Desymmetrization

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The Use of Silyl Ketene Acetals and Enol Ethers in the Catalytic Enantioselective Alkylative Ring Opening of Oxa/Aza Bicyclic Alkenes**

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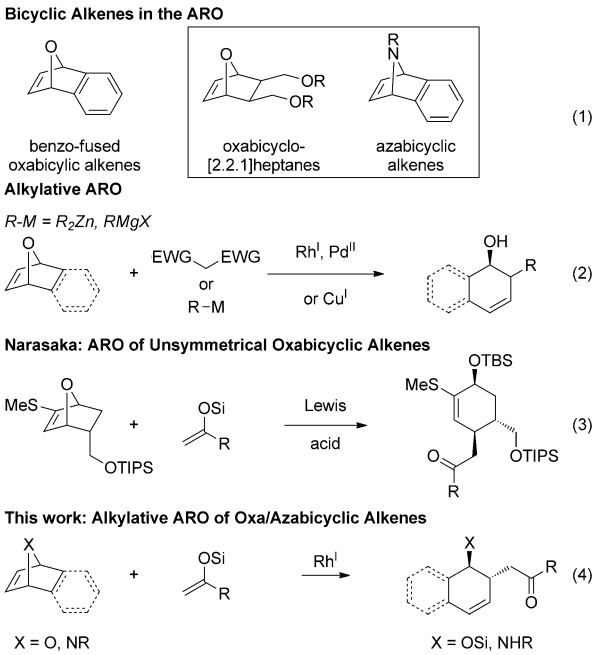
Abstract: *Silyl ketene acetals and enol ethers are employed as reactive and functional group tolerant nucleophiles in the enantioselective rhodium-catalyzed alkylative ring opening of a diverse class of oxa/azabicyclic alkenes. This method provides access to enantioenriched dihydronaphthalene and cyclohexene scaffolds, which have the potential to be derivatized toward core motifs of naphthoquinone and sesquiterpene natural products.*

The catalytic enantioselective ring opening of strained *meso* oxa/azabicyclic alkenes enables rapid access to chiral building blocks.[1] While significant efforts have been invested in the development of the asymmetric ring opening (ARO) of benzo-fused, oxabicyclic alkenes, reports on the ARO of the less-strained non-benzo-fused oxabicyclo-[2.2.1]heptanes[2] and azabicyclic alkenes[3] remain rare (Scheme 1). Overcoming the lack of reactivity of these challenging bicylic alkenes is desirable as this would provide access to highly substituted chiral cyclohexenes and aminodihydronaphthalenes. Although the alkylative ARO of oxa/azabicyclic alkenes has been demonstrated with hard organometallic reagents,[4] the enantioselective alkylative ring opening of oxabicyclo-[2.2.1]heptanes and azabicyclic alkenes has only been achieved with the use of dimethyl- and diethylzinc.[2a,b,f,3c,d] In general, the alkylative ARO has been limited in scope due to the instability and lack of accessibility of the organometallic reagents. Consequently, only simple alkyl fragments that lack functional group handles have been reported. While the use of malonates[2c,e] in the alkylative ARO has been reported, these nucleophiles are inherently limited in scope and reactivity by requirement for α,α-disubstitution of electron-withdrawing groups (Scheme 1). Thus, to effect the addition of a simple acetate fragment would entail reaction with malonate followed by decarboxylation. To address these limitations in the alkylative ARO, we have developed a general method for the direct addition of a variety of functionalized alkyl fragments to strained and less-strained oxa/azabicyclic alkenes.



Scheme 1. Alkylative asymmetric ring opening of bicyclic alkenes.

The need for a reactive yet versatile alkyl nucleophile led us to the use of silyl ketene acetals and enol ethers. In comparison to organometallic reagents, these nucleophiles are stable, can be prepared in a concise manner, react under much milder conditions, and are more functional group tolerant.[5] Although Narasaka[6] has reported two examples of the use of these reagents in reaction with unsymmetrical oxabicyclic alkenes using a Lewis acid, our work represents the first catalytic enantioselective variant. In analogy to the Mukaiyama aldol reaction,[7] the ring opening of oxabicyclic alkenes with silyl enolates involves a silyl group migration resulting in an in situ hydroxy protection. The general scope, functional group tolerance, and in situ hydroxy protection offer opportunities for further functionalization of the products such as accessing core motifs of chiral naphthoquinone and sesquiterpene lactone natural products (see Scheme 5).

We began our study on the ARO with a Rh precatalyst, Josiphos, oxanorbornene **1**, and silyl ketene acetal **2** in THF at 70 °C (Table 1). Screening of Rh catalysts suggested the importance of cationic [Rh(cod)$_2$OTf] (cod = cyclooctadiene)

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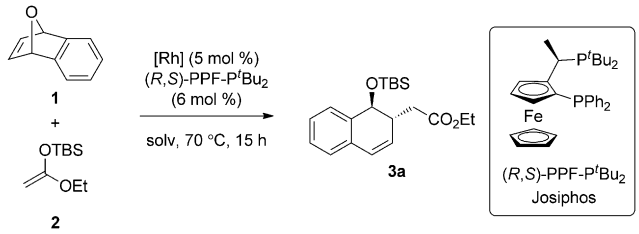
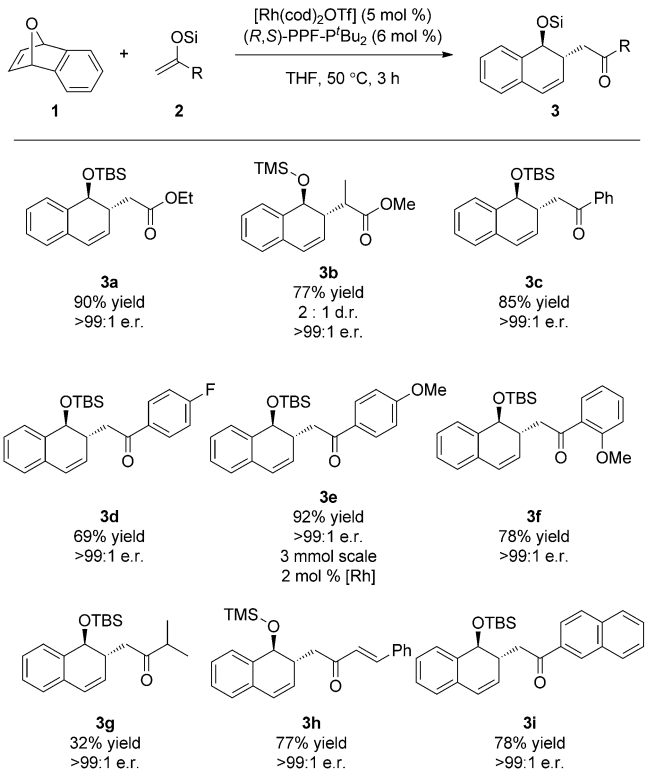
Table 1: Reaction optimization.[a]



Entry	[Rh]	Solv	Equiv **2**	Yield [%]	e.r.
1	$[Rh(cod)Cl]_2$	THF	1.5	0	–
2	$[Rh(cod)OH]_2$	THF	1.5	0	–
3	$[Rh(CO)_2Cl]_2$	THF	1.5	0	–
4	$[Rh(cod)_2OTf]$	THF	1.5	77	>99:1
5[b]	$[Rh(cod)_2OTf]$	THF	1.5	8	n.d.
6[c,d]	$[Rh(cod)_2OTf]$	THF	2.5	95 (90)	>99:1
7[c]	$[Rh(cod)_2OTf]$	Dioxane	2.5	47	n.d.
8[c]	$[Rh(cod)_2OTf]$	PhMe	2.5	0	–
9[c]	$[Rh(cod)_2OTf]$	MeCN	2.5	0	–

[a] Representative reaction conditions: [Rh] and Josiphos were added to a 2 dram vial under Ar atmosphere and 0.5 mL of solvent was added. The mixture was stirred for 10 min. **1** and **2** were dissolved in 1.5 mL of solvent and introduced into the vial via syringe. The mixture was stirred at the described temperature and time. Yields were determined by ^{1}H NMR spectroscopy. [b] [Rh] (2.5 mol%), Josiphos (3 mol%) were used. [c] Reaction conducted at 50°C. [d] Reaction time 3 h. Isolated yield in parenthesis.

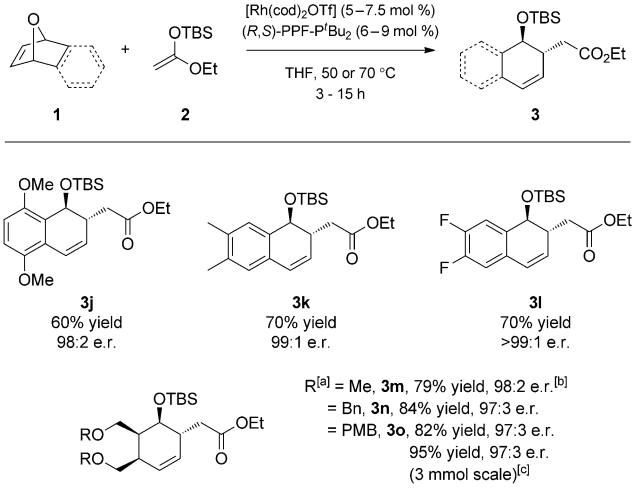


Scheme 2. Silyl nucleophile scope of the opening of oxabicyclic alkene **1**. See Table 1 and Supporting Information for details. E.r. based on silyl deprotection. Absolute stereoconfiguration of **3i** determined by X-ray crystallography.

over neutral Rh^I precursors for providing the desired reactivity (entries 1–4). We observed a 77% yield by NMR with full conversion (entry 4) and silyl group migration. Due to the nonpolar nature of the ring-opened products, the enantiomeric ratio of the products were measured after the cleavage of the silyl protecting group. Excellent e.r. (>99:1) was observed. While lowering the temperature of the reaction to 50°C did not affect the reaction, lowering the catalyst loading had a deleterious effect (entry 5). Optimal reactivity was observed with 2.5 equiv of the silyl ketene acetal (entry 6), affording the desired product in 90% yield while maintaining the enantioselectivity. Deviation from THF as the solvent gave poorer results.

Having established a high yielding and enantioselective method, we examined the scope of the reaction with respect to the nucleophile (Scheme 2). In general, silyl ketene acetals displayed higher reactivity, affording **3a** and **3b**. For silyl enol ethers, we found improved results upon adding $Zn(OTf)_2$ as a cocatalyst. We suspect that Zn^{2+} acts either as a Lewis acid that activates the bridgehead oxygen for the Rh oxidative insertion,[4a] or it may activate the nucleophile, forming a zinc enolate intermediate.[8] Various aryl silyl enol ethers underwent smooth reaction (**3c**–**3f**) and the reaction is amenable to scale up, at lower catalyst loading and under modified conditions (**3e**). An X-ray crystal structure of the enantiomer of **3i** after silyl deprotection revealed the absolute and relative stereoconfiguration (see Supporting Information). Although alkyl silyl enol ethers gave lower yields of the ring-opened products, the enantioselectivity remained excellent. While the diastereoselectivity remains to be improved (**3b**), we observed good to high yields while retaining the excellent enantioselectivity.

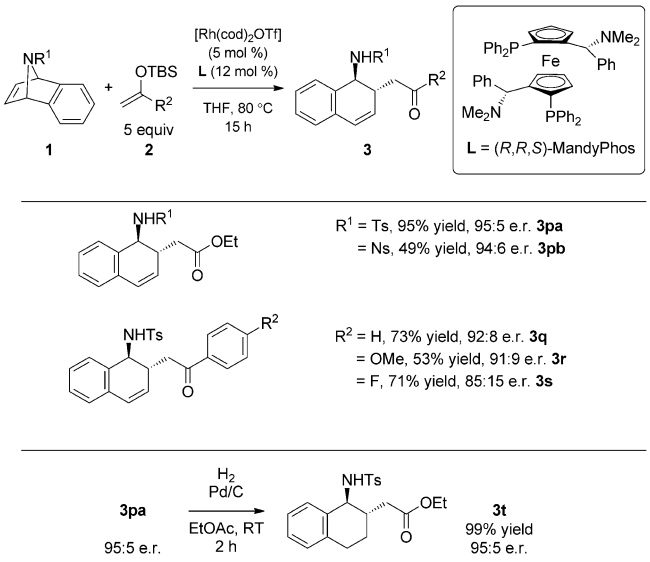
A variety of oxabicyclic alkene substrates reacted favourably with the silyl ketene acetals (Scheme 3). Both electron poor and rich substrates (**3j**–**3l**) were tolerated in the



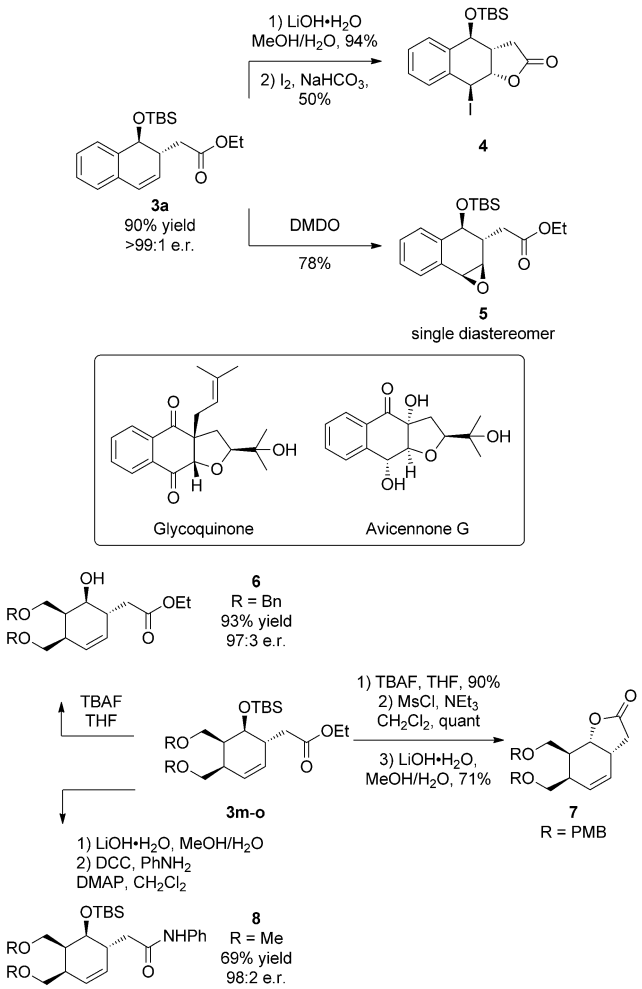
Scheme 3. Oxabicyclic alkene scope. See Table 1 and Supporting Information for reaction details. The e.r. values are based on silyl deprotection. [a] **2** (3 equiv), $[Rh(cod)_2OTf]$ (7.5 mol%), (*R*,*S*)-PPF-P*t*Bu_2 (9 mol%), 70°C, 15 h. [b] The e.r. is based on **8**, Scheme 5. [c] $[Rh(cod)_2OTf]$ (3.5 mol%), (*R*,*S*)-PPF-P*t*Bu_2 (4.5 mol%).

reaction. The reaction is also amenable to the use of the less reactive, oxabicyclo[2.2.1]heptanes, though at higher temperatures and catalyst loading (Scheme 3, footnote [a]). However, the catalyst loading can again be reduced when run on gram scale (**3o**). Excellent yields and enantioselectivities were maintained throughout. Direct access to the tetrasubstituted cyclohexenes is readily achieved.

We next examined the reaction scope with respect to azabicyclic alkenes (Scheme 4). Under the optimized conditions, we observed high yields and enantioselectivity



Scheme 4. Azabicyclic alkene scope and derivatization. Absolute stereoconfiguration of **3q** determined by X-ray crystallography. See Supporting Information for details.



Scheme 5. Further transformations of ARO products. See Supporting Information for reaction details.

employing the MandyPhos ligand. Similar to previous reports, the catalyst/ligand ratio is important for achieving the desired enantioselectivity, possibly by minimizing catalyst/nucleophile interaction prior to the enantiodiscriminating step.[3b] The sulfonyl aryl nitrogen protecting groups displayed the best reactivity (**3p**). *N*-Boc-azabicyclic alkenes did not undergo the desired reaction as the Lewis acidic reaction conditions promoted Boc-cleavage. With the addition of $Zn(OTf)_2$ as a cocatalyst, silyl enol ethers participated in the ring opening to afford **3q** and **3r**. While silyl group migration was observed in the crude product, the labile *N*-silylated product underwent deprotection upon treatment with silica gel. The ARO product **3pa** was hydrogenated to access the 2-alkyl-1-aminotetralin core **3t** with the *anti*-stereoconfiguration. This approach offers complementary reactivity compared to the asymmetric hydrogenation of tetrasubstituted cyclic enamides derived from tetralones,[9] which would provide these cores with the corresponding *syn*-stereoconfiguration.

We examined a number of modifications of the ring opening products which allow access to diverse structural motifs (Scheme 5). For the chiral dihydronaphthalene products, the alkene serves as a useful handle for derivatization. For example, adduct **3a** can be converted to iodolactone **4** or epoxide **5**. These products may provide access to a class of chiral naphthoquinones such as glycoquinone[10] or avicennone G,[11] which are congeners of podophyllotoxins,[12] and exhibit anti-bacterial and anti-proliferative properties. The silyl protecting group can also be removed efficiently with high yields (**6**). However, keeping the siloxy ether may be advantageous as saponification and amide coupling can proceed to afford **8**. In addition, lactonization of the ring opening products can access structural motif **7**, found in sesquiterpene lactones, such as eudesmanolides.[13]

In summary, we have developed the first enantioselective addition of silyl ketene acetals/enol ethers to a range of oxa/azabicyclic alkenes. The silyl enolates offer high functional group tolerance and react under mild conditions. The adducts of the alkylative ring opening provide access to a variety of structural motifs. Further investigations on reaction mechanism, scope, and synthesis of the aforementioned natural products are underway.

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