Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 1245

Organocatalysed synthesis of isoxazolines initiated by a chemoselective oxa-Michael reaction of *N*-BocNHOH†

R. Noël, V. Gembus, V. Levacher and J.-F. Brière*

Received 2nd December 2013,
Accepted 2nd January 2014

DOI: 10.1039/c3ob42406e

www.rsc.org/obc

An organocatalysed and chemoselective one-pot oxa-Michael-cyclocondensation reaction of *N*-BocNHOH to unsaturated α-ketoesters is reported which affords an original entry to enantioenriched 3-isoxazoline carboxylate derivatives as biorelevant heterocyclic frameworks.

Introduction

The organocatalysed hetero-Michael reaction emerged as a powerful synthetic methodology to create enantioselectively C–N or C–O bonds.[1,2] By means of bisnucleophiles such as hydroxylamines, a subsequent cyclisation step is allowed to construct, in a straightforward fashion, non-racemic isoxazolidine derivatives,[3] important heterocyclic frameworks frequently found in biologically active compounds (Fig. 1).[4,5]

In this context, few research groups have achieved an asymmetric organocatalysed domino hetero-Michael-cyclisation reaction towards the elaboration of isoxazolidine derivatives by addressing the NH *versus* OH chemoselectivity of hydroxylamine bisnucleophiles (Scheme 1).[6] Shibata and colleagues reported that native hydroxylamine led to a domino oxa-Michael-cyclocondensation reaction onto activated fluorinated-enones upon the asymmetric phase transfer catalytic regime with strong bases (Scheme 1a).[7] Pihko and collaborators elegantly used oximes as transient-nitrogen protected NH_2OH nucleophiles to form 3-unsubstituted 2-isoxazolines *via* an iminium catalysed oxa-Michael reaction followed by an acid promoted *trans*-imination cyclisation (Scheme 1a).[8] On the other hand, the group of Córdova performed an efficient iminium catalysed domino aza-Michael-hemiacetal formation reaction starting from commercially available *N*-BocNHOH **1a** (Scheme 1b).[9]

Alternatively, we would like to report here on an original domino oxa-Michael-hemiaminal formation reaction of *N*-BocNHOH **1a** making use of unsaturated α-ketoesters **2**, namely the 4-substituted 2-oxo-3-butenoates, upon Brønsted base catalysis (Scheme 1c).[10] This sequence not only reveals an uncommon O-chemoselectivity during the conjugated addition reaction of *N*-BocNHOH **1a** bisnucleophile, giving rise to

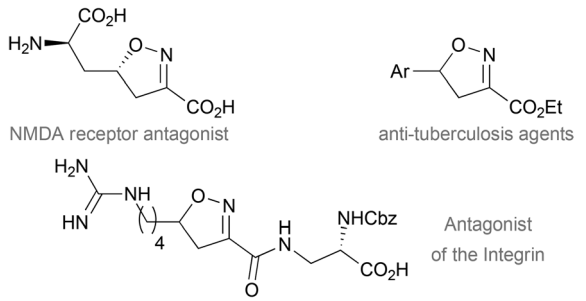
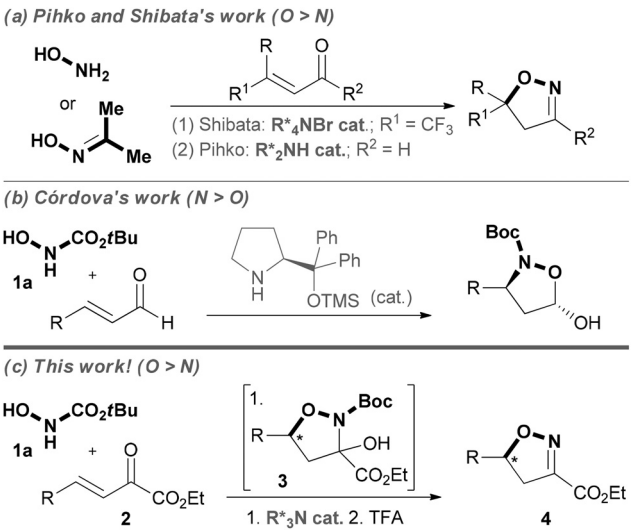


Fig. 1 Bioactive 3-isoxazolecarboxylate derivatives.



Scheme 1 Domino aza- *versus* oxa-Michael-cyclisation reaction.

Normandie Univ, COBRA, UMR 6014 et FR 3038; Univ Rouen; INSA Rouen; CNRS, IRCOF, 1 rue Tesnière, 76821 Mont Saint Aignan Cedex, France.
E-mail: jean-francois.briere@insa-rouen.fr; Fax: +33 235522464; Tel: +33 235522962

†Electronic supplementary information (ESI) available: Further experimental optimisations, procedures and compound characterisation data. See DOI: 10.1039/c3ob42406e

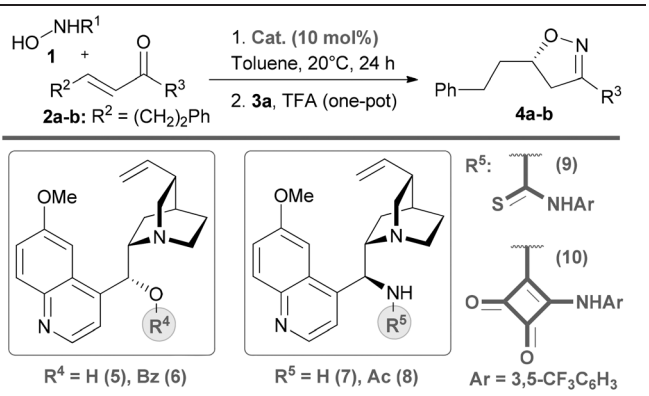
intermediate **3**, but eventually leads to a concise elaboration of biologically important isoxazolines **4** flanked by a carboxylate functional group at C3 after a simple acid promoted Boc removal (Scheme 1c *versus* Fig. 1).[11] Despite some seminal experimental observations concerning the oxa-Michael outcome of hydroxyurea $NH_2CONHOH$ with enals by Petrus and co-workers,[12] the asymmetric developments remain to be achieved. Towards this goal, we are pleased to describe the preliminary results towards an original asymmetric organocatalytic synthesis of 3-isoxazoline carboxylate derivatives. It is important to note that some of these chiral structures **4** were previously only directly accessible in a non-racemic form through enzymatic resolution or diastereoselective reaction.[13–15]

Results and discussion

At the onset of this project, it was shown that an *a priori* chemoselective oxa-Michael reaction of *N*-BocNHOH **1a** smoothly took place with unsaturated keto-ester **2a** in the presence of quinuclidine after 24 hours in toluene (Table 1, entry 2). Indeed, the starting materials **1a** and **2a** were recovered without Brønsted base (entry 1). The analyses of the crude reaction products mainly revealed two compounds which were assumed to be a mixture of cyclized hemi-aminal epimers **3a** (Scheme 1c, R = $(CH_2)_2Ph$) due to the absence of a ketone functional group by ^{13}C NMR (see ESI†). Next, the one-pot addition of trifluoroacetic acid (TFA) in excess easily provided the corresponding isoxazoline **4a** through a formal sequence involving both dehydration and Boc-removal events with an overall 63% yield. It is worthy of note that no isoxazoline **4a** formation was noticed in the presence of TFA alone (entry 3). This rules out an acid catalyzed formation of isoxazolidine **3a** from **2a** (Scheme 1c). With this original one-pot sequential oxa-Michael-cyclocondensation reaction in hand, we sought an asymmetric version but a screening of a large array of chiral Brønsted bases was required (see ESI† for an overview of screened conditions). Neither quinine derivatives **5**, **6** (C9–OH or C9–OBz) nor the 9-*epi*-amino homologues **7**, **8** (C9–NH_2 or C9–NHAc) were able to achieve a significant enantioselective transformation, although these organocatalysts furnished **4a** in good yields (Table 1; entries 4–7). To our delight, the bifunctional 9-*epi*-aminoquinines **9–10** led to improved enantioselective excesses ranging from 34% ee with C9-thiourea derived catalysts **9** to 55% ee with the C9-squaramide one QN-SQ **10** with good (82%) overall yields (entries 8 and 9).[16] Interestingly, increased enantiomeric excesses were measured by adding *N*-BocNHOH **1a** dropwise in solution to give up to 73% ee (entry 10). The origin of this phenomenon has not been fully understood so far, but constitutes a reproducible procedure in any subsequent reactions. The *N*-CbzNHOH **1b** and $NH_2CONHOH$ **1c** nucleophiles were also evaluated in the presence of squaramide catalyst **10** but lower selectivities of 35% and 58% ee respectively were measured (entries 11 and 12). But the most tedious issues with these *N*-functionalized hydroxylamine derivatives **1b** and **1c** were related to the delicate acid-promoted isoxazoline **4a** formation requiring adapted reaction conditions which eventually led to modest isolated yields lower than 16% (entries 11 and 12). Importantly, it was shown that no reaction occurred with enal **2b** in the presence of organocatalyst **10**. Accordingly, the required ester moiety on the 2-oxo-3-butenoate **4a** structure is probably an activated EWG for both unsaturated enone towards the oxa-Michael process with catalyst **10** and the ketone functional group during the hemi-aminal **3** formation.[10] In all likelihood a kinetically driven **O**-alkylation is occurring, evidently of the less sterically hindered moiety of *N*-BocNH**O**H **1a**,[17,18] and this C–**O** bond formation is secured by the subsequent cyclization to stable intermediate **3** (Scheme 1b *versus* 1c).[9a]

Next, we investigated the reaction conditions through the direct addition of *N*-BocNHOH **1a** in solution for practical reasons (Table 2). It was found that quinidine derived squaramide organocatalyst **11** (QD-SQ) (entry 1) could be employed instead of quinine QN-SQ with a slightly better ee but a reverse enantioselectivity (see Table 1, entry 10). The use of various aromatic solvents (entries 2 and 3, Table 2) did not improve

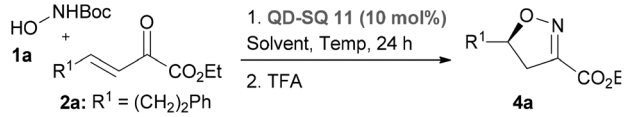
Table 1 Towards an enantioselective approach[a]



Entry	Cat.	R^1	R^3	Yield[b] (%)	ee[c] (%)
1	0	CO_2tBu (**1a**)	CO_2Et (**2a**)	0 (**4a**)	—
2	Quinuclidine	CO_2tBu (**1a**)	CO_2Et (**2a**)	63 (**4a**)	—
3	TFA[d]	CO_2tBu (**1a**)	CO_2Et (**2a**)	0 (**4a**)	—
4	**5**	CO_2tBu (**1a**)	CO_2Et (**2a**)	86 (**4a**)	5
5	**6**	CO_2tBu (**1a**)	CO_2Et (**2a**)	61 (**4a**)	—
6	**7**	CO_2tBu (**1a**)	CO_2Et (**2a**)	90 (**4a**)	1
7	**8**	CO_2tBu (**1a**)	CO_2Et (**2a**)	98 (**4a**)	0
8	**9**	CO_2tBu (**1a**)	CO_2Et (**2a**)	82 (**4a**)	34 (*S*)
9	**10**	CO_2tBu (**1a**)	CO_2Et (**2a**)	82 (**4a**)	55 (*S*)
10	**10**	CO_2tBu (**1a**)	CO_2Et (**2a**)	87 (**4a**)	(60)[e] 73[f]
11	**10**	CO_2Bn (**1b**)	CO_2Et (**2a**)	10 (**4a**)[g]	35(*S*)
12	**10**	$CONH_2$ (**1c**)	CO_2Et (**2a**)	16 (**4a**)[h]	58(*S*)
13	**10**	CO_2tBu (**1a**)	H (**2b**)	0 (**4b**)	—

[a] *N*-protected hydroxylamines **1** (0.11 mmol, 1.1 equiv.) as a solid were added in one-portion into a solution of unsaturated ketoesters **2a–b** (0.10 mmol, 1 equiv.), catalyst (0.01 mmol, 0.1 equiv.) in toluene (0.05 M); then TFA (1.0 mmol, 10 equiv.). [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC. [d] In the presence 0.1 or 30 equivalents of TFA. [e] The *N*-Boc hydroxylamine **1a** was added into a solution in one-portion. [f] The *N*-Boc hydroxylamine **1a** was added dropwise into a solution over 4 hours. [g] TFA was replaced by TMSI. [h] TFA was replaced by HCl in MeOH.

Table 2 Screening of conditions[a]



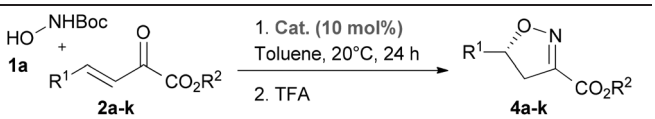
Entry	Solvent	Concentration	Temp. (°C)	Yield[b] (%)	ee[c] (%)
1	Toluene	0.05 M	20	87	69
2	*m*-Xylene	0.05 M	20	62	66
3	$PhCF_3$	0.05 M	20	82	63
4	MeCy	0.05 M	20	88	45
5	CH_2Cl_2	0.05 M	20	77	45
6	THF	0.05 M	20	86	55
7	MeCN	0.05 M	20	82	55
8	EtOH	0.05 M	20	79	61
9	Toluene	0.05 M	0	93	69
10	Toluene	0.1 M	20	86	59
11	Toluene	0.025 M	20	82	70

[a] Unsaturated ketoesters **2a** (0.10 mmol, 1 equiv.), *N*-Boc hydroxylamines **1a** (0.11 mmol, 1.1 equiv.) were added in one-portion into a solution, catalysts **10** or **11** (0.01 mmol, 0.1 equiv.), toluene (0.05 M); and then TFA (1.0 mmol, 10 equiv.). [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC.

the induction but less polar methylcyclohexane was detrimental and led to poor solubility issues (entry 4). On the other hand, moving from dichloromethane to more polar solvents decreased markedly the enantioselectivities (entries 5–8). The asymmetric outcome was insensitive to the decrease of temperature (entry 9) but the concentration has to be maintained at 0.05 M; otherwise lower enantiomeric excess was observed (entries 10–12).

Then, we evaluated this one-pot oxa-Michael-cyclocondensation sequence on various unsaturated α-ketoester derivatives **2** (Table 3). At that stage, it was found that 30 equivalents of TFA

Table 3 Scope of the reaction[a]



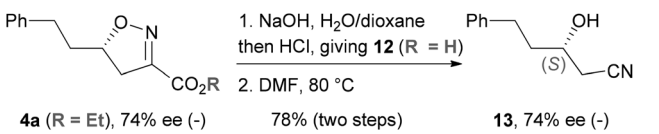
Entry	R^1	R^2	Catalyst[a]	Prod.	Yield[b] (%)	ee[c] (%)
1	$Ph(CH_2)_2$	Et (**2a**)	QN-SQ (**10**)	**4a**	87	74 (*S*)
2	$Ph(CH_2)_2$	Et (**2a**)	QD-SQ (**11**)	**4a**	82	76 (*R*)
3	$Ph(CH_2)_2$	Me (**2c**)	QN-SQ (**10**)	**4c**	87	72 (*S*)
4	iso-Butyl	Et (**2d**)	QN-SQ (**10**)	**4d**	82	68
5	Cyclohexyl	Et (**2e**)	QN-SQ (**10**)	**4e**	73	31
6	*n*-Heptyl	Et (**2f**)	QN-SQ (**10**)	**4f**	86	77
7	$EtO(CH_2)_2$	Et (**2 g**)	QN-SQ (**10**)	**4g**	80	67
8	$BnOCH_2$	Et (**2 h**)	QN-SQ (**10**)	**4h**	68	72
9	$H_2CCH(CH_2)_2$	Et (**2i**)	QN-SQ (**10**)	**4i**	79	78
10	Ph	Me (**2j**)	QN-SQ (**10**)	**4j**	21[d]	5
11	3,4-DiClPh	Me (**2k**)	QN-SQ (**10**)	**4k**	42[d]	8

[a] Unsaturated ketoesters (0.250 mmol, 1 equiv.), *N*-Boc hydroxylamine **1a** (0.275 mmol, 1.1 equiv.) were added dropwise into a solution over 4 hours, catalyst (0.025 mmol, 0.1 equiv.), toluene (0.05 M); then TFA (7.5 mmol, 30 equiv.). [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC. [d] Yield after 72 h.

provided more general conditions for the formation of isoxazolidines with various enones **2**. First of all, with this optimized protocol, it was found that quinine **10** or quinidine squaramide *pseudo*-enantiomer catalysts **11** could be used with a similar efficiency in order to furnish both *S*- or *R*-enantiomer of isoxazoline **4a** with 74–76% ee (entries 1 and 2).[19] Both methyl and ethyl ester isoxazolines **4a** and **4c** were synthesized with rather similar enantiomeric excesses (entries 1 *versus* 3). Although 4-iso-butyl 2-oxo-3-butenoate **2d** led to respectable 68% ee, the α-branched cyclohexyl pendant **2e** underwent a smooth transformation into **4e** in 73% yield albeit with lower 31% ee (entries 4 and 5). However, a longer *n*-heptyl alkyl chain was well tolerated giving rise to 77% ee (entry 6). Moreover, enones **2g–i** with an alkyl chain flanked by ethers or alkene functional groups furnished the corresponding isoxazolines **4g–i** with good yields and ee ranging from 67% to 78%. Although 4-alkyl substituted 2-oxo-3-butenoates **2a–i** allowed the formation of the corresponding isoxazolines **4a–i** with high yield and moderate to good enantiomeric excesses (entries 1–9), 4-aryl substituted derivatives **2j–k** revealed a slow oxa-Michael reaction rate with low enantiomeric excess (entries 10 and 11). This outcome has not been fully studied at the moment, but the more stable 4-aryl substituted enones **4j–k** might undergo an oxa-Michael addition under thermodynamic equilibrated conditions together with featuring a steric issue as seen with the lower enantiomeric excess obtained with the 4-cyclohexyl derivative **4e**.

Most of the 5-alkyl substituted 3-isoxazoline carboxylate derivatives being novel products, we sought to both determine their absolute configurations and probe useful chemical transformations (Scheme 2). Inspired by a previous study of Nishiyama and Pihko, we attempted the fragmentation of the oxazole ring.[20] To our delight, after a facile saponification reaction into carboxylic acid **12**, a straightforward decarboxylative-fragmentation took place on the crude product **12** at 80 °C to form the β-hydroxy acetonitrile **13** with excellent 78% yield over the two steps. This *S*-featuring known alcohol **6** was obtained without racemization providing accordingly the absolute configuration of precursor **4a**.[20b]

With this structure in hand, a plausible transition state is depicted in Fig. 2, stemming from previous proposals of Jørgensen and co-workers.[16,21] The α-ketoester would be recognized and activated through a double hydrogen bonding network of the squaramide moiety while the R^1-pendant is pointing away from the bulky quinuclidine part. Then, the *Si* face approach of the incoming oxygen-nucleophile is assisted by the top-face position of the tertiary amine.



Scheme 2 Transformation and determination of the absolute configuration.

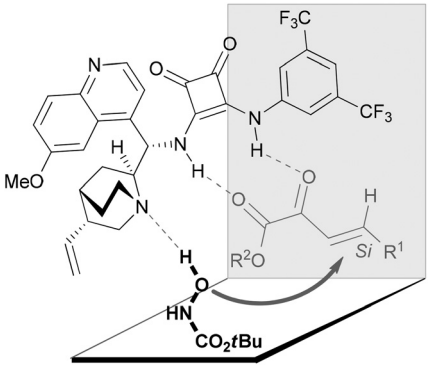


Fig. 2 Proposed transition state.

Conclusions

In summary, although *N*-BocNHOH was previously used in the aza-Michael reaction upon iminium organocatalysis with enals,[9a] we report in this paper an enantioselective oxa-Michael event of this bisnucleophile with unsaturated α-ketoesters upon Brønsted base catalysis. This original chemoselective process followed by a one-pot acid promoted cyclocondensation reaction affords a unique entry to non-racemic bio-relevant 3-isoxazoline carboxylate derivatives. The search for more efficient squaramide derived organocatalysts is currently of interest.

Experimental section

Solvents were purchased as dehydrated ones, and toluene or CH_2Cl_2 was distilled on CaH_2. All reagents were used as received unless otherwise indicated. Chromatographic purification of compounds was achieved with silica gel 60 (40–63 μm). Thin layer chromatography was carried out on silica gel 60 F_{254} (1.1 mm) with spot detection under UV light or phosphomolybdic acid or ninhydrin or $KMnO_4$ oxidation. ^{1}H NMR spectra were recorded on a Bruker AVANCE 300 at 300 MHz. Data appear in the following order: chemical shifts in ppm, number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), and coupling constant *J* in Hz. ^{13}C NMR spectra were acquired at 75.4 MHz operating with broad band ^{1}H decoupling. The hydrogen multiplicity was obtained by DEPT135. IR spectra were recorded on a Perkin Elmer IRTF 100 spectrometer using an ATR (Attenuated Total Reflectance) sampling with a solid dispersed or neat or on a Perkin Elmer IRFT 1650 with a solid dispersed on KBr pastille. Mp's were uncorrected. HRMS analyses were measured on a Q-TOF Micro WATERS spectrometer. HPLC analyses were performed with Daicel Chiralpack® or Daicel ChiralCel® columns (4.6 mm × 25 cm). A spectrosystem UV 1000 thermofisher detector and a chiral detector (polarimeter) JACSCO OR-1590 were used.

Representative procedure for compound 4a

To a solution of unsaturated ketoester **2a** (0.25 mmol) and catalyst 10 (15.8 mg, 0.025 mmol, 0.1 equiv.) in toluene (5 mL, 0.05 M) in a Schlenk flask was added dropwise over 4 h a solution of *N*-Boc hydroxylamine (36.6 mg, 0.275 mmol, 1.1 equiv.) in toluene (750 μL). After stirring for 24 h at 20 °C, TFA (580 μL, 7.6 mmol, 30 equiv.) was added and the resulting solution was stirred for 1 h. The reaction mixture was partitioned between a saturated aqueous $NaHCO_3$ solution (10 mL) and Et_2O (10 mL). The organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and filtered and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography to give the expected **4a** as a pale yellow oil (54 mg, 87%). R_f = 0.25 (petroleum ether–EtOAc: 9/1). $[\alpha]_D^{20}$ = −104.5 (*c* 1.01, $CHCl_3$, 74% ee). IR (neat) ν_{max} 3026, 2982, 2938, 2862, 1738, 1721, 1715, 1588, 1454, 1380, 1257, 1125, 1018, 934, 749 and 701 cm^{-1}. ^{1}H NMR (300 MHz; $CDCl_3$) δ_H 7.32–7.27 (2H, m), 7.23–7.18 (3H, m), 4.85–4.74 (1H, m), 4.35 (2H, q, *J* = 7.1 Hz), 3.25 (1H, dd, *J* = 11.0, 17.5 Hz), 2.85 (1H, dd, *J* = 8.3, 17.5 Hz), 2.84–2.67 (2H, m), 2.17–2.03 (1H, m), 1.96–1.84 (1H, m), 1.37 (3H, t, *J* = 7.1 Hz). ^{13}C NMR (75.4 MHz; $CDCl_3$) δ_C 161.0 (C), 151.5 (C), 140.8 (C), 128.7 (2 × CH), 128.5 (2 × CH), 126.3 (CH), 83.2 (CH), 62.2 (CH2), 38.6 (CH2), 36.9 (CH2), 31.5 (CH2), 14.3 (CH3). HRMS (ESI$^+$): calcd for $C_{14}H_{18}NO_3$ $[M + H]^+$: 248.1281; found: 248.1278. HPLC analysis: Daicel Chiralpak® AD-H (heptane–iPrOH = 98 : 2, flow rate 1.0 mL min^{-1}, UV 254 nm, t_{minor} = 15.0 min for *R* enantiomer; t_{major} = 19.9 min for *S* enantiomer, 74% ee).

Acknowledgements

This work has been partially supported by INSA Rouen, Rouen University, CNRS, EFRD and Labex SynOrg (ANR-11-LABX-0029). This work is part of the Immunochim project (no. 34209) funded by the European Union through a FEDER support engaged in region Haute-Normandie. We gratefully acknowledge the French National Research Agency (ANR) for the support as part of the ANR-08-JCJC-004301 project. We warmly thank the COST ORCA Action 0905 (Organocatalysis).

Notes and references

1 For reviews on organocatalysed aza-Michael reactions, see: (*a*) D. Enders, C. Wang and J. X. Liebich, *Chem.–Eur. J.*, 2009, **15**, 11058; (*b*) J. Wang, P. Li, P. Y. Choy, A. S. C. Chan and F. Y. Kwong, *ChemCatChem*, 2012, **4**, 917; (*c*) S. M. Kim and J. W. Yang, *Org. Biomol. Chem.*, 2013, **11**, 4737.

2 For reviews on oxa-Michael reactions, see: (*a*) C. F. Nising and S. Brase, *Chem. Soc. Rev.*, 2008, **37**, 1218; (*b*) E. Hartmann, D. J. Vyas and M. Oestreich, *Chem. Commun.*, 2011, **47**, 7917; (*c*) C. F. Nising and S. Brase, *Chem. Soc. Rev.*, 2012, **41**, 988.

3 For a review, see: D. Bonne, T. Constantieux, Y. Coquerel and J. Rodriguez, *Org. Biomol. Chem.*, 2012, **10**, 3969.

4 (*a*) W. J. Pitts, J. Wityak, J. M. Smallheer, A. E. Tobin, J. W. Jetter, J. S. Buynitsky, P. P. Harlow, K. A. Solomon, M. H. Corjay, S. A. Mousa, R. R. Wexler and P. K. Jadhav, *J. Med. Chem.*, 1999, **43**, 27; (*b*) Rakesh, D. Sun, R. B. Lee,

R. P. Tangallapally and R. E. Lee, *Eur. J. Med. Chem.*, 2009, **44**, 460; (*c*) L. Tamborini, A. Pinto, F. Mastronardi, M. C. Iannuzzi, G. Cullia, B. Nielsen, C. De Micheli and P. Conti, *Eur. J. Med. Chem.*, 2013, **68**, 33.

5 For examples of the synthesis of isoxazolidine derivatives through (3 + 2) cycloadditions, see: (*a*) K. V. Gothelf and K. A. Jørgensen, *Chem. Rev.*, 1998, **98**, 863; (*b*) M. Kissane and A. R. Maguire, *Chem. Soc. Rev.*, 2010, **39**, 845; (*c*) T. B. Nguyen, A. Martel, C. Gaulon, R. Dhal and G. Dujardin, *Org. Prep. Proced. Int.*, 2010, **42**, 387; (*d*) A. Moyano and R. Rios, *Chem. Rev.*, 2011, **111**, 4703; (*e*) H. Pellissier, *Tetrahedron*, 2012, **68**, 2197.

6 For selected examples of organocatalysed intramolecular oxa-Michael reactions of hydroxylamines, see: (*a*) Y. Kobayashi, Y. Taniguchi, N. Hayama, T. Inokuma and Y. Takemoto, *Angew. Chem., Int. Ed.*, 2013, **52**, 11114; (*b*) C. B. Tripathi and S. Mukherjee, *Angew. Chem., Int. Ed.*, 2013, **52**, 8450 and references therein (*c*) For other examples, see: L. Wang, X. Liu, Z. Dong, X. Fu and X. Feng, *Angew. Chem., Int. Ed.*, 2008, **47**, 8670.

7 K. Matoba, H. Kawai, T. Furukawa, A. Kusuda, E. Tokunaga, S. Nakamura, M. Shiro and N. Shibata, *Angew. Chem., Int. Ed.*, 2010, **49**, 5762.

8 (*a*) A. Pohjakallio and P. M. Pihko, *Chem.–Eur. J.*, 2009, **15**, 3960; (*b*) A. Pohjakallio, P. M. Pihko and U. M. Laitinen, *Chem.–Eur. J.*, 2010, **16**, 11325. For the conjugated addition of oximes, see: (*c*) L. Chang, D. Shang, J. Xin, X. Liu and X. Feng, *Tetrahedron Lett.*, 2008, **49**, 6663; (*d*) S. Bertelsen, P. Dinér, R. L. Johansen and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2007, **129**, 1536.

9 (*a*) I. Ibrahem, R. Rios, J. Vesely, G.-L. Zhao and A. Córdova, *Chem. Commun.*, 2007, 849; (*b*) For other selected examples, see: F. Pesciaioli, F. De Vincentiis, P. Galzerano, G. Bencivenni, G. Bartoli, A. Mazzanti and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2008, **47**, 8703; (*c*) I. Ibrahem, R. Rios, J. Vesely, G.-L. Zhao and A. Córdova, *Synthesis*, 2008, 1153; (*d*) O. V. Maltsev, A. S. Kucherenko, A. L. Chimishkyan and S. G. Zlotin, *Tetrahedron: Asymmetry*, 2010, **21**, 2659.

10 G. Desimoni, G. Faita and P. Quadrelli, *Chem. Rev.*, 2013, **113**, 5924.

11 For a previous Boc-removal approach for pyrazoline construction, see: M. Fernández, E. Reyes, J. L. Vicario, D. Badía and L. Carrillo, *Adv. Synth. Catal.*, 2012, **354**, 371.

12 R. Jacquier, J.-L. Olive, C. Petrus and F. Petrus, *Tetrahedron Lett.*, 1975, **16**, 2337.

13 For selected diastereoselective examples, see: (*a*) S. F. Martin, J. A. Colapret, M. S. Dappen, B. Dupre and C. J. Murphy, *J. Org. Chem.*, 1989, **54**, 2209; (*b*) K. Goldenstein, T. Fendert, P. Proksch and E. Winterfeldt, *Tetrahedron*, 2000, **56**, 4173; (*c*) C. D. Davies, S. P. Marsden and E. S. E. Stokes, *Tetrahedron Lett.*, 2000, **41**, 4229; (*d*) J. Romański, J. Jóźwik, C. Chapuis, M. Asztemborska and J. Jurczak, *Tetrahedron: Asymmetry*, 2007, **18**, 865; (*e*) G. Cremonesi, P. D. Croce, F. Fontana, C. Fiorelli and C. L. Rosa, *Tetrahedron: Asymmetry*, 2008, **19**, 2850; (*f*) A. Kraszewska, P. Rivera-Fuentes, C. Thilgen and F. Diederich, *New J. Chem.*, 2009, **33**, 386.

14 (*a*) S. Yang, W. Hayden and H. Griengl, *Monatsh. Chem.*, 1994, **125**, 469; (*b*) G. Cremonesi, P. D. Croce, A. Forni, M. Gallanti, R. Gandolfi and C. La Rosa, *Tetrahedron: Asymmetry*, 2009, **20**, 1940.

15 For a two step approach to isoxazoline *N*-oxides, see: (*a*) H. Jiang, P. Elsner, K. L. Jensen, A. Falcicchio, V. Marcos and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2009, **48**, 6844; (*b*) Z. Shi, B. Tan, W. W. Y. Leong, X. Zeng, M. Lu and G. Zhong, *Org. Lett.*, 2010, **12**, 5402.

16 For reviews on squaramides, see: (*a*) R. Ian Storer, C. Aciro and L. H. Jones, *Chem. Soc. Rev.*, 2011, **40**, 2330; (*b*) J. Alemán, A. Parra, H. Jiang and K. A. Jørgensen, *Chem.–Eur. J.*, 2011, **17**, 6890.

17 For an example of selective O-alkylation reactions of *N*-BocNHOH, see: S. D. Nielsen, G. Smith, M. Begtrup and J. L. Kristensen, *Chem.–Eur. J.*, 2010, **16**, 4557.

18 For an insightful discussion on the oxa-Michael reaction mechanism, see: L. Hintermann, J. Ackerstaff and F. Boeck, *Chem.–Eur. J.*, 2013, **19**, 2311.

19 The absolute configuration of isoxazoline **4a** was determined through structure similarity after chemical transformation, but the absolute configuration of the other 1,4-dihydroisoxazoles was proposed by analogy due to the similar priority of elution by chiral HPLC.

20 (*a*) T. Ogamino and S. Nishiyama, *Tetrahedron*, 2003, **59**, 9419; (*b*) A. Pohjakallio, P. M. Pihko and J. Liu, *J. Org. Chem.*, 2010, **75**, 6712.

21 H. Jiang, M. W. Paixão, D. Monge and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2010, **132**, 2775.