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Desymmetrization of *meso* [3.2.1]oxabicyclic systems using metal-catalysed asymmetric intramolecular C–H insertion

Xiaomei Zhang [†], Zhengning Li [‡], John C. K. Chu, Pauline Chiu [*]

Department of Chemistry, The University of Hong Kong, Pokfulam Road, Hong Kong, Hong Kong

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ABSTRACT

Diazoketone derivatives of *meso* 8-oxabicyclo[3.2.1]octen-3-ones were desymmetrized by an intramolecular C–H insertion mediated by chiral copper and dirhodium catalysts to generate oxatricyclic systems with up to 5 contiguous stereogenic centres and 50% ee.

8-Oxabicyclo[3.2.1]oct-6-en-3-ones such as **1a** and **1b** are useful substrates in organic synthesis (Fig. 1).[1] Their utility has been inextricably linked to their ready accessibility from (4 + 3) cycloadditions of oxyallyl cations with furans,[2] and the resultant rigid and sterically biased frameworks, which allow functional group conversions to proceed stereoselectively and in a predictable manner.[3] These and related oxabicyclic compounds have already been used in the synthesis or synthetic studies of many natural products, including crocacin C,[4] scopoline derivatives,[5] ionomycin,[6] and callystatin A,[7] and cortistatin A.[8]

In addition, *meso* oxabicyclic compounds such as **1a**–**d** (Fig. 1), having up to five pro-stereogenic centres, are poised for desymmetrization to yield enantiomerically enriched products as intermediates for the synthesis of natural products. Various strategies have been employed to accomplish enantioselective desymmetrization. The use of a stoichiometric amount of chiral base generates enantiomerically enriched enolates which are captured as silyl enol ethers, or acylated to give desymmetrized β-ketoesters.[9] Alternatively, desymmetrization has been achieved using Brown's asymmetric hydroboration on the alkene.[10] Enantioselective alkylative and reductive ring opening desymmetrization strategies have also been developed to yield highly functionalized and stereodefined homochiral cycloheptanes.[11]

The insertion of a carbene, generated from the decomposition of α-diazocarbonyl compounds,[12] into a C–H bond is an established reaction to synthesize rings, particularly five-membered rings.[13] This transformation can be achieved with only catalytic amounts of metal complexes, and generates nitrogen as the only by-product. Furthermore, a wealth of chiral dirhodium or copper catalysts has already been developed for metal carbene formation from diazo substrates, and provides a rich resource for tuning the selectivity.

We proceeded to investigate a C–H insertion strategy to achieve the desymmetrization of the oxabicyclo[3.2.1]octane framework, which was unprecedented in the literature. We envisioned that an intramolecular asymmetric C–H insertion reaction could concomitantly desymmetrize the *meso* bicyclic system as well as escalate the molecular complexity through a C–C bond formation, yielding a [5,7]-fused carbobicyclic ring system. Our first study examined the use of chiral rhodium catalysts which achieved up to 44% ee in the desymmetrization.[14] We herein communicate our further studies of this C–H insertion reaction in the context of oxabicyclic diazoketoester, diazoketone and diazoester substrates, and the screening of chiral copper catalysts.

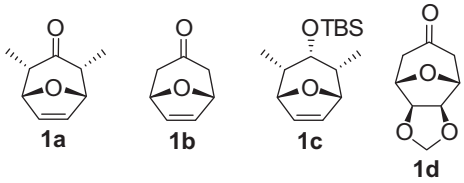

Figure 1. *Meso* oxabicyclo[3.2.1]octane derivatives.

* Corresponding author. Tel.: +852 2859 8949; fax: +852 2857 1586.
E-mail address: pchiu@hku.hk (P. Chiu).
† Present address: Key Laboratory for Asymmetric Synthesis and Chirotechnology of Sichuan, Chengdu Institute of Organic Chemistry, Chengdu, PR China.
‡ Present address: College of Environmental and Chemical Engineering, Dalian University, Dalian, PR China.

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In our previous work,[14] we have described our efforts to desymmetrize oxabicyclic diazoketoester **2a** by enantioselective C–H insertion. After screening a range of chiral dirhodium catalysts, the enantioselectivities observed for **3a** were generally low.[15] The highest ee obtained was 30% using Rh_2(*S*-BPTTL)$_4$[16a] (Fig. 2) in refluxing dichloroethane (Table 1, entry 1).

In an effort to improve the enantioselectivity, we synthesized and subjected the substrates **2b** and **2c** to reaction to probe whether the size of the ester group (R^1) in diazoketoesters **2** would have an impact (Table 1).[17] In the event, although moderate to good yields of insertion product **3a** were still obtained, the ee's were inferior compared to the reaction of **2a**, whether R^1 was more or less sterically demanding (Table 1, entries 2–4). Whereas the size of the R^1 group in diazoketoester derivatives has been found to affect the enantioselectivity in the rhodium carbene C–H insertion reactions,[18] in this particular C–H insertion it appeared to have little effect. We also synthesized diazoketone **2d** to examine whether a bulkier protecting group on the hydroxyl functionality would have any impact on the reaction. However, this only led to a deteriorated yield, without any improvement in the enantioselectivity (Table 1, entries 4 and 5).

Substrates **2** were not highly reactive for carbene formation and C–H insertion, because these diazoketoesters were stabilized by two electron-withdrawing groups. Carbene formation required relatively high reaction temperatures, which are not conducive to promote good enantioselectivities in the subsequent C–H insertion reaction.

Therefore, we turned our attention to another class of substrates, diazoesters **4a**–**b**, which should yield to carbene formation readily. These substrates are synthesized as shown in Scheme 1. Stereoselective reduction of **1a** with SmI_2 provided equatorial alcohol **5**.[19,20] Alcohol **5** reacted with an acyl ketene generated from the thermolysis of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one to afford β-ketoester **6**.[21] Deacetylative diazo transfer secured **4a**.[22] Diazoester **4b** was synthesized from alcohol **5** in one-pot through acylation and diazo transfer.

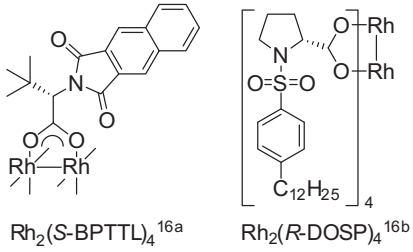
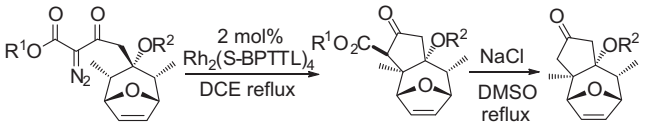


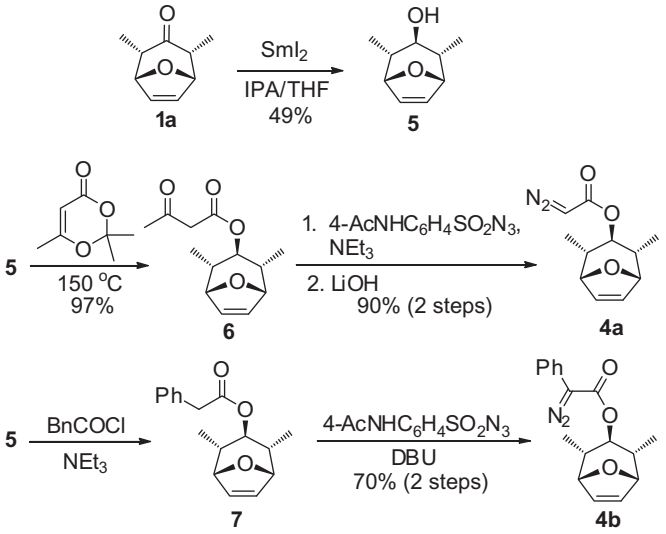
Figure 2. Chiral dirhodium catalysts.[16]

Table 1
Desymmetrization of **2b**–**2d**



Entry	Substrate	Yield (%)	ee[a] (%)
1[b]	**2a**, R^1 = Et, R^2 = TMS	**3a**, 73	30.3
2	**2b**, R^1 = Me, R^2 = TMS	**3a**, 83	22.4
3[c]	**2b**, R^1 = Me, R^2 = TMS	**3a**, 83	25.4
4	**2c**, R^1 = *t*-Bu, R^2 = TMS	**3a**, 89	23.0
5	**2d**, R^1 = *t*-Bu, R^2 = TBS	**3b**, 64	25.2

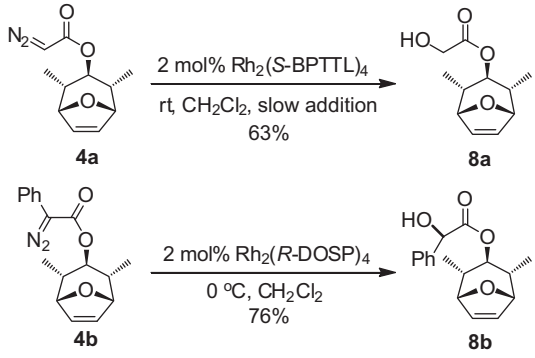
[a] Absolute configuration of the major enantiomer was not determined.
[b] Ref. 14.
[c] Reaction was carried out at 60 °C.



Scheme 1. Synthesis of **4a** and **4b**.

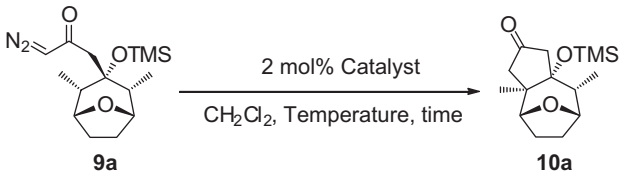
Indeed for diazoesters **4a** and **4b**, carbene formation occurred upon treatment with rhodium catalysts at room temperature or below. Unfortunately, neither afforded the desired C–H insertion product. Diazoester **4a** underwent dimerization when treated with rhodium under typical reaction conditions.[23] When a syringe pump was employed to minimize the reaction concentration of **4a**, O–H insertion was the predominant pathway to give **8a** as product (Scheme 2).[24] Similarly, **4b** underwent O–H insertion under rhodium catalysis to give **8b**.[25] A possible explanation for **4a** and **4b** being unwilling to undergo C–H insertion was that the ester preferred to adopt an extended conformation,[26] thus disfavouring cyclization and undermining the C–H insertion process, giving way to other carbene reaction pathways.

Finally, we examined the desymmetrization of diazoketones **9a–b**, which was also more reactive towards carbene formation compared with diazoketoesters **2**. The synthesis of these substrates had been described previously.[14] Indeed, the treatment of **9a** with $Rh_2(OAc)_4$ at room temperature for 2 h resulted in an 85% yield of **10a** (Table 2, entry 1). Our previous study on rhodium catalysis of this reaction found that Rh_2(*S*-BPTTL)$_4$ promoted the conversion of **9a** to **10a** with ee up to 44% (Table 2, entry 2). We proceeded to also screen some chiral copper complexes as catalysts in this reaction (Fig. 3),[27] as there has been cases in which copper has been



Scheme 2. Attempted desymmetrization of **4a** and **4b**.

Table 2
Desymmetrization of **9a**

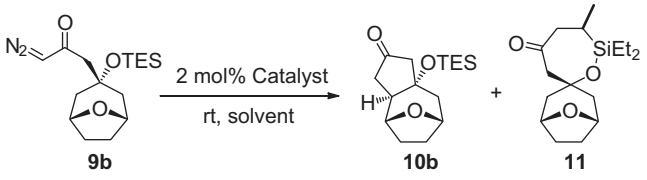


9a **10a**

Entry	Catalyst/temperature	Time (h)	Yield (%)	ee[a] (%)
1[b]	$Rh_2(OAc)_4$/rt	2	85	—
2[b]	Rh_2(*S*-BPTTL)$_4$/rt	10	85	44.0
3	[Cu(**L1**)](OTf)$_2$/rt	12	75	0.0
4	[Cu(**L2**)](OTf)$_2$/rt	12	72	−20.1[c]
5	[Cu(**L3**)](OTf)$_2$/ rt	12	76	−22.4[c]
6	[Cu(**L4**)](OTf)$_2$/rt	12	74	2.8
7	[Cu(**L5**)](OTf)$_2$/rt	12	68	−2.7[c]
8	[Cu(**L2**)](OTf)$_2$/−20 °C	18	71	−32.0[c]
9	[Cu(**L3**)](OTf)$_2$/−20 °C	18	77	−14.6[c]

[a] Absolute configuration of the major enantiomer was not determined.
[b] Ref. 14.
[c] A minus sign indicates the opposite enantiomer.

Table 3
Desymmetrization of **9b**



9b **10b** **11**

Entry	Catalyst/solvent	Yield (%)		ee (%) of **10b**[a]
		10b	**11**	
1[b]	$Rh_2(OAc)_4/CH_2Cl_2$	77	0	—
2[b]	Rh_2(*S*-BPTTL)$_4/CH_2Cl_2$	33	57	17.2
3	[Cu(**L2**)](OTf)$_2/CH_2Cl_2$	14	50	−22.6[c]
4	[Cu(**L3**)](OTf)$_2/CH_2Cl_2$	NR		—
5	[Cu(**L2**)](OTf)$_2/CHCl_3$	31	0	−44.2
6	[Cu(**L3**)](OTf)$_2/CHCl_3$	73	0	−50.3

[a] Absolute configuration of the major enantiomer not determined.
[b] Ref. 14.
[c] A minus sign indicates the opposite enantiomer.

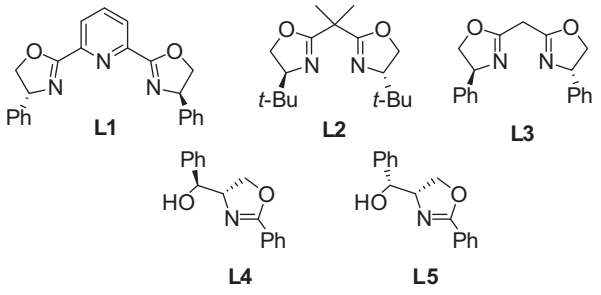


Figure 3. Chiral ligands for copper employed in our studies.[27]

superior to chiral rhodium catalysts in some C–H insertion reactions.[28] Although enantioselectivities of about 20% ee were observed at room temperature, using [Cu(**L2**)](OTf)$_2$ at a lower reaction temperature of −20 °C resulted in an improved ee of 32% (Table 2, entries 4, 8).[29]

For the less hindered diazoketone substrate **9b**, which does not possess flanking methyl substituents, reaction with $Rh_2(OAc)_4$ also proceeded readily at room temperature (Table 3, entry 1).[30] Previous studies found that the highest ee attained in the desymmetrization of **9b** was only 17% ee with Rh_2(*S*-BPTTL)$_4$ as catalyst (Table 3, entry 2).[14] In fact, the carbene predominantly underwent another C–H insertion reaction at the triethylsilyl group to afford siloxane **11** as the major product.[31] The use of [Cu(**L2**)](OTf)$_2$ promoted the formation of the desired **10b**, but also accompanied by **11** as the major product (Table 3, entry 3). When solvent was switched to $CHCl_3$, another medium commonly used in carbene formations, a dramatic improvement in both chemoselectivity and enantioselectivity was observed. Using [Cu(**L2**)](OTf)$_2$ as catalyst, **10b** was obtained as the exclusive product, albeit in a moderate yield (Table 3, entry 5). Finally, when [Cu(**L3**)](OTf)$_2$ was employed, the yield of **10b** improved to 73%, along with attaining the highest ee of 50% in the desymmetrization reaction (Table 3, entry 6).[32]

In summary, we have examined an asymmetric intramolecular C–H insertion strategy for the desymmetrization of representative oxabicyclic diazoketoesters, diazoketones and diazoesters. The best desymmetrization result was achieved for diazoketone **9b**, which reacted with chiral copper complex [Cu(**L3**)](OTf)$_2$ as catalyst in chloroform to generate [5,7]-fused carbobicyclic ketone **10b** bearing four stereocentres with up to 50% ee. This is one of the few cases in which chiral copper catalysts mediated a carbene reaction with higher chemoselectivity and enantioselectivity than chiral rhodium catalysts. Additional chiral copper complexes, anion and solvent effects will be studied in the future.

Acknowledgments

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Supplementary data

Supplementary data (the detailed experimental procedures syntheses of substrates, desymmetrization reactions and the characterizations of all compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.026.

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