ChemComm

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COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2013, **49**, 11665

Received 27th September 2013,
Accepted 17th October 2013

DOI: 10.1039/c3cc47397j

www.rsc.org/chemcomm

Highly enantioselective synthesis of chiral 7-ring O- and N-heterocycles by a one-pot nitro-Michael–cyclization tandem reaction†

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A concise enantioselective approach to synthesise medium-sized 7-ring O- and N-heterocycles has been developed. The synthetic strategy relies on an organocatalytic nitro-Michael–nitrile oxide cycloaddition tandem reaction, leading to the corresponding chiral benzoxe- and benzazepine derivatives containing an additional fused dihydroisoxazoline ring in good yields and excellent enantioselectivities (up to 97% ee).

Oxygen and nitrogen containing medium-sized heterocycles are important common structural motifs found in numerous biologically active and natural products.[1] Much attention has been paid to the construction of 7-ring systems such as benzoxe- and benzazepines due to their interesting and broad range of biological applications[2] as antibacterial compounds,[2b] diverse receptor agonists,[2c,d] or regulators of metabolic disorders like insulin secretion.[2e] Some examples of such natural and bioactive derivatives are shown in Fig. 1.

Despite their structural significance, the development of efficient enantioselective methodologies for the synthesis of such 7-ring heterocycles remains a big challenge.[3] Although important advances have already been made using asymmetric strategies based on transition-metal-catalysis, such as Pd (*e.g.* Heck),[4] Rh (*e.g.* olefin hydroacylation),[5] Mo (*e.g.* ring closing metathesis (RCM))[6] or Ir/Ru (*e.g.* allylic amination–RCM sequence)[7] catalysis, organocatalytic processes are still quite rare.[8]

Herein, we report an easy and alternative metal-free one-pot procedure for the synthesis of various chiral benzoxa- and benzazepine derivatives. Our synthetic design involved an asymmetric organocatalyzed nitro-Michael addition[9,10] followed by an *in situ* nitrile oxide generation–intramolecular cycloaddition tandem reaction (Scheme 1).[11]

Initially, the two steps involved in the synthetic sequence were studied independently. Thus, the enantioselective nitro-Michael addition reaction between β-nitro styrene derivative **2a** as a model substrate and methylmalonate **3a** in the presence of 10 mol% of bifunctional thiourea–cinchona catalyst **1a** in *o*-xylene was first carried out.[12] The corresponding addition product **4a** was obtained in excellent yield and enantioselectivity (99%, 96% ee). Next, **4a** was subjected to the reaction with Boc_2O in the presence of 20 mol% of DMAP as a base at 90 °C for 3.5 h in the same solvent (*o*-xylene) used in the first step.[12,13] Under these conditions the corresponding nitrile oxide intermediate is generated *in situ* and can further be cyclized with the olefin present in the side chain of the molecule to form the desired 7-ring, along with a fused

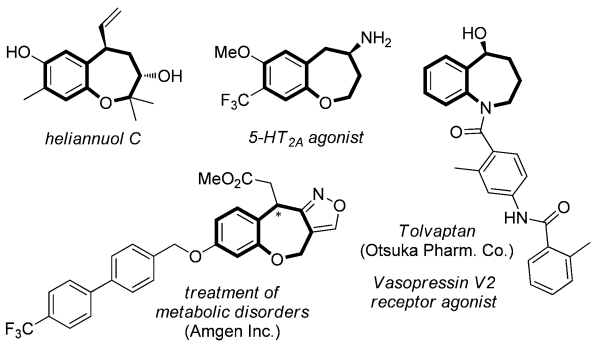
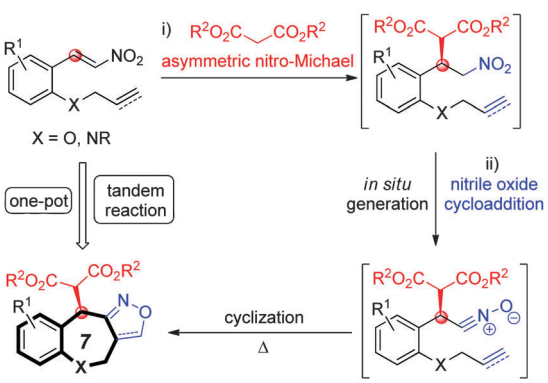


Fig. 1 Some selected bioactive 1-benzoxe- and benzazepines.



Scheme 1 Approach to synthesise chiral benzoxe- and benzazepines.

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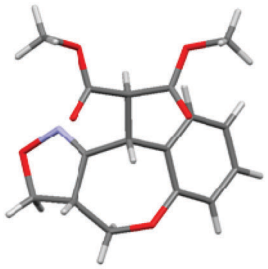
† Electronic supplementary information (ESI) available: Optimization studies, experimental procedures, characterization, NMR spectra of compounds, HPLC (**4a** and **5**), and X-ray ORTREP and the CIF-file for (3a*R*,10*R*)-**5a**. CCDC 961434. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc47397j

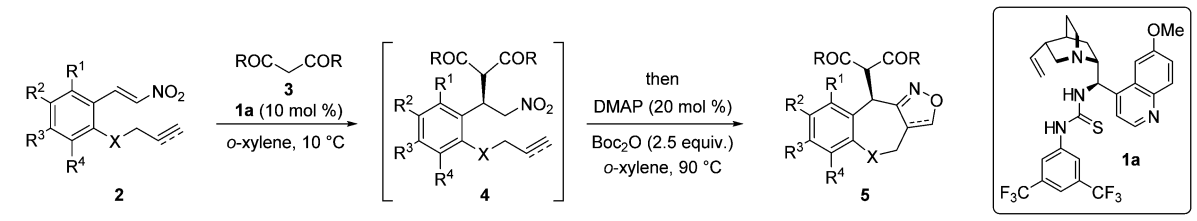


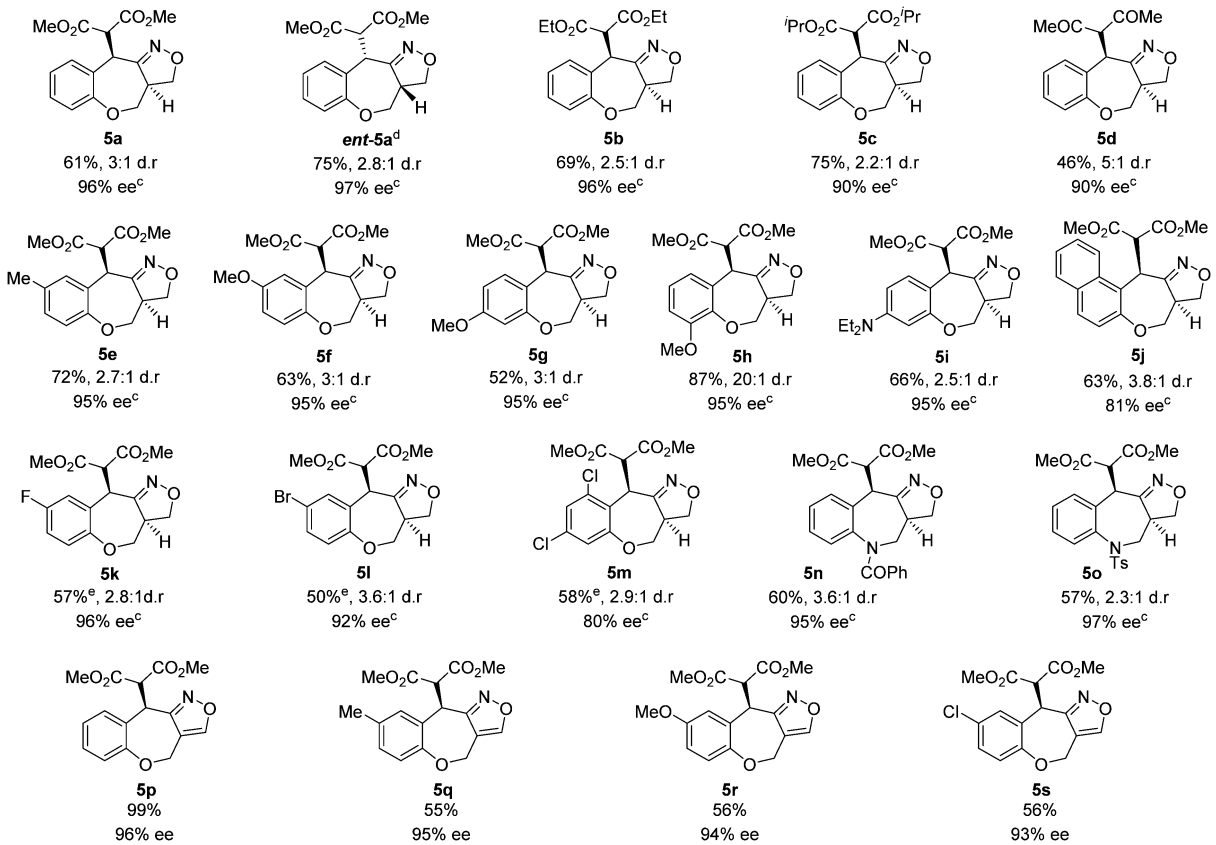
(3a*R*,10*R*)-**5a**

Scheme 2 X-Ray structure of the major diastereoisomer of **5a**.

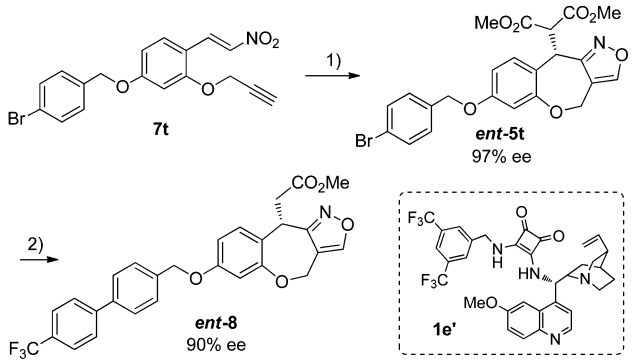
dihydroisoxazoline 5-ring. The desired product **5a** was then formed in 75% NMR-yield as a 3 : 1 diastereomeric mixture. To our delight, the cyclization reaction proceeded without erosion of the enantioselectivity (96% ee, for both diastereomers), and **5a** was isolated in a good 60% yield. Moreover, the absolute configuration of **5a** was determined to be (3a*R*,10*R*) by X-ray crystallographic analysis (Scheme 2).[14] Assuming that the initial enantioselective addition occurs in the *Re*-face of the olefin and the nitrile oxide cycloaddition reaction takes place with retention of the chiral information at C10, the configuration of all further synthesized derivatives **5** was accordingly assigned by analogy. Having proved the feasibility of the two steps involved in the sequence, the one-pot synthesis was carried out (Table 1). Similar results were obtained for compound **5a** (96% ee, 61%/2-step yield), showing the compatibility of these transformations in a one-pot fashion. It is also important to note that the enantiomer ***ent*-5a** can also be attained in 97% ee when using the pseudo-enantiomer catalyst **1b** derived from quinine instead of quinidine. The scope of the one-pot reaction was then explored. Besides **3a**, different activated methylene compounds **3** such as ethyl or iso-propyl substituted malonates and a β-diketone were also efficiently employed as nucleophiles. They led to similar

Table 1 One-pot synthesis of chiral benzoxapine and benzazepine derivatives **5**[a,b]





[a] Catalyst **1a** (10 mol%), **2** (0.2 mmol) and **3** (0.24 mmol) in *o*-xylene (0.2 M) at 10 °C for 4–7d; then DMAP (20 mol%) and Boc_2O (2.5 equiv.) in *o*-xylene at 90 °C for 3.5 h. [b] Isolated yields and ee determined for the final products by chiral HPLC. [c] Same ee for both diastereoisomers. [d] Use of the pseudoenantiomer catalyst **1b** prepared from quinine. [e] A nitrile side-product **6** was also obtained (see ESI).



1) i) **1e'** (10 mol %), **7t** (1 equiv.) and **3a** (1.2 equiv.) in CH_2Cl_2 (0.2 M) at r.t. (60%); ii) DMAP (20 mol %) and Boc_2O (2.5 equiv.) at 90 °C (58%). 2) ***ent*-5t** (1 equiv.), $Pd(PPh_3)_4$ (5 mol %), Ar-$B(OH)_2$ (1.2 equiv.), dioxane, 150 °C (99%).

Scheme 3 Synthetic application of the methodology.

excellent enantioselectivities (90–96% ee) and good overall yields (46–75%) on the corresponding benzoxepines **5b–d** (Table 1, first row). Moreover, the reaction showed a broad scope and substitution tolerance of the aryl moiety. Thus, both electron donating (**2e–i**) and withdrawing (**2k** and **2l**) groups at the β-nitrostyrenes provided high enantioselectivities (92–96% ee). However, the reaction was significantly affected by steric hindrance. Accordingly, precursors possessing two *ortho* substituents on the arene, such as **2j** and **2m**, led to a slight decrease in the enantioselectivity (81 and 80% ee, **5j** and **5m** respectively). Lastly, the one-pot nitro-Michael–cycloaddition reaction with the nitrogen-containing substrates **1n** and **1o** and the *O*-propargyl (**1p–s**) instead of the *O*-allyl unit [Table 1, last row] was carried out. The N-COPh **5n** and N-Ts **5o** substituted benzazepines were formed within 95 and 97% ee and in 60 and 57% yield, respectively. The benzoxapine–isoxazoles **5p–s** were also obtained in homogenous high enantioselectivity and good to excellent overall yields (55–95%).

After demonstrating the scope of this approach, the synthesis of the biologically active benzoxepine ***ent*-8**[2e] was pursued (Scheme 3). To achieve this goal the squarimide-cinchona **1e′** was employed as catalyst. Thus, the cyclic product ***ent*-5t** could be obtained in an excellent 97% ee.[15,16] Finally, ***ent*-5t** was subjected to a Suzuki coupling with 4-trifluoromethylphenylboronic acid and *in situ* decarboxylation reaction to directly build the desired product ***ent*-8** in 99% yield and 90% ee.

In conclusion, we have developed a highly enantioselective one-pot method for the synthesis of a variety of optically active seven-membered O- and N-heterocycles. The presented approach is based on a one-pot enantioselective organocatalytic nitro-Michael addition–nitrile oxide cycloaddition sequence. The corresponding heterocyclic derivatives, 1-benzoxe- and benzazepines, were obtained in moderate to good yields and excellent enantioselectivities. Finally, the applicability of this methodology was demonstrated by the straightforward synthesis of ***ent*-8**, which is an efficient derivative for the treatment of metabolic disorders.

The Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft, and Prof. Frank Glorius are acknowledged for generous support. R.R. thanks Münster University within the Bonusprogram for a predoctoral contract.

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14 CCDC 961434 ((3a*R*,10*R*)-**5a**).
15 In this particular case, the isolation of the addition intermediate ***ent*-4t** was necessary to avoid the erosion of enantioselectivity during the cyclization process in the presence of the remaining starting materials.
16 The highly demanding benzoxepines **5t** and ***ent*-5t** were obtained in a moderate 70% ee and low 33–34% yields under the standard one-pot conditions using **1a** and **1b** as catalysts, respectively. The 2 step approach provided the Michael adduct in 35% yield and 95% ee (in DCM) and the benzoxepine in 94% ee (21% overall yield). To improve the conversion of the nitro-Michael step, the squarimide catalyst **1e′** was employed at r.t. in DCM for 7 days (***ent*-4t**: 60%, 97% ee).