Isomerization

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Rhodium-Catalyzed Asymmetric Cycloisomerization and Parallel Kinetic Resolution of Racemic Oxabicycles

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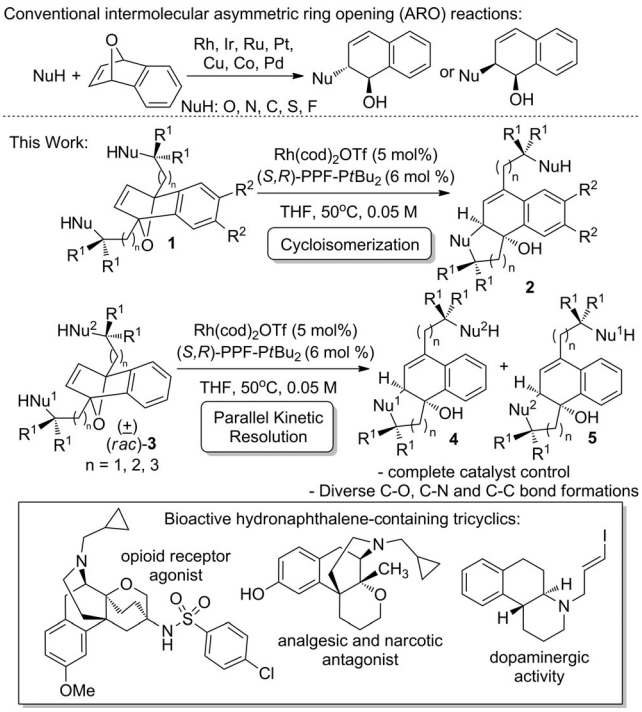
Abstract: *While desymmetrizations by intermolecular asymmetric ring-opening reactions of oxabicyclic alkenes with various nucleophiles have been reported over the past two decades, the demonstration of an intramolecular variant is unknown. Reported herein is the first rhodium-catalyzed asymmetric cycloisomerization of meso-oxabicyclic alkenes tethered to bridgehead nucleophiles, thus providing access to tricyclic scaffolds through a myriad of enantioselective C–O, C–N, and C–C bond formations. Moreover, we also demonstrate a unique parallel kinetic resolution, whereby racemic oxabicycles bearing two different bridgehead nucleophiles can be resolved enantioselectively.*

Herein, we report an unprecedented desymmetrization of *meso*-oxabicyclic alkenes **1**, bearing various bridgehead nucleophiles, by an intramolecular enantioselective rhodium-catalyzed cycloisomerization (Scheme 1). We also introduce a new class of nucleophile which forms C–C bonds, and describe a unique asymmetric parallel kinetic resolution (PKR) of racemic oxabicycles **3** arising from differential attack by two internal nucleophiles.

The rhodium-catalyzed intermolecular asymmetric ring-opening (ARO) reaction of oxabicycles has been an intensively investigated field in our research group over the past two decades, and the power of this protocol in generating enantioenriched hydronapthalene frameworks has been well documented with a diverse range of nucleophiles (Scheme 1).[1,2] Moreover, many other research groups have made contributions to this field by demonstrating the utility of various metals such as iridium, ruthenium, platinum, copper, cobalt, nickel, and palladium to effect intermolecular oxabicycle ARO transformations.[3]

In contrast, the intramolecular cycloisomerization of *meso*-oxabicycles such as **1** is unknown, and would offer new opportunities to access scaffolds which are otherwise challenging (Scheme 1).[4] Therefore, we initiated our research in the cycloisomerization of the *meso*-substrates **1**, whereby a successful execution would directly generate tricyclic scaffolds such as **2**. Moreover, these tricyclic hydronapthalene core structures contain motifs which are present in a wide range of bioactive molecules with known activities as opioid receptor agonists, analgesic, and narcotic antagonists. Some are also known to possess dopaminergic activities (Scheme 1),[5] thus making this protocol an especially attractive one.



Scheme 1. Comparison of known ARO reactions with the newly developed cycloisomerization and parallel kinetic resolution. cod = 1,5-cyclooctadiene, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran.

It is important to emphasize that desymmetrization utilizing internal nucleophiles is still rare in catalysis,[6] and to date mostly occur with oxygen nucleophiles. Recent achievements include bromocyclization on alkenes using internal oxygen nucleophiles by the groups of Hennecke, Kamashima, and Kan, as well as Yeung, using chiral phosphate salts and Brønsted base catalysis.[7a–d] A chiral phosphoric acid catalyzed desymmetrization of *meso*-diols by acetalization was recently reported by Sun and co-workers.[7e] Transition metal catalyzed examples are scarce. In 1995, Trost

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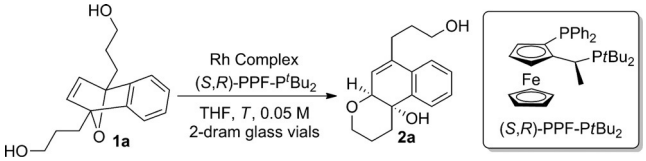
and co-workers reported a desymmetrization of *meso* bis-urethanes by employing asymmetric palladium catalysis.[7f] One very recent case of diol desymmetrization by intramolecular hydroalkoxylation of allenes using gold(I) catalysis is reported by Toste and co-workers.[7g] Therefore, we envision that a successful execution of a rhodium-catalyzed asymmetric cycloisomerization of diverse bis-nucleophile-tethered oxabicycles would result in a significant advance in this area.

We initiated our investigation by utilizing our model bridgehead diol containing a *meso*-oxabicyclic alkene **1a** as the test substrate (Table 1). The first-generation [{Rh-

Table 1: Optimization of the rhodium-catalyzed cycloisomerization.[a]



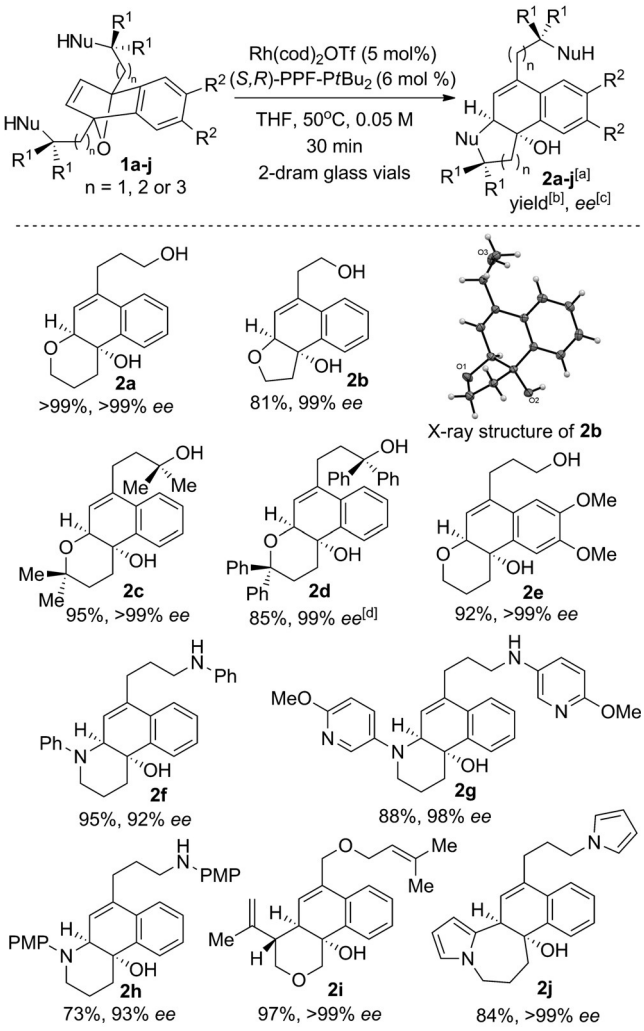
Entry	[Rh] (Cat./L)[b]	*T* [°C]	*t* [h]	Yield [%][c]	*ee* [%][d]
1	$[\{Rh(cod)Cl\}_2]$ (4:8)	80	15	22[e]	n.d.
2	$[\{Rh(cod)Cl\}_2]$ AgOTf, TBAI (4:8)	80	15	25[e]	n.d.
3	$[\{Rh(cod)OH\}_2]$ (4:8)	80	15	5[e]	n.d.
4	$Rh(cod)_2OTf$ (5:6)	80	15	96	97
5	$Rh(cod)_2OTf$ (5:6)	80	2	>99	98
6	$Rh(cod)_2OTf$ (5:6)	50	0.5	>99	>99

[a] All reactions were conducted on **1a** (0.2 mmol) in 4 mL solvent (0.05 M with respect to **1a**). [b] Cat./L in units of mol%/mol%. [c] Yield of product isolated after flash column chromatography. [d] Determined by HPLC analysis using chiral stationary phases. [e] Yield determined by NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. TBAI = tetra-*n*-butylammonium iodide.

$(cod)Cl\}_2]$ catalyst resulted in a low yield of the target product (Table 1, entry 1) and the second-generation rhodium iodide catalyst did not improve the yields (Table 1, entry 2). The fourth-generation $[\{Rh(cod)OH\}_2]$ was also not effective in this reaction (Table 1, entry 3), and only trace amounts of product were detected. Fortunately, the third-generation cationic $Rh(cod)_2OTf$ furnished the target product smoothly at 80 °C with excellent yield and enantioselectivity (Table 1, entry 4). Further screening of solvents revealed that toluene and 1,4-dioxane both gave quantitative yields and excellent *ee* values (see the Supporting Information).

Utilizing DCE slightly diminished the yield of the isolated product to 76% while retaining the excellent *ee* value (see the Supporting Information). Interestingly, using acetonitrile completely shuts down the reaction, and we attribute it a poisoning of the active rhodium complex, since acetonitrile can function as a competing ligand (see the Supporting Information). Finally, we arrived at the optimized reaction conditions after lowering the temperature to 50 °C, and thus showed that this reaction is extremely facile, with almost quantitative yields and excellent *ee* values obtained after only 30 minutes (Table 1, entry 6).

With the optimized reaction conditions in hand, we proceeded to expand the substrate scope of this methodology

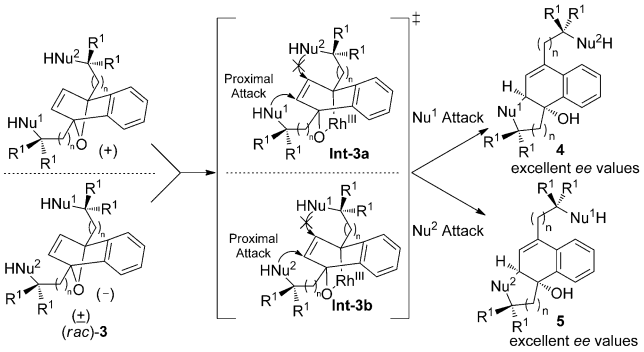


Scheme 2. Scope of the rhodium-catalyzed cycloisomerization: [a] All reactions were conducted on **1a–j** (0.2 mmol) in 4 mL THF (0.05 M with respect to **1a–j**). For X-ray structure thermal ellipsoids shown at 50% probability. [b] Yield of the isolated **2a–j** after flash column chromatography. [c] Determined by HPLC analysis using chiral stationary phases. [d] This reaction requires 2 h. PMP = *p*-methoxyphenyl.

(Scheme 2). We realized that this protocol has an extremely broad substrate scope, thus providing access to a wide variety of tricyclic structures **2a–j** with good to excellent yields and excellent *ee* values. Oxabicyclic substrates bearing oxygen nucleophiles are very well tolerated in this desymmetrization methodology, thus furnishing six-membered ring pyrano and five-membered ring furano fused hydronapthalene scaffolds **2a–d** by a hydroalkoxylation-type C–O bond-forming reaction. The oxabicycle **1e** containing dimethoxy substituents also yielded the target product **2e** with excellent yield and *ee* value. In addition, the *meso*-oxabicycles **1f–h**, bearing an amine tethered to the bridgehead, were also suitable substrates in this protocol and generated the tricyclic piperidine fused hydronapthalenes **2f–h** by a hydroamination-type C–N bond-forming reaction. The enantioselective C–N bond formation also proceeded with good to excellent yields and excellent *ee* values.

The versatility of this protocol is further augmented by expanding the scope to include new enantioselective C–C bond-forming reactions. Access to **2i** and **2j** with very good to excellent yields and excellent *ee* values was achieved (Scheme 2). The formation of **2i** arises from an *ene*-type cycloisomerization, which showcases a new mode of nucleophilic carbon reactivity previously unseen in the intermolecular ARO reaction. An additional stereogenic center is generated diastereoselectively in this instance, to form **2i** as a single diastereomer. Furthermore, the Friedel–Crafts-type cycloisomerization reaction is also successfully demonstrated utilizing pyrrole as a carbon nucleophile on the bridgehead tether, thus furnishing **2j** through a rare 7-*exo-trig* cyclization. The absolute configurations of our products are assigned by analogy to the X-ray crystal structure of **2b**.[8]

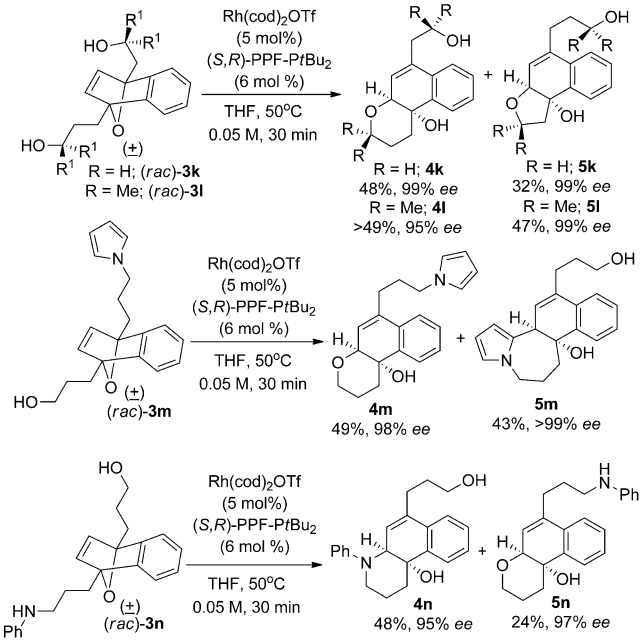
In an effort to deepen our understanding of the catalyst control in the cycloisomerization, racemic oxabicycles bearing two differentiated bridgehead nucleophiles were synthesized. We designed a unique PKR reaction[9] where two different products arose from selective nucleophilic attack, with excellent *ee* values when starting from racemic **3**. This process is possible because of the highly selective oxidative addition of the cationic Rh^{I}/(*S*,*R*)-PPF-P*t*Bu_2 complex into the distal C–O bond in both enantiomers of (*rac*)-**3** to generate the intermediates **Int-3a** and **Int-3b** (Scheme 3), thus enabling exclusive attack from the two proximal tethered nucleophiles in an S_N2' fashion.



Scheme 3. Mechanistic basis of the parallel kinetic resolution (PKR).

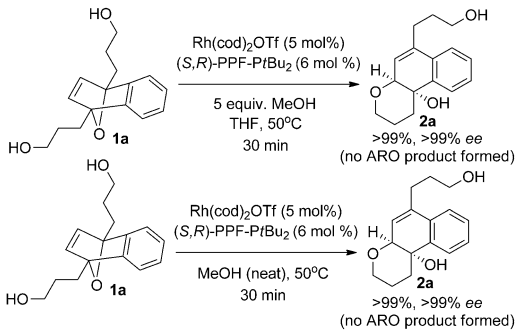
The selectivity of the PKR is demonstrated by the capability of this protocol to resolve two constitutional isomers with different ring sizes (**4k**,**l** and **5k**,**l**), between oxygen and carbon nucleophiles (**4m** and **5m**), as well as between oxygen and nitrogen nucleophiles (**4n** and **5n**), all with excellent enantioselectivities (Scheme 4).[10] The absolute configurations of the PKR products are also confirmed by analogy to the X-ray crystal structures of **4k** and **5m**.[8]

We were interested in probing the mechanistic details of the cycloisomerization by perturbing the reaction with methanol as an external nucleophile. The objective was to create a competition between the internal and external nucleophiles in the crucial proton-transfer step.[11] The resulting product distribution allowed us to better understand the intricate relationship between the favorability of the



Scheme 4. Scope of the PKR: [a] All reactions were conducted on (*rac*)-**3k–n** (0.2 mmol) in 4 mL THF (0.05 M with respect to **3k–n**). [b] Yield of **4** and **5** isolated after flash column chromatography. [c] Enantioselectivities determined by HPLC analysis using chiral stationary phases.

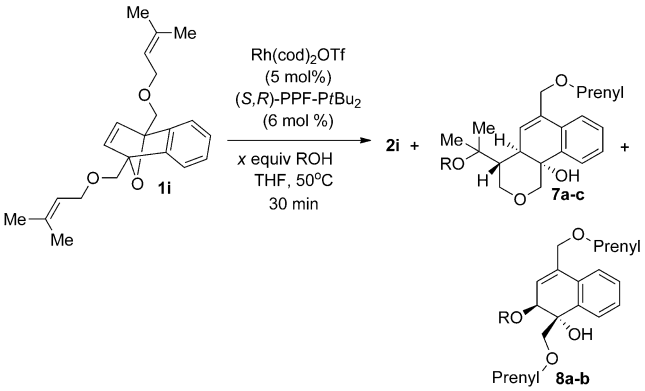
cycloisomerization versus the conventional ARO reaction. Two initial test experiments gave exclusively **2a** when **1a** was reacted in the presence of 5 equivalents of MeOH or using MeOH as the solvent (Scheme 5), thus showing the much greater propensity for internal nucleophilic attack to occur.



Scheme 5. Control experiments with **1a** in the presence of MeOH.

When **1i** was reacted with increasing amounts of MeOH in the cycloisomerization, an unexpected product was identified (Table 2). We detected a competition between the ARO reaction (**8a**,**b**) and a new pathway yielding **7a** (Table 2, entries 2–4). Further investigation revealed that as the quantity of MeOH increases towards 50 equivalents, the yield of **7a** increases to a maximum of 59 % (Table 2, entry 4). However, 100 equivalents of MeOH switches the primary mechanism towards formation of more **8a** and less **7a**

Table 2: Perturbation experiments with ROH as an external nucleophile.



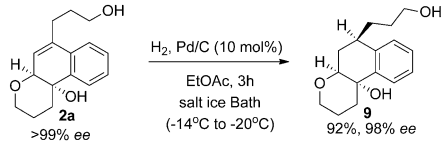
Entry	ROH (equiv)	Yield [%][b] (*ee* [%])[c]		
		2i	**7a–c**	**8a–b**
1	No ROH	97 (>99)	–	–
2	MeOH (5)	45 (>99)	40 (>99)	Traces
3	MeOH (20)	29 (>99)	54 (>99)	14 (97)
4	MeOH (50)	15 (>99)	59 (>99)	24 (99)
5	MeOH (100)	9 (>99)	54 (>99)	33 (97)
6[d]	Neat MeOH	–	39 (>99)	50 (97)
7	*i*PrOH (50)	40 (>99)	47 (>99)	8 (>99)
8	*t*BuOH (50)	80 (>99)	19 (>99)	–

[a] All reactions were conducted on **1i** (0.2 mmol) in 4 mL THF. [b] Yield of product isolated after flash column chromatography. [c] Enantioselectivity given within parentheses determined by HPLC analysis using chiral stationary phases. [d] Reaction was conducted in neat anhydrous MeOH (4 mL) instead of THF.

(Table 2, entry 5). Performing the reaction in neat MeOH gave **8a** as major product (50% yield) and **7a** as minor product (39%). The formation of **7** is proposed to go through a cationic trapping pathway reminiscent of biomimetic cationic cyclizations.[11–13] Further investigation with 50 equivalents of *i*PrOH (Table 2, entry 7) and *t*BuOH (Table 2, entry 8) also revealed the dependence of the cationic cyclization pathway upon the steric hindrance of the proton source, with increasing yields of **2i** and diminishing yields of **7** as the steric hindrance of the alcohol increases. It is noteworthy to point out that **2i**, **7**, and **8** were generated with excellent *ee* values in all cases, independent of the quantity of alcohol added. Hence, the proton perturbation experiments revealed alternating mechanisms towards three distinct products and depend upon the quantity of the added external proton source.

We also demonstrated that our protocol is amenable to scaling up through a gram-scale reaction of **1a**, using a reduced catalyst loading (see the Supporting Information), generating **2a** with very good yield and excellent *ee* value (88%, >99% *ee*). Moreover, we further exploited enantioenriched **2a** as a chiral framework in a diastereoselective hydrogenation of the trisubstituted alkene, a reaction which installs an additional stereogenic center to give **9** as the sole diastereomer, presumably by selective hydrogenation on the sterically more accessible convex face (Scheme 6).

In conclusion, we demonstrate for the first time an asymmetric rhodium-catalyzed cycloisomerization of bis-



Scheme 6. Diastereoselective hydrogenation.

nucleophile tethered oxabicyclic alkenes, which furnishes tricyclic motifs that possess privileged scaffolds prevalent in biologically relevant molecules. A parallel kinetic resolution was also demonstrated, where racemic oxabicyclic alkenes bearing two different bridgehead nucleophiles can be resolved into two constitutional isomers enantioselectively by selective internal nucleophilic attack. Proton perturbation experiments with an external nucleophile led to a deeper understanding of the intricacies of alternating pathways due to competitive proton transfer between internal and external nucleophiles. A cationic cyclization pathway was also uncovered in the proton perturbation experiments. Further investigations are currently underway.

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[9] Our previous studies of regiodivergent resolution on ARO of racemic oxabicycles showed that substrate control diminishes the *ee* value of one of the regioisomers, whereas the parallel kinetic resolution described here is strictly catalyst controlled, thus yielding both constitutional isomers with excellent *ee* values: a) R. Webster, C. Böing, M. Lautens, *J. Am. Chem. Soc.* **2009**, *131*, 444 – 445; Based on a reviewer's comment, we detected a transcriptional error in Scheme 5 and Table 1 of our previous manuscript, Ref. [9a]. The ligand used should be (*S*,*R*)-PPF-P*t*Bu$_2$ instead of (*R*,*S*)-PPF-P*t*Bu$_2$ to give the enantiomers drawn in Ref. [9a]. For selected reviews: b) J. R. Dehli, V. Gotor, *Chem. Soc. Rev.* **2002**, *31*, 365 – 370; c) E. Vedejs, M. Jure, *Angew. Chem. Int. Ed.* **2005**, *44*, 3974 – 4001; *Angew. Chem.* **2005**, *117*, 4040 – 4069; d) R. R. Kumar, H. B. Kagan, *Adv. Synth. Catal.* **2010**, *352*, 231 – 242; e) L. C. Miller, R. Sarpong, *Chem. Soc. Rev.* **2011**, *40*, 4550 – 4562.

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[12] See the Supporting Information for postulated mechanism of cycloisomerization, PKR, and cationic cyclization pathway towards **7**.

[13] Re-subjecting **2i** to the rhodium-catalyzed cycloisomerization conditions using MeOH as the reaction solvent did not yield **7a**, thus precluding the formation of **7a** from **2i** by rhodium catalysis.

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