Highly enantioselective carbon–carbon bond formation by Cu-catalyzed asymmetric [2,3]-sigmatropic rearrangement: application to the syntheses of seven-membered oxacycles and six-membered carbocycles†

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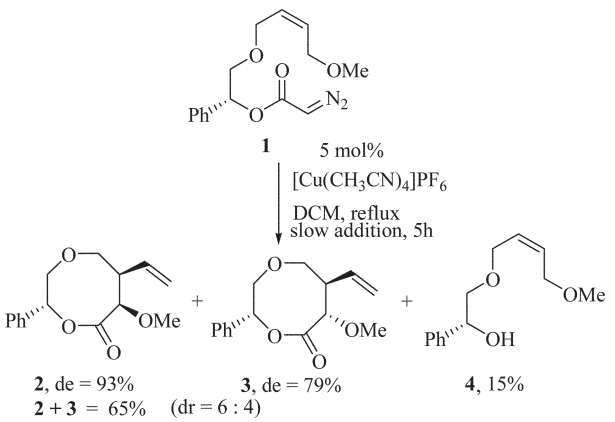
A concise route for the syntheses of enantioenriched functionalized scaffolds of medium-sized oxacycles and carbocycles employing the chiral auxiliary-mediated Cu-catalyzed ylide formation/[2,3]-sigmatropic rearrangement as a key step was developed.

In recent years there has been a resurgence of interest in therapeutic targets based on the structures of bioactive natural products.[1] Oxacycles and carbocycles possessing pharmacophoric active sites are common structural features of various biologically active natural products.[2] Owing to their biological activity coupled with complexity, they have become attractive targets for synthesis. The design and synthesis of enantiomerically pure medium-sized oxacycles and carbocycles have attracted a great deal of attention due to the concept of small molecular entities for drug discovery and development.[3] The strategies that were developed for preparing such molecules were found to be inadequate.[4] Recently, Doyle *et al.* have developed an impressive catalytic bis-oxazoline Cu-catalyzed asymmetric [2,3]-sigmatropic rearrangement of diazoacetate derived from allyl-substituted 1,2-benzenedimethanol. Despite their best efforts, the resulting product showed only 65% ee, thereby restricting the further applicability of this reaction.[5] The erosion in enantioselectivity appears to be due to the flexible conformations of the 11-membered oxonium ylide transition state, leading to the product in only moderate enantioselectivity. We reason that steric and electronic factors, which may stabilize oxonium ylide conformation and its subsequent [2,3]-sigmatropic rearrangement, could lead to highly enantioselective carbon–carbon bond formation. Herein, we disclose our preliminary results relating to this object and its relevance for the synthesis of medium-sized carbocycles and oxacycles.

Initially, we examined the (*R*)-phenylethylene glycol tethered with diazoacetate and methoxy *cis*-butene **1** (Scheme 1) as a test substrate. The precursor **1** was prepared in five steps from (*R*)-mandelic acid. The Cu-catalyzed[6] (5 mol%) reaction of **1** in DCM at reflux temperature led to a diastereomeric mixture of **2** and **3** in a 6 : 4 ratio (*syn* : *anti*) but the diastereomeric excess was found to be moderate (**2**, 93% de and **3**, 79% de). Along with **2** and **3**, 15% of **4** was also isolated. To identify another class of auxiliary that would allow highly enantioselective carbon–carbon bond formation, we examined a C_2-symmetric diol tethered with diazoacetate and methoxy *cis*-butene **5a** as starting material.



Scheme 1

The Cu-catalyzed (5 mol%)‡ reaction of **5a** using identical conditions resulted in **6a** and **7a** in 68% yield§ with a similar diastereomeric ratio (dr = 6 : 4 *syn* : *anti*) but with a substantial increase in diastereomeric excess (**6a**, 99.8% de and **7a**, 99.8% de) (Scheme 2). The diastereomers **6a** and **7a** were separated by silica gel column chromatography and their stereochemical assignment was established by the vicinal coupling constant to the proton on the methoxy-substituted carbon (J_{anti} 5.7 Hz > J_{gauche} 3.2 Hz) as well as NOE studies. In **6a**, the presence of strong NOEs (H_e–H_d, H_d–H_b, H_b–H_i) and a weak NOE of H_e–H_b indicates that these are in the same plane (Fig. 1).

Additionally, a medium range NOE between H_f and OMe confirms that H_a and H_b are in *cis* conformation. Whereas, in **7a**, the presence of an NOE (H_a–H_f) and (H_b–H_i) indicates that these protons are nearer, and the absence of an NOE (H_f–OMe) shows that they are in opposite planes, and hence, H_a and H_b are in *trans* conformation.

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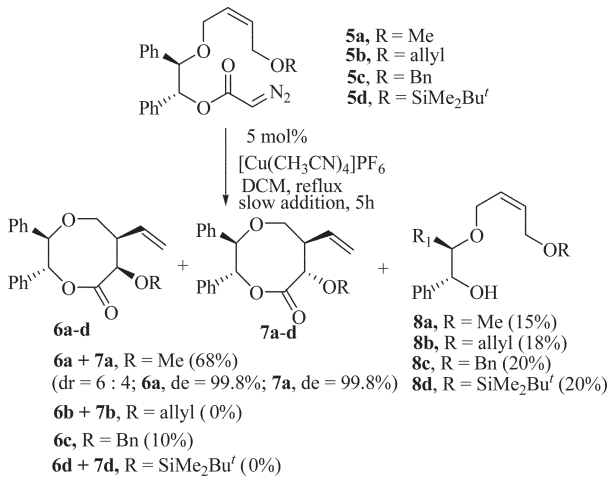
† Electronic supplementary information (ESI) available: Synthesis and analytical data. CCDC reference number 690682. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b810770j



Scheme 2

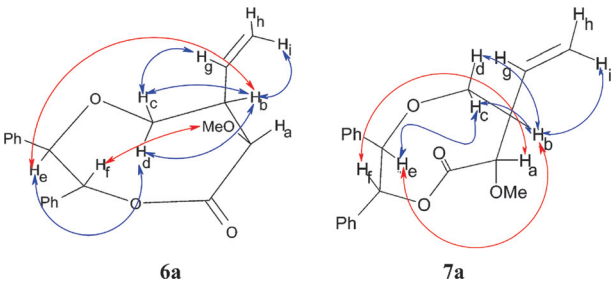


Fig. 1 NOE study of **6a** and **7a**.

The de values of **6a** and **7a** were determined by chiral HPLC analysis in comparison with a racemic mixture. The major *syn* isomer **6a** and minor *anti* isomer **7a** showed >99.8% de.

The stereochemical outcome of products **6a** and **7a** could be rationalised on the basis of the oxonium ylide transition state of the corresponding **6a*** and **7a***, wherein the C_2-symmetric 1,2-diphenylethane serves as a template for the formation of highly enantioselective C–C bond formation (Scheme 3). Significantly, in contrast to the previous reports,[5b] no trace of intramolecular cyclopropanation product was observed in this transformation.

Further, we prepared the substrates **5b–d** and subjected them to the same protocol. In the case of **5b**, only a trace of the terminal cyclopropanated product was isolated. Substrate **5c** resulted in product **6c** (10%) *via* the expected ylide formation/[2,3]-sigmatropic rearrangement along with a major unidentified product (40%). Under otherwise identical conditions, with the substrate **5d**, neither the [2,3]-sigmatropic rearrangement products **6d** and **7d** nor the cyclopropanated product was formed.

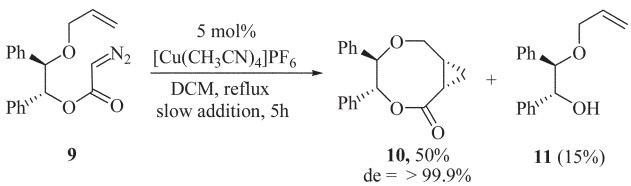
In order to increase the diastereoselectivity, we have evaluated **5a** with a spectrum of catalysts such as $Rh_2(pfb)_4$ (pfb = perfluorobutyrate), $Rh_2(OAc)_4$, and Rh_2(octanoate). To our surprise only trace of *syn* product **6a** (5–8%) along with **8a** (~30%) were isolated with each of the Rh precursors.

To ascertain chemoselectivity, we have synthesized an allyl-tethered diazo C_2-symmetric substrate **9**. The Cu-catalyzed (5 mol%) diazodecomposition of **9** in DCM at reflux temperature resulted exclusively in the cyclopropanation product **10** in 50% yield with >99.9% de along with **11** (15%) (Scheme 4). The relative stereochemistry (*S*,*R*) of **10** was confirmed by X-ray crystallography (Fig. 2).

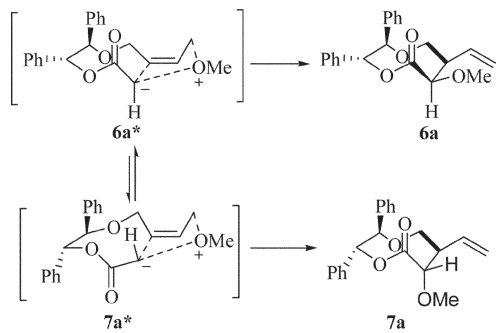
Finally, the products derived from the [2,3]-sigmatropic rearrangement were conveniently elaborated to the synthesis of medium-sized oxacycles and carbocycles. To this end, **6a** was converted to a diol by LAH reduction in THF, and subsequent protection of the primary alcohol as the TBDMS ether was followed by removal of the chiral auxiliary in liq. NH_3 at −78 °C which led to **12** (81% from **6a**).

The resulting primary alcohol **12** was protected as the benzyl ether, and subsequent *p*-toluenesulfonic acid (PTSA)-assisted cleavage of the TBDMS group furnished **13**. Allylation of primary alcohol **13** with allyl bromide using NaH in THF afforded **14** (86%). A one-pot RCM/dihydroxylation sequence followed by acetonide protection of **14** resulted in **15** and **16** (6 : 4) as separable diastereomers in 60% yield.[7] Similarly, the diastereomers **17** and **18** were achieved from **7a** using an identical sequence of steps as above in an overall 37.6% yield (Scheme 5).[8]

With a notion to prepare functionalized carbocycles, **13** was subjected to oxidation to give **19** in 90% yield. A catalytic allylation[9] of **19** led to **20** as a separable diastereomeric mixture (8 : 2) in 61% isolated yield. The major diastereomer **20** was separated through column chromatography and was



Scheme 4 Cu-catalyzed cyclopropanation of **9**.



Scheme 3 Oxonium ylide transition states of **6a** and **7a**.

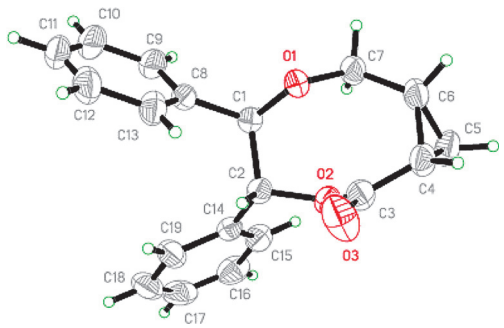
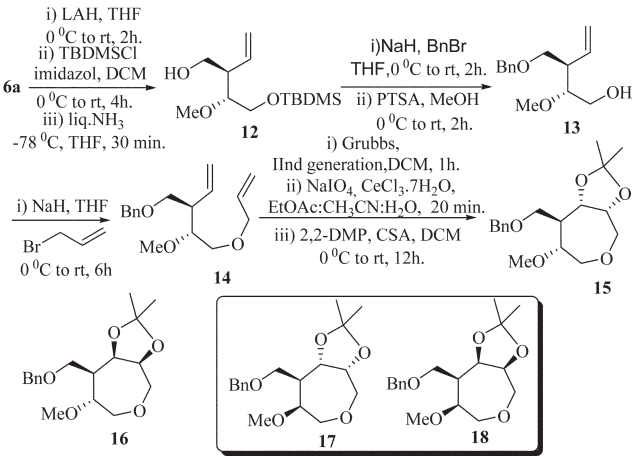
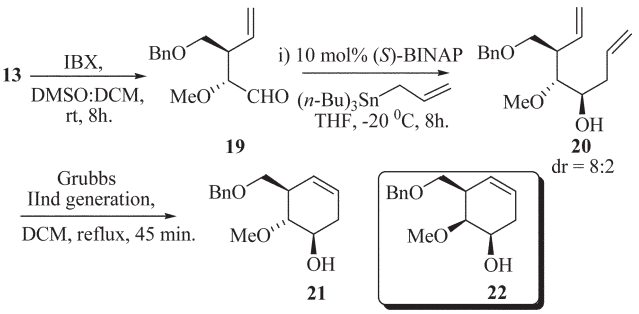


Fig. 2 ORTEP representation of **10** with 50% probabilty.



Scheme 5 Syntheses of functionalized oxacycles.



Scheme 6 Syntheses of functionalized carbocycles.

subjected to ring-closing metathesis (RCM) reaction employing a Grubb's second generation catalyst, furnishing **21**, which has an option for further elaboration by means of various addition reactions. The diastereomer **22** was generated from **7a** following an identical sequence of steps as above in an overall 42.8% yield (Scheme 6).

In conclusion, we have accomplished a concise enantioselective route for the syntheses of functionalized scaffolds of medium-sized oxacycles and carbocycles employing a chiral auxiliary-mediated Cu-catalyzed ylide formation/[2,3]-sigmatropic as a key step. Additionally, the complementary sense of enantioenriched molecules of oxacycles has been synthesized using an antipode of C_2-symmetric (*S*,*S*)-diol, thus generating a library of target molecules.[10] Further work is under progress for the synthesis of carbocyclic analogues based on oseltamivir phosphate, an important anti-influenza drug, as motif.[11]

Notes and references

‡ Reaction also proceeded with 1 and 2 mol% of catalyst loading. The resulting product showed with same dr and de, but slightly decreased yields were obtained [**6a** + **7a** = 55% (1 mol%), 58% (2 mol%), respectively].

§ **Experimental and spectral data of 6a**. A solution of diazoacetate **5a** (1 g, 2.73 mmol) in DCM (60 mL) was added using a syringe pump (12 mL h^{-1}) to tetrakis(acetonitrile)copper(I) hexafluorophosphate (51 mg, 5 mol%) dissolved in DCM (60 mL) under reflux conditions for a period of 5 h. After completion of the addition, the resulting reaction mixture was allowed to cool to rt, then the solvent was removed under reduced pressure. The crude residue was subjected to column chromatography (silica gel, 100–200 mesh) eluting with hexane–EtOAc (97 : 3) to give **7a** (*anti*) (250 mg, 27%) and **6a** (*syn*) (380 mg, 41%) including recovered **8a** (122 mg, 15%). **6a**: solid, mp 120 °C, $[\alpha]_{24}^{D}$ −74.0 (*c* 0.01, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29–7.17 (m, 6H), 7.10 (d, J = 6.5 Hz, 2H), 6.98 (d, J = 6.5 Hz, 2H), 6.13 (ddd, J_1 = 17.0, J_2 = 11.0, J_3 = 8.7 Hz, 1H), 5.94 (d, J = 9.0 Hz, 1H), 5.29–5.26 (m, 2H), 4.37 (d, J = 9.7 Hz, 1H), 4.22 (dd, J_1 = 6.5, J_2 = 11.6 Hz, 1H), 4.16 (d, J = 5.8 Hz, 1H), 3.93 (d, J = 10.3 Hz, 1H), 3.51 (s, 3H), 3.30–3.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 137.0, 135.1, 133.7, 128.6, 128.2, 128.0, 127.5, 127.3, 118.4, 96.1, 86.9, 80.0, 74.0, 58.4, 50.3. IR (KBr): 3473, 3084, 2938, 2890, 1745, 1454, 1209, 1116, 986, 698 cm^{-1}; MS (ESIMS): m/z 338.9 ($M + H^+$), 321, 242, 197; HRMS (ESIMS): Calculated for $C_{21}H_{22}O_4Na$, 361.1415, Found 361.1415.

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6 For this transformation, among the surveyed catalysts $Cu(CH_3CN)_4PF_6$ turned out to be the best. The electropositive Cu attached to a large counter anion appears to be essential to initiate the reaction. We have also evaluated other Cu sources such as $Cu(OTf)_2$, $CuCl_2$, $Cu(OAc)_2$, Cu(pivalate)$_2$, Cu(acac)$_2$, $CuSO_4$, and CuI, but none gave the observed product.

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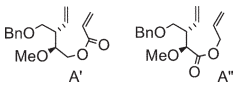
8 We also attempted the synthesis of functionalized seven-membered lactones. Unfortunately, compounds **A′** and **A″** did not undergo the RCM reaction.



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10 The preferential conformations of **15**, **16**, **17**, **18**, **21**, **22** [compounds generated using the (*R*,*R*)-diol], **6a″**, **7a″**, **15″** and **17″** [compounds generated using the (*S*,*S*)-diol], have been characterised by NMR data (see ESI†).

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