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Communication

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Desymmetrization of *meso*-Dibromocycloalkenes through Copper(I)-Catalyzed Asymmetric Allylic Substitution with Organolithium Reagents

Shermin S. Goh,[†,§] Sureshbabu Guduguntla,[†] Takashi Kikuchi,[‡,¤] Martin Lutz,[※] Edwin Otten,[†] Makoto Fujita,[‡] and Ben L. Feringa.[†,*]

† Stratingh Institute for Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands.

§ Institute of Materials Research and Engineering, 2 Fusionopolis Way, Innovis #08-03, Singapore 138634.

‡ Department of Applied Chemistry, University of Tokyo, 7-3-1, Hongo, Bukyo-ku, Tokyo, Japan 113-8656.

¤ Rigaku Corporation, 3-9-12 Matsubara-cho, Akishima-shi, Tokyo 196-8628, Japan.

※ Bijvoet Center for Biomolecular Research, Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands.

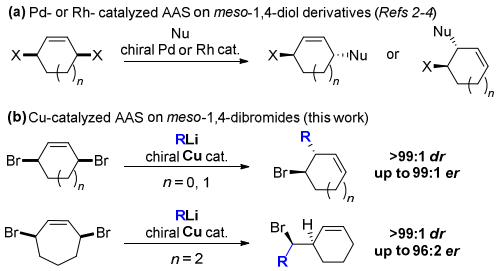
Supporting Information Placeholder

ABSTRACT: The highly regio- and enantioselective (up to >99:1 *dr*, up to 99:1 *er*) desymmetrization of *meso*-1,4-dibromocycloalk-2-enes using asymmetric allylic substitution with organolithium reagents to afford enantioenriched bromocycloalkenes (ring size of 5 to 7) has been achieved. The cycloheptene products undergo an unusual ring contraction. The synthetic versatility of this Cu(I)-catalyzed reaction is demonstrated by the concise stereocontrolled preparation of cyclic amino alcohols, which are privileged chiral structures in natural products and pharmaceuticals, and widely used in synthesis and catalysis.

The enantioselective desymmetrization of *meso* compounds is one of the most powerful strategies in organic synthesis.[1] It enables the formation of compounds with multiple stereocenters in a single step from readily accessible σ-symmetric precursors. In the case of *meso*-cycloalk-2-ene-1,4-diol derivatives, desymmetrization by asymmetric allylic substitution (AAS) is a powerful tool for the construction of enantiomerically enriched functionalised cyclic products,[2] which have found ample use in the total syntheses of various natural products.[3] Depending on the choice of nucleophile (soft or hard) and metal catalyst, the reaction can result in either α- or γ-substitution, with either retention or inversion of configuration. The most commonly employed procedure is the Pd-catalyzed desymmetrization, which is usually performed with soft nucleophiles to give S_N2-products (Scheme 1a).[2,3] A viable alternative is the Rh-catalyzed desymmetrization using arylboronic acids,[4] which give S_N2 or S_N2' products depending on the ligand at Rh. These processes, albeit highly versatile at producing chiral building blocks, rely on precious metal catalysts. In contrast, there are markedly few examples of the Cu(I)-catalyzed desymmetrization, which generally employs hard nucleophiles to provide S_N2' products.[5] Sawamura and co-workers have utilized the Cu-catalyzed asymmetric boryl substitution in conjuction with allylation to afford a formal S_N2 substitution with electrophiles.[6]

The Cu(I)-catalyzed AAS with organometallic nucleophiles, pioneered by Bäckvall and van Koten in 1995,[7] is an effective method to synthesize tertiary carbon stereocenters.[8] While many different metal catalysts and organometallic nucleophiles could be used for AAS,[9] the readily available organolithium reagents were considered too reactive to be utilized in catalytic asymmetric C-C bond formation until the 2011 disclosure by Feringa *et al*. using allylic bromides as substrates, forming S_N2' products with high regio- and enantioselectivities.[10] In recent years our group has extended this protocol,[11] most notably to the use of allylic-chlorides and -ethers,[11a,b] aryllithium nucleophiles,[11c,d] and also to the formation of highly challenging all-carbon quaternary stereocenters.[11b,d] We envisaged that the AAS strategy with organolithium reagents could be applied to the desymmetrization of *meso* compounds. Herein, we report the highly regio- and enantioselective (up to >99:1 *dr*, up to 99:1 *er*) desymmetrization of *meso*-2-cycloalkene-1,4-dibromides using Cu(I)-catalyzed AAS with organolithium reagents to afford enantioenriched bromocycloalkene synthons (Scheme 1b).

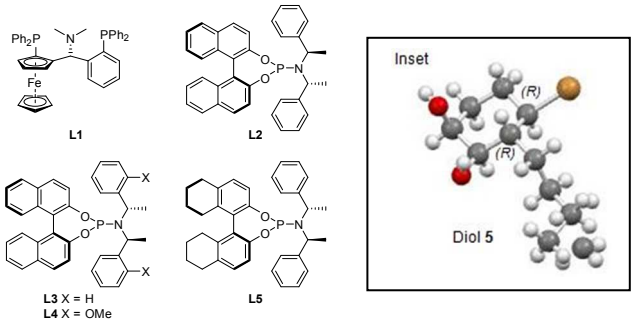
Scheme 1. Desymmetrization of *meso*-1,4-cycloalkenediol derivatives



Optimization of the desymmetrization reaction began with *meso*-3,6-dibromocyclohex-1-ene **1** as model electrophile and commercially available *n*-BuLi as nucleophile in the presence of a catalytic amount of $CuBr{\cdot}SMe_2$ and chiral ligand. The racemic reaction with PPh_3 as ligand (Table 1, Entry 1) proceeded to full conversion to give *trans*-4-bromo-3-butylcyclohexene **2d** as the major product (from S_N2' substitution) in 91% yield. The double addition product **3** (9%) was also observed; its formation most probably occurs via a S_N2-type substitution followed by a S_N2'-type substitution on the allylic bromide intermediate. Taniaphos

L1, which was an effective chiral ligand in the acyclic AAS,[10] was initially tested (Entry 2). Unfortunately, no conversion was observed which (based on models) was attributed to steric interactions between **L1** and cyclohexene **1**. We then switched to the phosphoramidite ligand class,[12] which have previously been used in the desymmetrization of *meso*-cyclic bis(diethyl phosphates) by Cu-AAS using organozinc reagents.[5b,c] With (*S,R,R*)-phosphoramidite **L2**, only partial conversion was observed, and the desired product had low *er* (Entry 3). When (*S,S,S*)-phosphoramidite **L3** was tested, 90% conversion (98:2 *er*) to the desired product was found (Entry 4). When this transformation was performed on multigram scale, analytically pure **2d** was obtained in 89% yield and 99:1 *er*. Neither a more electron-rich phosphoramidite **L4** nor a more flexible octahydrophosphoramidite **L5** could enhance this result (Entries 5 & 6). When a 9:1 *cis/trans* mixture of starting material was subjected to the optimized conditions with **L3**, the enantioselectivity was maintained (99:1 *er*) and the product **2d** could be isolated in 80% yield (Entry 7); *trans*-**1** was almost entirely recovered. This prompted us to investigate the reaction with racemic *trans*-**1** under the same conditions (Entry 8). Unsurprisingly, the reaction did not proceed to full conversion and formation of some *cis*-4-bromo-3-butylcyclohex-1-ene **4** was also observed. The absolute configuration of **2d** was determined by X-ray crystallography of diol **5** (Table 1, inset),[13] resulting in a Flack parameter of x = 0.04(2).

Table 1. Screening of ligands for AAS-desymmetrization of *meso*-dibromocyclohexene 1 with *n*-BuLi [a]



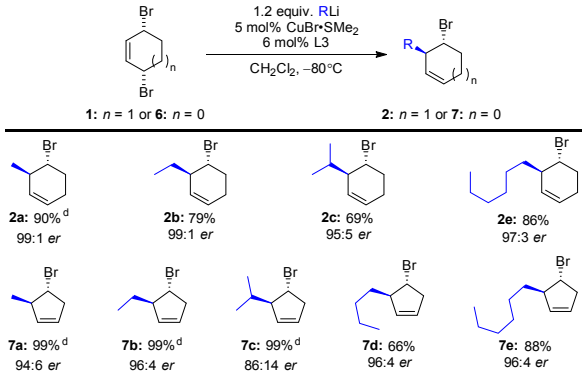
Entry	Ligand	**2d**:**1**:**3**:**4** [b]	**2d**, *er* / % [c]
1	PPh_3	91:0:9:0	50:50
2	**L1**	0:100:0:0	-
3	**L2**	52:42:6:0	47:53
4	**L3**	90:0:10:0	98:2
5	**L4**	92:0:8:0	95:5
6	**L5**	91:0:9:0	88:12
7 [d]	**L3**	92:8:0:0 (80%) [e]	99:1
8 [f]	**L3**	48:30:12:10	54:46

[a] Conditions: *meso*-**1** (0.2 mmol) in CH_2Cl_2 (2 mL). *n*-BuLi (0.24 mmol, 1.6 M solution in hexanes diluted to a final concentration of 0.24 M) was added over 2 h. [b] Determined by GC–MS and ^{1}H NMR. [c] *Er* determined by chiral GC. [d] A 9:1 *cis*/*trans*-mixture of **1** was used. [e] Isolated yield of **2d** on 0.2 mmol scale; increases to 89% on 10 mmol scale (see SI). [f] Racemic *trans*-**1** was used. Inset: Ball-and-stick representation of the X-ray crystal structure of diol **5**.

Chiral HPLC confirmed that a single diastereomer of **5** with four contiguous stereocenters was obtained (>99:1 *dr*, 99:1 *er*) after Upjohn dihydroxylation of **2d**.

With the optimized conditions in hand (Entry 4), we proceeded to examine the scope of the reaction. Continuing with the 6-membered substrate **1** (Scheme 2), addition of commercially available alkyllithium reagents afforded the AAS products **2a-e** with excellent enantioselectivities (up to 99:1 *er*). Only isopropyl-bearing product **2c** had a slightly lower *er* (95:5), possibly a result of the steric bulk of the isopropyl group. The reaction worked similarly well for *meso*-3,5-dibromocyclopentene **6** to generate products **7a-e** in good yields with up to 96:4 *er* (Scheme 2).

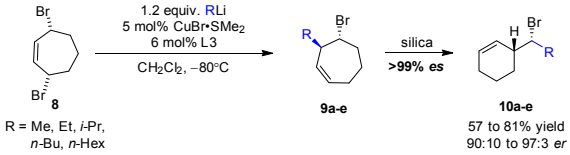
Scheme 2. Alkyllithium scope for desymmetrization of 5- and 6-membered *meso*-cyclic allylic dibromides 1 and 6 [a,b,c]



[a] Conditions: *meso*-**1** (9:1 *cis*/*trans*) or **6** (0.2 mmol) in CH_2Cl_2 (2 mL). RLi (0.24 mmol, diluted to a final concentration of 0.24 M) was added over 2 h. [b] Isolated yields. [c] *Er* determined by chiral GC. [d] GC yields reported due to product volatility (see SI).

When *meso*-3,7-dibromo-cycloheptene **8** was used in the desymmetrization reaction with alkyllithium reagents (Scheme 3), the expected products **9a-e** (>99:1 *dr*) were initially obtained with *er* values ranging from 90:10 to 97:3, based on NMR and chiral GC. However, when purification of these 7-membered rings **9a-e** was attempted by flash column chromatography on silica, only their corresponding cyclohexene analogs **10a-e** were isolated with complete stereospecificity. A detailed structural analysis, mechanistic and theoretical study to elucidate this remarkable ring contraction is reported separately.[14]

Scheme 3. Desymmetrization-rearrangement of 7-membered *meso*-cyclic allylic dibromide 8 [a,b,c]

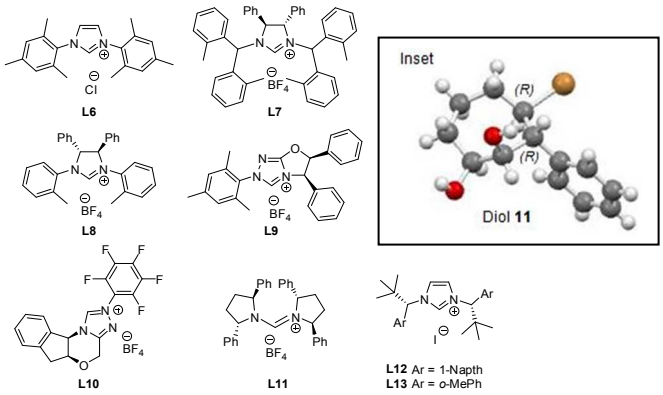


[a] Conditions: (i) *meso*-**8** in CH_2Cl_2 (2 mL). RLi (0.24 mmol, diluted to a final concentration of 0.24 M) was added over 2 h; (ii) silica, pentane. [b] Isolated yields. [c] *Er* of **9a-e** and **10a-e** determined by chiral GC to be the same, so *es* >99%.

We hypothesized that a phenyl substituent would stabilize the desymmetrization product i.e. chiral cycloheptene **9**, enabling its isolation. We have previously reported that N-heterocyclic carbenes (NHC) are the most suitable ligand class for asymmetric allylic arylation (AAAr).[11c,d] As such, we screened, besides achiral **L6** as control, several chiral NHC ligands for the desymmetrization of dibromocycloheptene **8** by with phenyllithium (Table 2). While the dihydroimidazolium-based ligands **L7** and **L8** gave

excellent conversion, the *er* was poor to moderate (Entries 2 and 3). In contrast, triazolium-based ligands **L9** and **L10** gave poorer conversions (Entries 4 and 5). Gratifyingly, we found that imidazolium salt **L12** was a suitable NHC precursor; in conjunction with $CuBr{\cdot}SMe_2$ and NaO*t*-Bu, this catalytic system afforded the desired 4-bromo-3-phenylcycloheptene **9f** in 83% isolated yield with 95:5 *er* (Entry 7). In accordance with our prediction, and in sharp contrast with alkyl analogs **9a-e**, this product was stable to base-treated silica and could be isolated. The absolute configuration of **9f** was determined to be (*R*,*R*) by X-ray crystallography of diol **11** (Table 2, inset),[15] which was obtained *via* diastereoselective Upjohn dihydroxylation (88:12 *dr*, 96:4 *er* as determined by chiral HPLC).

Table 2. Screening of ligands for AAAr-desymmetrization of *meso*-dibromocycloheptene 8 with PhLi [a]

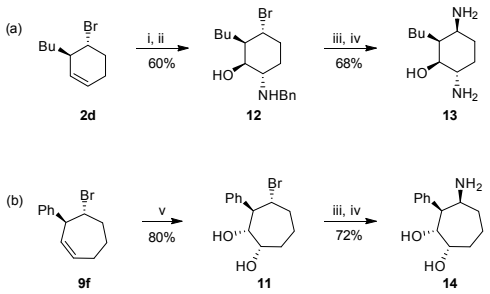


Entry	Ligand	9f:8 [b]	9f, *er* / % [c]
1	**L6**	>99:1	50:50
2	**L7**	>99:1	12:88
3	**L8**	>99:1	53:47
4	**L9**	82:18	41:59
5	**L10**	68:32	21:79
6	**L11**	86:14	23:77
7	**L12**	>99:1 (83) [d]	5:95
8	**L13**	71	18:82

[a] Conditions: *meso*-**8** (0.2 mmol) in CH_2Cl_2 (2 mL). PhLi (0.30 mmol, 1.9 M solution in di-*n*-butyl ether diluted with hexanes to a final concentration of 0.30 M) was added over 2 h. [b] Determined by GC–MS and ^{1}H NMR. [c] *Er* determined by chiral GC. [d] Isolated yield of **9f**. Inset: Ball-and-stick representation of the X-ray structure of diol **11**.

Cyclic amino alcohols are structural elements found in numerous natural products e.g. tropane alkaloids,[16] and are privileged scaffolds in medicinal chemistry e.g. atropine and cocaine.[18b] Having access to a variety of enantioenriched bromocycloalkenes of various ring sizes *via* the AAS-desymmetrization protocol, we next demonstrated the versatility of these products by the concise stereocontrolled synthesis of cyclic amino alcohols (Scheme 4). Reaction of cyclohexene **2d** with *m*-CPBA afforded a 71:29 diastereomeric mixture of epoxides. Ring opening of the epoxide with benzylamine catalyzed by silica under neat conditions was selective for the major epoxide isomer, affording *trans*-1,2-aminoalcohol derivative **12** in 60% yield over two steps. S_N2 substitution of bromide **12** with sodium azide followed by hydrogenation yielded *trans*-1,4-diamino-2-alcohol **13** with four contiguous stereocenters (Scheme 4a). The 7-membered analog cycloheptene **9f** undergoes diastereoselective Upjohn dihydroxylation (88:12 *dr*) to afford *cis*-1,2-diol **11** in 80% yield, which was readily transformed into aminodiol **14** *via* substitution and hydrogenation (Scheme 4b).

Scheme 4. Derivatization of desymmetrization products towards cyclic aminoalcohols.



Conditions: (i) *m*-CPBA (1.2 equiv.), PhMe, RT; (ii) $BnNH_2$ (1.2 equiv.), silica (10 wt%), 80 °C; (iii) NaN_3 (3 equiv.), DMF, 80 °C; (iv) H_2 (1 atm), Pd/C (20 mol%), EtOAc; (v) OsO_4 (4 mol%), NMO (1.5 equiv.), acetone/H_2O (3:1).

Aminodiol **14** is a direct precursor to 2-phenyl-tropan-6α-ol using the cyclization strategy described by Pollini *et al*.[17] These 8-azabicyclo[3.2.1]octanes[18] represent an important scaffold of bioactive tropane alkaloids natural products such as schizanthines, baogongtengs and calystegines.[16b,19] Thus, our synthesis of aminodiol **14** represents an efficient route to phenyl-substituted analogs of these natural products and drug targets (see Figure 1).

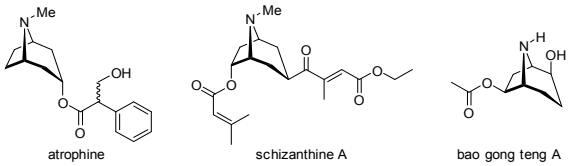


Figure 1. Examples of tropane alkaloids with the 8-azabicyclo[3.2.1]octane framework

In summary, the highly regio- and enantioselective desymmetrization of *meso*-dibromocycloalkenes with ring size ranging from 5 to 7 *via* Cu-AAS with organolithium reagents has been demonstrated. Phosphoramidite **L3** is the preferred ligand for alkyllithium reagents while for arylation NHC was found to be the ligand of choice. These findings represent an efficient method to access enantioenriched cyclic bromoalkenes; the synthetic utility of the products is demonstrated by the concise synthesis of chiral multifunctional cyclic aminoalcohols, which are a privileged scaffold for natural products, pharmaceuticals and asymmetric synthesis.

ASSOCIATED CONTENT

Supporting Information

Experimental details and characterisation data are provided (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

†,*E-mail: b.l.feringa@rug.nl

Notes

The authors declare no competing financial interests.

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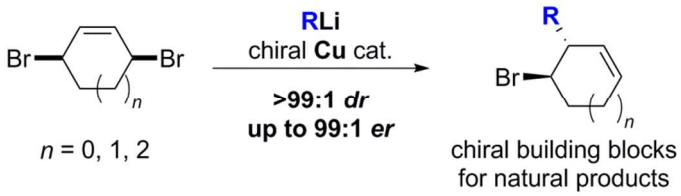

n = 0, 1, 2

chiral building blocks
for natural products