given in Table 2. The mixture was then concentrated under vacuum and the residue was analysed by ^{1}H NMR spectroscopy to establish the *endo*/*exo* ratio. The crude product was purified by flash chromatography, as per the reaction in CH_2Cl_2.

Procedure for the reaction in ball mill: the ball-milling reactor was filled with *I* (53 mg; 0.25 mmol), catalyst (0.05 mmol) and *IIa* (0.165 mL; 2 mmol) and the contents ground for the time given in Table 2. The reaction mixture was washed with CH_2Cl_2, concentrated under vacuum and the residue was analysed by ^{1}H NMR spectroscopy to establish the *endo*/*exo* ratio. The crude product was purified by flash chromatography as per the reaction in CH_2Cl_2.

Procedure for synthesis of (4S,5R)-2-benzyl-5-ethyl-4-formyl-3-phenylisoxazolidine (endo-IIIb)

Nitrone *I* (50 mg, 0.237 mmol) was added to the mixture of pent-2-enal (116 μL, 1.183 mmol), catalyst (0.040 mmol), H_2O (2 μL, 0.12 mmol) and well-dried ionic liquid (2 mL) and the mixture was stirred at 20 °C. The reaction course was monitored by TLC analysis (SiO_2, hexane/AcOEt (φ_r = 3 : 1)) and an-

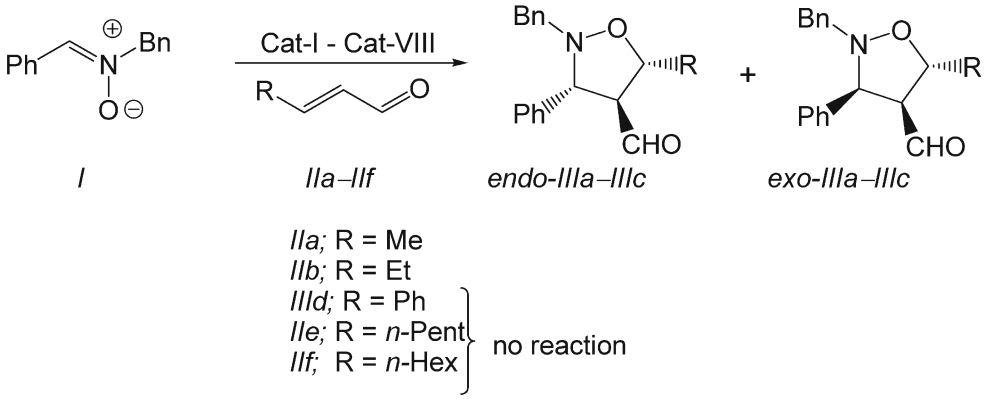


Fig. 1. Dipolar cycloaddition of nitrone *I* with aldehydes *II*.

other portion of pent-2-enal (23 μL, 0.237 mmol) was added after 20 h and 48 h. After 64 h, the mixture was extracted with *t*-BuOMe (8 × 3 mL). The combined organic extracts were washed with water (2 × 5 mL) and brine (5 mL), dried (Na_2SO_4) and the solvent evaporated. The products were separated by flash chromatography (SiO_2, hexane/Et_2O (φ_r = 20 : 1), λ = 213 nm) (Shen et al., 2012).

Reaction in the flow microreactor: the reaction was conducted in a reactor consisting of an 0.5 mL-mixing unit and a 24 mL-heated (60 °C or 80 °C) retention unit and three inlets (Fig. 3). The reagents were introduced using a syringe pump. The solution of aldehyde (12.5 mmol) was introduced into one inlet at a flow-rate of 0.05 mL min^{-1}, while a solution of the catalyst (0.5 mmol) and H_2O (1.25 mmol) in the same solvent was introduced from the other inlet at the same flow-rate. The total output was 0.1 mL min^{-1}. After mixing these reagents, *I* (2.5 mmol) was introduced via the third inlet in the same solvent at a flow-rate of 0.1 mL min^{-1}. The total output was 0.2 mL min^{-1} (2 h of residence time). The collected solution was concentrated under reduced pressure and the residues were purified by flash chromatography (SiO_2, heptane/AcOEt (φ_r = 10 : 1)) to afford the title compound.

Procedure for synthesis of (4S,5R)-2-benzyl-4-formyl-3-phenyl-5-propylisoxazolidine (endo-IIIc)

Nitrone *I* (53 mg, 0.25 mmol) was added to the mixture of hex-2-enal (120 μL, 1.00 mmol), catalyst Cat-IV · HCl (13 mg, 0.05 mmol), H_2O (2 μL, 0.125 mmol) and well-dried ionic liquid IL-VI (2 mL) and the mixture was stirred at 20 °C. The reaction course was monitored by TLC analysis (SiO_2, hexane/AcOEt (φ_r = 3 : 1)). Other portions of hex-2-enal (120 μL, 1.00 mmol) were added after 20 h and after 48 h (60 μL, 0.5 mmol). The mixture was extracted with *t*-BuOMe (8 × 3 mL). The combined organic extracts were washed with water (2 × 5 mL) and brine (5 mL), dried (Na_2SO_4) and the solvent evaporated, then the products were separated by flash chromatography (SiO_2, hexane/Et_2O (φ_r = 20 : 1), λ = 213 nm) (Shen et al., 2012).

General procedure for reduction of III to IV

To the solution of *IIIa–IIIc* in absolute EtOH (1 mL), $NaBH_4$ (3 eq.) was added. The reaction was quenched with H_2O and after 30 min the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic phase was dried (Na_2SO_4), filtered, concentrated and purified by flash chromatography (SiO_2, hexane/AcOEt (φ_r = 7 : 3)) (Shen et al., 2012).

Results and discussion

The dipolar cycloaddition of (*Z*)-*N*-benzylidene-1-phenylmethanamine oxide (*I*) with α,β-unsaturated aldehydes *II* affords isoxazolidines *III*. These isoxazolidines are typically obtained as a mixture of *endo* and *exo*-diastereoisomers (Fig. 1).

Endo-diastereoisomers were separated by flash chromatography and converted to corresponding alcohols *IV* by $NaBH_4$ reduction (Fig. 2). The absolute configurations of alcohols *IV* were determined by comparing the retention times of chiral-phase HPLC with the values in the literature; see experimental section for details.

A range of organocatalysts Cat-I–Cat-VIII (Fig. 3) was tested in the reactions of nitrone *I* with aldehydes *II*. As a selection principle, the catalyst's capacity to participate in an iminium activation was chosen, as dipolar cycloadditions with α,β-unsaturated aldehydes proceed via the corresponding iminium salt generated from the aldehyde (Jen et al., 2000). Accordingly, proline methyl ester (Cat-I), two prolinol silyl ethers (Cat-II and Cat-III) and several MacMillan-type imidazolidinones (Cat-IV–Cat-VIII) were used.

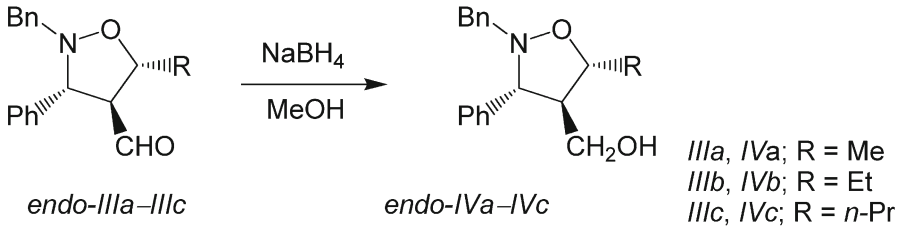


Fig. 2. Reduction of aldehydes *III* to alcohols *IV*.

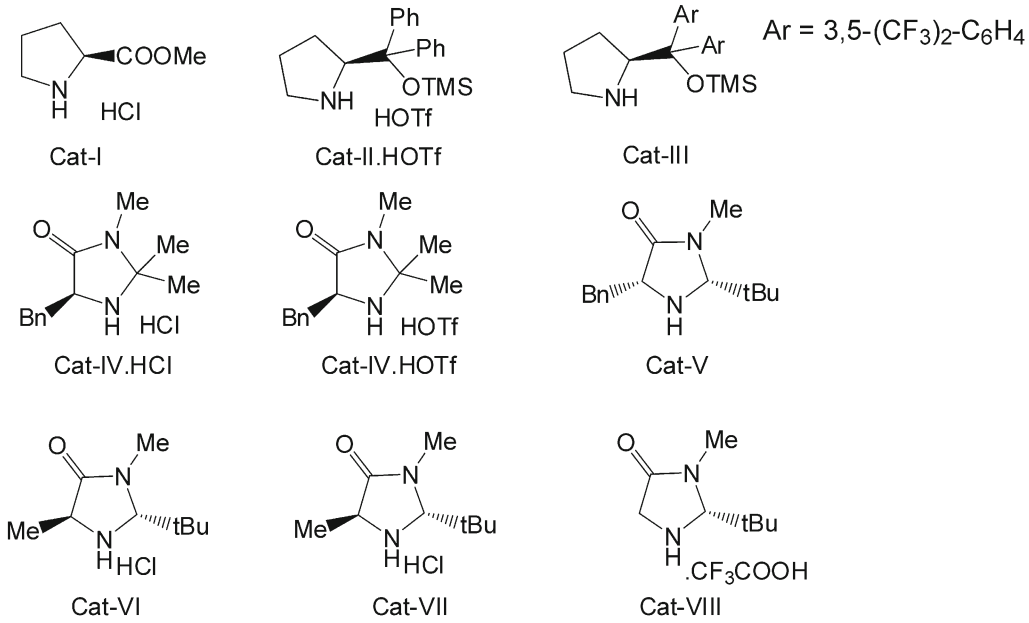


Fig. 3. Organocatalysts used in this study.

Dipolar cycloaddition in ionic liquids

For purposes of comparison, the study began with the reaction of nitrone *I* with crotonaldehyde (*IIa*) in CH_2Cl_2 as one of the classical organic solvents. These types of dipolar cycloaddition reactions are, typically, quite slow, the reaction of nitrone *I* with aldehyde *IIa* and catalyst Cat-I at 5 °C serving as a good example. After 4 d, the isoxazoline *IIIa* was isolated with an overall yield of 45 %, with mediocre diastereoselectivity (*endo*/*exo* = 62 : 38) and virtually no enantioselectivity. In the ionic liquid 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4, IL-I; Fig. 2), the yield and enantiomeric ratio were similar to those in CH_2Cl_2, but the diastereoselectivity increased to 80 : 20 (Table 2, Entries 1 and 2). Diastereoselectivity increased yet further (*endo*/*exo* = 92 : 8) when the MacMillan catalyst Cat-IV · HOTf was used, although the product *IIIa* was isolated with only a 20 % yield. When the catalyst Cat-IV · HCl was employed in [bmim]BF_4 (IL-I) at 5 °C; the product *IIIa* was isolated with a 21 % yield with an *endo*/*exo* ratio of 79 : 21 and e.r. (*endo*) 91 : 9. An increase in the reaction temperature to 40 °C resulted in increasing the yield of isoxazoline *IIIa* from 21 % to 48 %. However, this also led to decreases in diastereoselectivity (*endo*/*exo* 64 : 36) and enantioselectivity (e.r. 69 : 31, for *endo*-*IIIa*).

As cycloadditions of crotonaldehyde (*IIa*) in ionic liquids afforded promising results, 1,3-dipolar cycloadditions of nitrone *I* with pent-2-enal (*IIb*) in various ionic liquids were also studied. The structures of the ionic liquids used are depicted in Fig. 4.

Ionic liquids IL-I–IL-III and IL-VI are miscible with H_2O, in contrast with ionic liquids IL-IV and IL-V. This property had an intriguing effect on the enantioselectivity of the reaction. The presence of H_2O is essential for achieving high conversion, as well as good stereoselectivity. However, a further increase in the amount of H_2O reduced both the yield and enantioselectivity. The best results were attained using 50 mole % of H_2O (Lemay et al., 2007). Cycloadditions of nitrone *I* with aldehyde *IIb* in ionic liquids were performed using catalyst Cat-IV · HCl at ambient temperature over 3 d and H_2O (50 mole %) was added to the mixtures to enhance the catalytic turnovers. The product *IIIb* was obtained with rather low yields in the experiments with the ionic liquids IL-I–IL-III. Also, diastereoselectivities were only moderate (*endo*/*exo* ratio of 63 : 37–69 : 31) and the reactions were al-

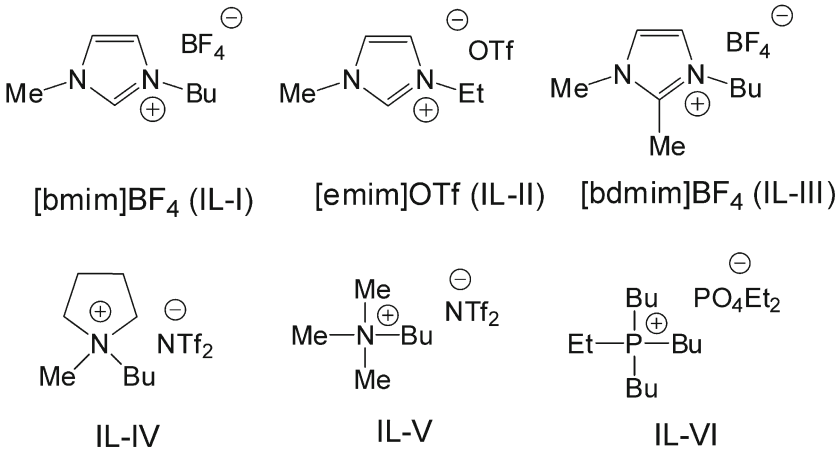


Fig. 4. Structures of ionic liquids.

most non-enantioselective as the enantiomeric purity of product *IIIb* was negligible (e.r. 52 : 48–56 : 44) (Table 2, Entries 6–8). Interestingly, the *exo*-product from the reaction in IL-III was obtained with e.r. 90 : 10. The situation was different with the ionic liquids immiscible with H_2O. Under otherwise identical conditions, the chemical yield as well as the diastereomeric and enantiomeric purity of the isoxazoline *IIIb* increased. The product *IIIb* was isolated with a 47 % yield and with an *endo*/*exo* ratio of 83 : 17, when IL-IV was used as a solvent. The *endo*-isomer was obtained with *e.r.* of 75 : 25 and the *exo*-isomer with e.r. of 77 : 23 (Table 2, Entry 9). The cycloaddition of nitrone *I* with aldehyde *IIb* proceeded similarly in ionic liquid IL-V. Product *IIIb* was isolated with a 51 % yield and its diastereomeric composition was *endo*/*exo* 76 : 24. The enantiomeric purity of compound *endo-IIIb* decreased slightly to 66 : 34, whereas the enantiomeric ratio for *exo-IIIb* increased to 85 : 15 (Table 2, Entry 10). The cycloaddition of nitrone *I* with aldehyde *IIb* in phosphonium ionic liquid IL-VI did not take place at all.

The cycloadditions of nitrone *I* with aldehyde *IIb* afforded product *IIIb* with the highest yield in ionic liquid IL-V. However, the enantiomeric purity of product *IIIb* was relatively low with catalyst Cat-IV · HCl. Accordingly, several other organocatalysts were tested in this ionic liquid (Table 2, Entries 12–16). The best diastereoselectivity (*endo*/*exo* = 83 : 17) was attained with catalyst Cat-II · HOTf. On the other hand, the highest enantioselectivity of the cycloaddition was observed when catalyst Cat-III was used (e.r. (*endo-IIIb*) 83 : 17).

The low yields of cycloadducts were also caused, at least in part, by the instability of starting α,β-unsaturated aldehydes in the presence of the catalyst in ionic liquids. A blank experiment, without the nitrone, revealed that aldehyde *IIb* decomposed to a significant degree after 24 h.

The reaction of nitrone *I* with hex-2-enal (*IIc*) using Cat-IV · HCl in ionic liquid IL-V with 50 mole % of H_2O afforded product *IIIc* with a 32 % yield with an *endo*/*exo* ratio of 63 : 37 and e.r. (*endo*) of 72 : 28 (Table 2, Entry 17). The dipolar cycloaddition of nitrone *I* did not proceed with cinnamaldehyde (*IId*), oct-2-enal (*IIe*) neither with non-2-enal (*IIf*) under the same conditions. In general, complex mixtures of products were obtained from these reactions.

Other non-standard reaction conditions

To improve the yields and selectivities of the dipolar cycloadditions of nitrone *I* with aldehydes *II*, these reactions were carried out under several other non-standard reaction conditions. Solvent-free conditions in a ball mill, ionic liquids under ultrasonic as well as microwave irradiation, reaction under high pressure and reaction in a flow system were evaluated.

Mechanochemical activation during ball-milling often increases reaction rate due to higher reactant concentrations and more effective molecular contacts under solvent-free conditions (James et al., 2012). In the ball mill, product *IIIa* was obtained with a 28 % yield with an *endo*/*exo* ratio of 89 : 11 and high enantiomeric purity e.r. (*endo*) of 94 : 6 (Table 3, Entry 1). The reaction was conducted in the vibrational ball mill in two or four 90 min cycles (3 h or 6 h in total). The longer reaction time, 6 h, had no effect on the reaction outcome (Table 3, Entry 2). Although the yield appears to be rather low, it should be noted that several days are required to obtain a similar result in the solution. It is unclear why the yield did not improve with time, but this may be due to catalyst decomposition as a result of mechanochemical stress or the intrinsically higher temperatures entailed during ball-milling. Similar results were also obtained with aldehyde *IIb*. The corresponding product *IIIb* was isolated with a 30 % yield and with an *endo/exo* ratio of 67 : 33 and enantiomer ratio of 73 : 27 (*endo-IIIb*) (Table 3, Entry 3). As one of the reactants is a liquid, the

Table 3. Dipolar cycloaddition of nitrone *I* with aldehydes *IIa* and *IIb* under various conditions

Entry	Catalyst	Reaction conditions	Yield/%	*Endo*/*exo* ratio[a]	Enantiomeric ratio of *endo*-*III*[b]
1	Cat-IV · HCl	ball-milling, 3 h	28	89 : 11	94 : 6 (*IIIa*)
2	Cat-IV · HCl	ball-milling, 6 h	24	88 : 12	90 : 10 (*IIIa*)
3	Cat-IV · HCl	ball-milling, 3 h	30	67 : 33	73 : 27 (*IIIb*)
4	Cat-IV · HCl	ball-milling, 3 h + Celite®[c]	34	67 : 33	76 : 24 (*IIIb*)[d]
5	Cat-II · HOTf	ball-milling, 6 h	23	79 : 21	85 : 15 (*IIIa*)
6	Cat-IV · HCl	CH_2Cl_2, MW, 6 h, 80 °C, 0.8 MPa	46	83 : 17	79 : 21 (*IIIa*)
7	Cat-IV · HCl	CH_2Cl_2, 13 MPa, 24 h	35	86 : 14	84 : 16 (*IIIa*)
8	Cat-VI	CH_2Cl_2, 13 MPa, 24 h	21	83 : 17	72 : 28 (*IIIa*)
9	Cat-IV · HCl	IL-I, ultrasound, 16 h	40	71 : 29	68 : 32 (*IIIa*)
10	Cat-IV · HCl	IL-V, ultrasound, 20 h	37	66 : 34	54 : 46 (*IIIb*)
11	Cat-IV · HCl	IL-IV, MW, 5 h, 90 °C	0	–	–
12	Cat-IV · HCl	flow microreactor, CH_2Cl_2, 2 h, r.t.[e]	14	66 : 34	81 : 19 (*IIIb*)
13	Cat-IV · HCl	flow microreactor, $MeNO_2$, 2 h, 60 °C[e]	22	99 : 1	94 : 6(*IIIb*)
14	Cat-IV · HCl	flow microreactor, $MeNO_2$, 2 h, 80 °C[e]	28	99 : 1	97 : 3 (*IIIb*)

Reactions were carried out with 0.25 mmol of nitrone (*I*) and 0.05 mmol of organocatalyst, reactions in flow microreactors with 2.5 mmol of *I* and 0.5 mmol of Cat-IV · HCl. *a*) Determined by ^{1}H NMR of crude product; *b*) enantiomeric ratio was determined by HPLC on chiral stationary phase (aldehyde *III* was first converted into corresponding alcohol *IV*); *c*) 200 mg Celite® was used; *d*) e.r. for *exo*-*IIIb* 71 : 29; *e*) residence time in reactor.

addition of an inert solid material was tried; this often helps in such situations under solvent-free conditions (Thorwirth et al., 2010). An addition of Celite® led to a slightly higher yield of isoxazolidine *IIIb* (34 %) (Table 3, Entry 4). The activity of catalyst Cat-II · HOTf in the ball mill was also evaluated, but it was less effective than catalyst Cat-IV · HCl (Table 3, Entry 5).

The dipolar cycloadditions of nitrone *I* with cyclohex-2-enone, cyclopent-2-enone, (*E*)-nitrostyrene and 1-benzyl-1*H*-pyrrole-2,5-dione under solvent-free conditions in the ball mill for 3 h using Cat-IV · HCl did not proceed and only unreacted starting materials were detected in the reaction mixtures. The reaction of the nitrostyrene was also performed with chiral thiourea derivatives in the ball mill, but without any positive effect on the reaction.

It is known that cycloaddition reactions entail large negative changes in the volume of activation as the reaction progress from starting material via transition state to products (Turro et al., 1987). As a result of this effect, cycloadditions often proceed better under high pressure. Accordingly, the cycloaddition of nitrone *I* with crotonaldehyde (*IIa*) using catalyst Cat-IV · HCl was performed under increased pressure. The first experiment was performed under microwave irradiation in a closed reaction vessel. When a low-boiling solvent is used in such a case, the pressure in the vessel increases as the temperature rises above its boiling point. CH_2Cl_2 was used at 80 °C, which generated a pressure of approximately 800 kPa. After 6 h, product *IIIa* was isolated with a 46 % yield with a high *endo*/*exo* ratio (83 : 17) and mediocre enantiomer purity (e.r. 79 : 21) (Table 3, Entry 6). Surprisingly, the reaction at a considerably higher pressure (13 MPa) in a high-pressure reactor resulted in a lower yield (35 %), but similar diastereoselectivity (d.r. 86 : 14) and slightly better enantioselectivity (e.r. 84 : 16) (Table 3, Entry 7). When catalyst Cat-VI was used instead of Cat-IV · HCl, the overall yield of product *IIIa* declined to 21 %, the *endo*/*exo* ratio was unchanged and the enantiomer purity decreased to e.r. of 72 : 28 (Table 3, Entry 8).

Ultrasound accelerates a number of organic reactions as a result of the extreme temperatures and pressures which occur during cavitation (Cravotto & Cintas, 2006). Accordingly, the cycloaddition of nitrone *I* with aldehydes *IIa* and *IIb* was evaluated under ultrasonic conditions. The reaction of crotonaldehyde (*IIa*) afforded product *IIIa* with a 40 % yield in ionic liquid IL-I (Table 3, Entry 9). The addition using aldehyde *IIb* proceeded similarly in ionic liquid IL-V under ultrasonic irradiation. After 20 h, product *IIIb* was isolated with a 37 % yield with a diastereomeric ratio of approximately 2 : 1. Both adducts *endo*- and *exo*-*IIIb* were obtained in almost racemic form, possibly due to the forcing conditions under ultrasonic irradiation (Table 3, Entry 10). A notable feature of the ultrasound application is a significant reduction in the reaction time. To obtain a similar yield under standard conditions, a much longer time, often several days, was needed. An attempt was also made to test the effect of microwaves without higher pressures, hence an experiment was performed in one of the ionic liquids, because ionic liquids have negligible vapour pressure and as highly polar media transmit microwave energy effectively. However, the reaction of nitrone *I* with aldehyde *IIb* in ionic liquid IL-IV under microwave irradiation was not accelerated and only the starting material was detected after 5 h at 90 °C (Table 3, Entry 11).

Finally, the possibility of adapting the dipolar cycloaddition to continuous flow conditions was examined. Continuous flow is of particular interest in con-

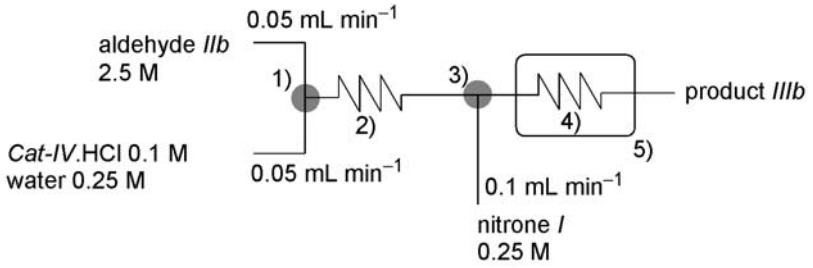


Fig. 5. Experimental set-up for reactions in flow microreactor: 1 – T-mixer (Teflon); 2 – residence time unit 0.5 mL (Teflon tubing); 3 – LTF MS mixer (glass); 4 – residence time unit 24 mL (Teflon tubing); 5 – heating bath.

nection with an immobilised catalyst (Puglisi et al., 2013). It has not, however, been so thoroughly investigated for homogeneous catalytic reactions (Zhao & Ding, 2013). For this purpose, the instrument set-up represented in Fig. 5 was used. In the initial experiments, product *IIIb* was obtained with a 14 % yield with an *endo*/*exo* ratio of 66 : 34 and e.r. (*endo*) of 81 : 19, when CH_2Cl_2 was used as a solvent. Slightly better yields were achieved in nitromethane, which is the best solvent under standard conditions (22 % at 60 °C and 28 % at 80 °C). Interestingly, the reaction proceeded highly diastereoselectively as only diastereoisomer *endo-IIIb* was detected in the crude reaction mixture. In addition, product *IIIb* was obtained with a high enantiomeric purity e.r. of 94 : 6 at 60 °C and 97 : 3 at 80 °C (Table 3, Entries 12–14). The main limitation applying to the flow system is also a very slow reaction. In the flow reactor, residence time cannot be prolonged deliberately, which limits the obtaining of high yields of the products. Nevertheless, the efficiency of the flow system is evident, as isoxazoline *IIIb* was obtained with a 28 % yield in only 2 h.

Conclusions

Nine different organocatalysts were tested, and the reactions were performed in six different ionic liquids as well as CH_2Cl_2 under high pressure. The effect of ultrasound, microwave irradiation and ball-milling as well as the flow microreactor process was detailed. The chemical yields of the cycloaddition products were only medium, which seemingly restricts synthetic applications. The reaction appears to be intrinsically problematic under a range of experimental conditions, often giving rise to several side-products. For example, the α,β-unsaturated aldehydes used in ionic liquid experiments undergo decomposition in the absence of nitrone, providing aldehydic by-products, as was proved in the blank experiment. On the other hand, the medium yields achieved under solvent-free conditions and in the flow system are balanced by the considerably shorter reaction times needed to achieve these still synthetically relevant yields. Furthermore, the products were often isolated with high diastereomeric and enantiomeric ratios. From among the ionic liquids, the greatest diastereoselectivity was observed in [bmim]BF_4 (*endo*/*exo* 92 : 8). Under solvent-free conditions, the *endo* isomer was isolated with a high enantiomeric purity e.r. of 94 : 6. Even higher selectivities were observed in the flow microreactor, where the reaction of pent-2-enal in nitromethane afforded the product with an *endo*/*exo* ratio of 99 : 1 and an enantiomer ratio of 97 : 3.

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