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Desymmetrizations of *meso* oxabicyclic compounds by asymmetric C–H insertion

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Abstract—*meso* Oxabicyclo[3.2.1]diazoketones underwent intramolecular C–H bond insertion to generate oxatricyclic compounds bearing fused cyclopentanones upon reaction with rhodium catalysts. Using the chiral catalyst Rh_2(*S*-BPTTL)$_4$, 44% ee was achieved in this desymmetrization reaction.

Oxabicyclo[3.2.1]octenones, readily assembled via the cycloaddition of oxyallyl cations with furans, are substrates with tremendous synthetic potential (Fig. 1).[1] In an oxabicyclic substrate such as **1a**, four of the seven carbon atoms of the carbocyclic framework are stereochemically defined. The remaining carbon atoms are reaction sites, which could be further functionalized with high and predictable stereoselectivity on the basis of the steric bias provided by the rigid template of the oxabicyclic framework.[2] Thus, reduction and silylation of **1a** and **1b** selectively afford **2a** and **2b**, respectively. Much effort has been devoted to exploiting these substrates for synthesis.

Symmetrical oxabicyclic substrates provide an additional opportunity for chiral synthesis whereby prochiral functionalities can be transformed into stereocenters by enantioselective desymmetrization reactions. Asymmetric hydroboration oxidation on oxabicyclo[3.2.1]-octenes **2a** and **2b** has been induced at the olefinic two-carbon bridge, generating *exo* alcohols with enantiomeric excesses of 95% and 96%, respectively.[3] Lautens et al. have been very successful in effecting enantioselective alkylative and reductive desymmetrizing reactions of substrates such as **2a** and **2b** with concomitant ring opening, using chiral organometallic reagents and reducing agents to yield optically-enriched cycloheptenols.[4] The application of this methodology to the synthesis of natural products such as ionomycin demonstrates the power of this strategy to efficiently assemble complex stereochemical arrays.[5]

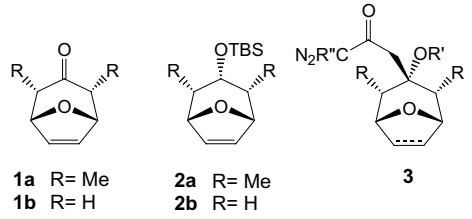

Figure 1.

Desymmetrizations based on reactions of the ketone at the three-carbon bridge of **1a** and **1b** include Simpkins' asymmetric deprotonation using homochiral bases.[6] The silyl enol ether trapped after deprotonation could be obtained in 85–88% ee. This desymmetrization reaction has been utilized in a synthesis of the pseudoguaianolide skeleton and subunits of scytophycin C.[7,8]

One of our current interests is to explore novel synthetic possibilities provided by the oxabicyclic template. In particular, we were interested in investigating desymmetrization reactions of oxabicyclic substrates via the formation of new carbon–carbon bonds, so that new stereogenic centers would be generated concomitantly with an escalation in the complexity of the molecular framework. Our attention was focused on the generation and reaction of metal carbenes, and the desymmetrization of these substrates via intramolecular C–H bond insertion in substrates such as **3** (Fig. 1).[9] Reaction at two sites were deemed possible at the outset of these investigations. Carbene insertion into the C–H bond of the adjacent carbon would be favored due to the kinetic formation of a five-membered ring and would generate

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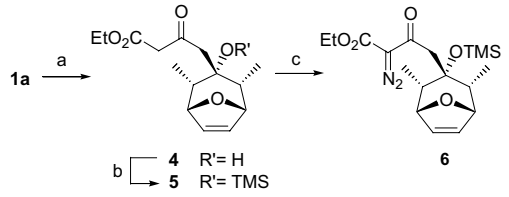
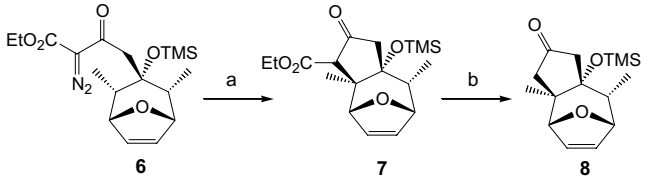
fused cyclopentanone structures related to perhydroazulenes. Insertion at the bridgehead position to form a six-membered ring may also be possible because of the activation of that C–H bond by the oxygen substituent.[9f] However, geometrically, this approach was expected to be more strained.

The investigation of the course of the C–H insertion reaction began with the synthesis of the oxabicyclo[3.2.1]diazoketone substrates such as **3**. To be an efficient strategy overall, the synthesis of this diazoketone substrate must be concise. Thus, oxabicyclic ketone **1a** was treated with the dianion of methyl acetoacetate to generate exclusively the axial alcohol **4** in excellent yield (Scheme 1). The propensity for delivery of nucleophiles *syn* to the oxygen bridge is well precedented.[2] The hydroxyl group was protected as the trimethylsilyl ether **5**. Finally, diazo transfer using 4-acetylaminobenzenesulfonyl azide provided the novel diazoketone **6**, in three steps from the oxabicyclic precursor.

The reaction of diazoketone **6** with a catalytic amount of dirhodium acetate generated a single product in 73% yield (Scheme 2). It was identified to be ketoester **7**, as a tautomeric mixture with its enol form. This mixture was difficult to handle in analysis. However, the ketoester was readily decarboxylated under Krapcho conditions to give cyclopentanone **8**. Carbene insertion had occurred exclusively to form a *cis*-fused [5,7]-carbobicyclic system, in which five contiguous stereocentres have been generated in just one step.



Scheme 1. Reactions and conditions: (a) ethyl acetoacetate, NaH, *n*-BuLi, 95%; (b) TMSOTf, 2,6-lutidine, CH_2Cl_2, 93%; (c) 4-acetylaminobenzene-sulfonyl azide, Et_3N, MeCN, 77%.



Scheme 2. Reactions and conditions: (a) cat. $Rh_2(OAc)_4$, CH_2Cl_2, 73%; (b) NaCl, DMSO, reflux, 86%.

Eight different chiral rhodium catalysts (Fig. 2) were then screened to ascertain the level of enantioselectivity that can be induced in this desymmetrization reaction, including two catalysts, Rh_2(*S*-NPV)$_4$ and Rh_2(*S*-NPTL)$_4$, which have been prepared by us for the first time.[10–13] The results are shown in Table 1. Since substrate **6** is a rather stable diazoketone, decomposition by the catalysts were generally slow, and vigorous reaction conditions (i.e., high reaction temperatures) were used to fully consume the substrate within a reasonable reaction time in some cases. Using 2–4 mol% catalysts, most reactions resulted in good yields of desymmetrized product **8**, but the enantioselectivities were not high, the maximum achieved being 30.3% ee.[14]

The preparation of diazoketones such as **9a** and **9b** were then examined because these substrates are more reactive towards metal-catalyzed decomposition than **6**. Thus, a wider range of rhodium catalysts would be able to induce the reaction under milder conditions.[15] Furthermore, derivatization of the products by decarboxylation before analysis would not be necessary. The synthesis of diazoketone **9a** began with the addition of the lithium enolate of *tert*-butyl acetate to oxabicyclic ketone **1a** to generate alcohol **10a** (Scheme 3). Treatment with TMSOTf accomplished in one step both the protection of the hydroxyl group and the cleavage of the ester to give acid **11a**. Reduction removed the olefin functionality that would engage in cycloaddition with diazomethane.[16] After activation of the acid, diazomethane was administered to give diazoketone **9a**.

The analogous synthesis of **9b** started with oxabicyclic ketone **1b** (Scheme 3). It was found that when TMSOTf was used to protect alcohol **10b**, the resultant compound obtained upon workup was not desired **11c**, but desilylated hydroxyacid **11d**. This was probably because the TMS-protected alcohol **11c** was less hindered than **11a** and more susceptible to hydrolysis to **11d** upon workup. Using TESOTf, however, the desired silylated acid **11b** was obtained. A similar sequence of reactions converted **11b** to diazoketone **9b**.

The decomposition of diazoketone **9a** with rhodium resulted in the exclusive formation of cyclopentanone **13** in 85% yield (Table 2, entry 1).[17] Using chiral rhodium catalysts, the yields were good to excellent. The enantioselectivities observed were higher, the best ee achieved being 44.0%. It is interesting to note that for the reac-

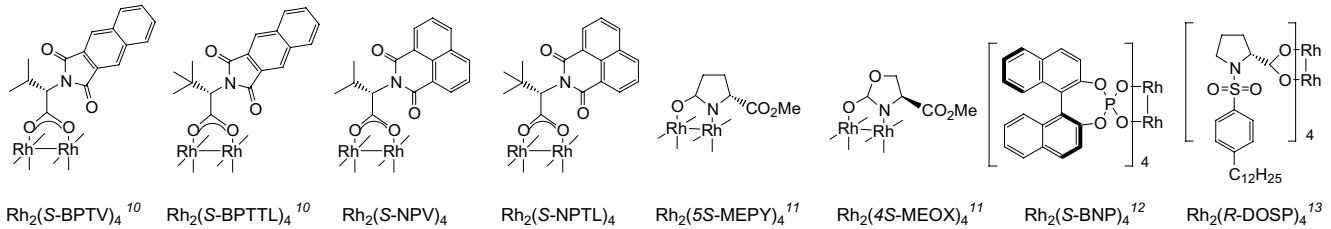
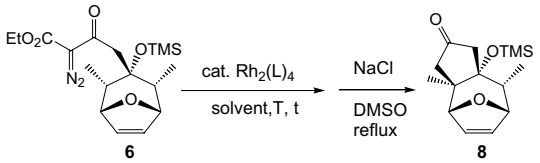


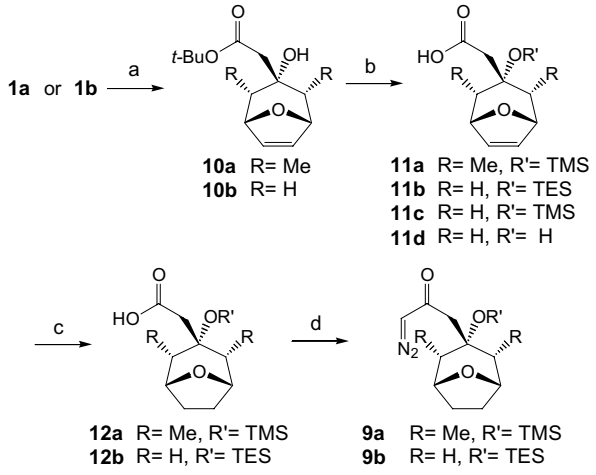
Figure 2. Chiral rhodium catalysts used in this study.

Table 1. Reaction of **6** with chiral rhodium catalysts



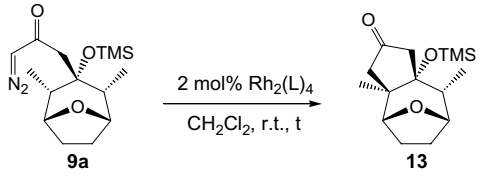
Entry	$Rh_2(L)_4$ (mol%)	Solvent	T (°C)	t (h)	Yield (%)	Ee (%)[a]
1	Rh_2(*S*-BPTV)$_4$ (2)	CH_2Cl_2	rt	20	74	14.9
2	Rh_2(*S*-BPTTL)$_4$ (2)	$ClCH_2CH_2Cl$	Reflux	2	**73**	**30.3**
3	Rh_2(*S*-NPV)$_4$ (2)	$ClCH_2CH_2Cl$	Reflux	2	73	20.8
4	Rh_2(*S*-NPTL)$_4$ (2)	$ClCH_2CH_2Cl$	Reflux	2	76	16.9
5	Rh_2(5*R*-MEPY)$_4$ (4)	$ClCH_2CH_2Cl$	Reflux	2	70	1.4
6	Rh_2(4*S*-MEOX)$_4$ (4)	$ClCH_2CH_2Cl$	Reflux	2	77	2.0
7	Rh_2(*S*-BNP)$_4$ (2)	PhH	rt	2	70	11.7
8	Rh_2(*R*-DOSP)$_4$ (2)	CH_2Cl_2	rt	12	66	8.2

[a] Enantiomeric excesses (ee) of **8** were determined by analytical HPLC on an OD column, 4% *i*-PrOH/hexane, flow rate 1 mL/min, 230 nm; absolute configuration of major enantiomer of **8** not determined.



Scheme 3. Reactions and conditions: (a) CH_3CO_2 *t*-Bu, LHMDS, −78 °C 97% for **10a**; 80% for **10b**; (b) TMSOTf, 2,6-lutidine, CH_2Cl_2, 70% for **11a**; TESOTf, 2,6-lutidine, CH_2Cl_2, 98% for **11b**; (c) H_2, Pd/C, EtOH, 99% for **12a**, 92% for **12b**; (d) isobutylchloroformate, Et_3N, CH_2N_2, 28% for **9a**, 14% for **9b**.

Table 2. Reaction of **9a** with rhodium catalysts



Entry	$Rh_2(L)_4$	t (h)	Yield (%)	Ee (%)[a]
1	$Rh_2(OAc)_4$	2	85	—
2	Rh_2(*S*-BPTV)$_4$	4	83	30.3
3	**Rh_2(*S*-BPTTL)$_4$**	**10**	**85**	**44.0**
4	Rh_2(*S*-NPV)$_4$	4	83	11.8
5	Rh_2(*S*-NPTL)$_4$	10	65	2.4
6	Rh_2(5*R*-MEPY)$_4$	4	61	1.4
7	Rh_2(4*S*-MEOX)$_4$	6	59	6.3
8	Rh_2(*S*-BNP)$_4$	2	92	18.3
9	Rh_2(*R*-DOSP)$_4$	2	95	5.8

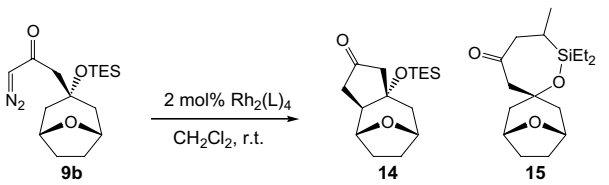
[a] Enantiomeric excesses (ee) of **13** were determined by analytical HPLC on an OD column, 3% *i*-PrOH/hexane, flow rate 1 mL/min, 300 nm; absolute configuration of major enantiomer of **13** not determined.

tions of both diazoketones **6** and **9a**, Hashimoto's catalyst, Rh_2(*S*-BPTTL)$_4$, induced higher enantioselectivity in the C–H insertion than the Rh_2(*S*-BPTV)$_4$ catalyst, while the opposite trend had been observed in the tandem carbene cyclization cycloaddition reaction.[10]

The rhodium catalyzed reaction of diazoketone **9b** gave a 77% yield of the cyclopentannelation product **14** related to the pseudoguaianolides.[18] The use of the more bulky, chiral rhodium catalysts generated two products (Table 3). One was the expected product **14** with low enantioselectivities, but a major, unanticipated side product arose from carbene insertion into the C–H of the triethylsilyl protecting group, forming a seven-membered silanyloxacycle **15**.[19] Not only was the change in the site of reaction unexpected, but C–H insertion leading to the formation of a seven-membered ring ketone was also unusual. However, differences in the sites of C–H insertion due to variations of the ligand have been observed previously.[20]

Herein we have shown that symmetrical oxabicyclic diazoketones undergo intramolecular C–H insertion catalyzed by rhodium to form desymmetrized cyclopentanone products, generating up to five contiguous stereocentres in one step. Although the enantiomeric excesses obtained in this reaction at this stage are moderate and require further optimization, this work represents the first study of this kind of desymmetrization reaction of oxabicyclic compounds, and represents an efficient entry into the stereochemically-defined [5,7]-fused carbocyclic ring systems. Future studies will examine the reactions of more diazoketone substrates **3** where the R″ group would be varied, as well as additional chiral catalysts to improve the enantioselectivity of this desymmetrization reaction.

Table 3. Reaction of **9b** with rhodium catalysts



Entry	$Rh_2(L)_4$	t (h)	Yields (%)		Ee of **14** (%)[a]
			14	**15**	
1	$Rh_2(OAc)_4$	2	77	0	—
2	Rh_2(*S*-BPTV)$_4$	6	50	25	15.2
3	Rh_2(*S*-BPTTL)$_4$	12	33	57	17.2
4	Rh_2(*S*-NPV)$_4$	6	42	51	5.3

[a] Enantiomeric excesses (ee) of **14** were determined by analytical HPLC on an OD column, 3% *i*-PrOH/hexane, flow rate 1 mL/min, 300 nm; absolute configuration of major enantiomer of **14** not determined.

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14. Characterization of (±)-**8**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29 (dd, $J = 6.1$, 1.5 Hz, 1H), 6.21 (dd, $J = 6.1$, 1.6 Hz, 1H), 4.43 (t, $J = 2.8$ Hz, 1H), 4.29 (d, $J = 1.2$ Hz, 1H), 3.13 (d, $J = 19.2$ Hz, 1H), 2.41 (s, 2H), 2.14 (d, $J = 19.1$ Hz, 1H), 1.87–1.83 (m, 1H), 0.98 (s, 3H), 0.84 (d, $J = 7.1$ Hz, 3H), 0.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.5, 132.4, 132.3, 83.1, 82.6, 80.8, 51.3, 49.1, 45.1, 40.1, 20.6, 11.6, 2.23; EI-HRMS m/z Calcd for $C_{15}H_{24}SiO_3$ (M^+): 280.1495; Found 280.1492.
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17. Characterization of (±)-**13**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (dd, $J = 7.4$, 3.5 Hz, 1H), 3.87 (d, $J = 7.4$ Hz, 1H), 3.07 (d, $J = 19.1$ Hz, 1H), 2.42 (s, 2H), 2.22–2.11 (m, 2H), 2.06 (d, $J = 19.0$ Hz, 1H), 1.78–1.71 (m, 3H), 1.03 (s, 3H), 0.85 (d, $J = 7.0$ Hz, 3H), 0.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.7, 80.3, 79.3, 79.1, 49.8, 49.2, 46.6, 40.6, 24.6, 23.9, 20.5, 11.4, 2.2; EI-HRMS m/z Calcd for $C_{15}H_{26}SiO_3$ (M^+): 282.1651; Found 282.1645.
18. Characterization of (±)-**14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36–4.32 (m, 1H), 4.22 (dm, $J = 7.5$ Hz, 1H), 2.60 (ddm, $J = 19.2$, 11.9 Hz, 1H), 2.48 (ddm, $J = 19.0$, 9.1 Hz, 1H) 2.43–2.41 (m, 2H), 2.36–2.20 (m, 3H), 2.03–1.88 (m, 2H), 1.75 (d, $J = 2.9$ Hz, 2H), 0.97 (t, $J = 7.6$ Hz, 9H), 0.62 (q, $J = 7.6$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.3, 75.4, 74.9, 55.9, 49.1, 41.7, 41.5, 28.0, 27.4, 7.1, 6.5; EI-HRMS m/z Calcd for $C_{16}H_{28}SiO_3$ (M^+): 296.1808; Found 296.1810.
19. Characterization of (±)-**15**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37 (br, 2H), 2.77 (d, $J = 12.3$ Hz, 1H), 2.51 (dd, $J = 15.1$, 4.9 Hz, 1H), 2.42 (d, $J = 12.3$ Hz, 1H), 2.39 (dd, $J = 15.1$, 11.1 Hz, 1H), 2.22 (d, $J = 7.6$ Hz, 2H), 1.94 (ddd, $J = 14.1$, 8.5, 4.3 Hz, 2H), 1.87–1.82 (m, 2H), 1.62–1.61 (m, 2H), 1.22–1.10 (m, 1H), 1.06–0.96 (m, 9H), 0.77–0.64 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.6, 73.9, 73.8, 72.4, 58.0, 49.4, 44.6, 44.1, 28.1, 28.0, 15.6, 15.4, 7.0, 6.6, 4.2; EI-HRMS m/z Calcd for $C_{16}H_{28}SiO_3$ (M^+): 296.1808; Found 296.1804.
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