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Efficient Enantioselective Synthesis of Functionalized Tetrahydropyrans by Ru-Catalyzed Asymmetric Ring-Opening Metathesis/Cross-Metathesis (AROM/CM)

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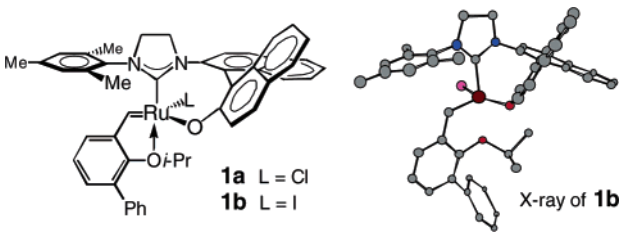
Recent research in these laboratories has led to the development of chiral Mo-[1] and Ru-based complexes[2] that promote asymmetric olefin metathesis reactions; the resulting methods offer unique and efficient pathways for the preparation of versatile optically enriched organic molecules.[3] Our investigations have been partly concerned with the development of catalytic asymmetric ring-opening/cross-metathesis reactions (AROM/CM), since catalytic ring-opening metathesis has proven to be of significant value in organic synthesis.[4] A reason for the potential of catalytic AROM/CM is that it may allow direct access to *heterocyclic* structures in high optical purity.[5] Thus far, however, nearly all Mo- or Ru-catalyzed AROM/CM processes have involved transformations of strained norbornenes that deliver functionalized cyclopentanes.

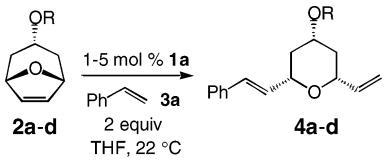
Herein, we report efficient and highly enantioselective Ru-catalyzed AROM/CM reactions of significantly less strained oxabicyclic olefins; these transformations allow access to a wide range of 2,6-disubstituted pyrans,[6] building blocks found in numerous biologically significant molecules.[7] Catalytic AROM/CM reactions afford functionalized pyrans in up to 98% ee, are performed at ambient temperature, and do not require solvent.[8] Transformations are catalyzed by 1−5 mol % **1a** and a new complex **1b**; similar to **1a**, Ru−iodide **1b** is air stable. We provide data demonstrating that **1b** initiates reactions with significantly higher asymmetric induction than those obtained with chloride **1a**.



As illustrated in entry 1 of Table 1, reaction of unsaturated bicyclic alcohol **2a**[9] proceeds readily at 22 °C to >98% conversion in 90 min with 5 mol % **1a** to afford **4a** in 94% ee and 80% isolated yield.[10] In the presence of 1 mol % **1a**, the desired pyran is generated in 94% ee and 74% isolated yield (entry 2), albeit at a slower rate. Ru-catalyzed enantioselective desymmetrization of benzyl ether **2b** proceeds to completion in 1 h to afford **4b** in 96% ee (entry 3). As shown in entry 4 of Table 1, methyl ether **4c** is generated efficiently in 86% ee. However, Ru-catalyzed desymmetrization of silyl ether **2d** delivers **4d** in only 46% ee (entry 5). In most cases shown in Table 1, complex **1a** is recovered in good yield (see below for recycling studies).

Because of the efficiency and enantioselectivity in reactions of alcohol **2a** (entries 1 and 2, Table 1), and since the corresponding products can be converted to other derivatives, the Ru-catalyzed AROM/CM of this substrate was further investigated. Initially, our studies involved reactions promoted by Ru complex **1a**; the corresponding data are summarized in entries 1, 3, 5, 7, and 9 of Table 2. When electron-rich (entry 1) or electron-poor styrene partners (entries 3 and 5) are used, olefin metatheses proceed to >98% conversion within a few hours to afford the desired pyrans in 80−88% ee and 68−78% yield (after chromatography). Catalytic AROM/CM with the sterically demanding styrene **3e** (entry 7) affords pyran **8d** in 90% ee and only 43% yield, likely because the slower reacting terminal olefin allows oligomerization of **2a** to

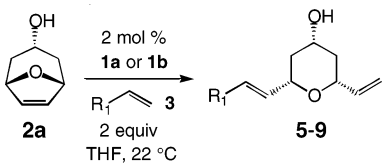
Table 1. Ru-Catalyzed AROM/CM of **2a**−**d** with Styrene



entry	R		time (h); conversion (%)[a]	mol % **1a**	product[b]	yield (%)[c]	recycled catalyst yield (%)[c]	ee (%)[d]
1	H	**2a**	1.5; >98	5	**4a**	80	94	94
2[e]	H	**2a**	12; >98	1	**4a**	74	<5	94
3	Bn	**2b**	1; >98	5	**4b**	70	65	96
4	Me	**2c**	0.8; >98	5	**4c**	71	70	86
5	TBS	**2d**	1; >98	5	**4d**	81	96	46

[a] Determined by ^{1}H NMR analysis. [b] Trans olefin (>98%). [c] Isolated yields of purified products. [d] Determined by chiral HPLC and ^{1}H NMR (see Supporting Information for details). [e] Reaction carried out in a 0.2 M solution of THF (vs 0.1 M).

Table 2. Ru-Catalyzed AROM/CM of **2a** with Various Olefins



entry	R_1			time (h); conversion (%)[a]	product[b]	yield (%)[c]	recycled catalyst yield (%)[c]	ee (%)[d]
1	*p*-OMeC$_6$H$_4$	**3b**	**1a**	1; >98	**5**	78	85	80
2[e]	*p*-OMeC$_6$H$_4$	**3b**	**1b**	9; >98	**5**	**69**	30	**96**
3	*p*-CF$_3$C$_6$H$_4$	**3c**	**1a**	1; >98	**6**	68	55	88
4	*p*-CF$_3$C$_6$H$_4$	**3c**	**1b**	12; >98	**6**	**60**	20	**98**
5	*p*-BrC$_6$H$_4$	**3d**	**1a**	3.5; >98	**7**	70	50	86
6	*p*-BrC$_6$H$_4$	**3d**	**1b**	15; >98	**7**	**68**	30	**95**
7	*o*-MeC$_6$H$_4$	**3e**	**1a**	2; >98	**8**	43	62	90
8	*o*-MeC$_6$H$_4$	**3e**	**1b**	18; >98	**8**	**70**	25	**94**
9[e]	Cy	**3f**	**1a**	13.5; 96	**9**	72	<5	60
10[f]	Cy	**3f**	**1b**	2; 98	**9**	**58**	58	**59**

[a−d] See Table 1. [e] Reactions carried out in dichloroethane. [f] Reaction run neat.

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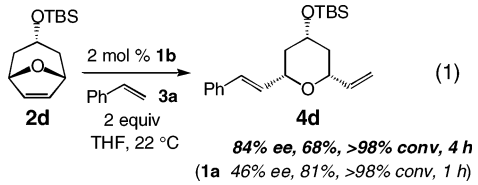
become a competitive pathway.[11] Catalytic desymmetrization in the presence of the aliphatic olefin in entry 9 is slower than those with styrenes, affording the desired pyran in 60% ee.[12]

Although the reactions in Table 2 proceed with appreciable enantioselectivity, the levels of optical purity are lower than those seen with the reaction of **2a** and styrene (entries 1 and 2, Table 1). To address this shortcoming, we decided to synthesize and examine the catalytic activity of chiral iodide complex **1b**. This initiative was inspired by a disclosure by Grubbs,[2c] who reported that addition of NaI to a solution of a chiral Ru−dichloride phosphine complex in certain cases leads to enhancement in enantioselectivity of ring-closing metathesis. The increase in asymmetric induction was attributed to the formation of a Ru−diiodide, although a discrete carbene was not isolated and characterized. Since Ru complexes bearing bidentate aryl carbenes are stable to silica gel chromatography,[13] we decided to synthesize, purify, and utilize chiral iodide complex **1b** and determine unambiguously whether it can promote AROM/CM processes with improved enantioselectivity (compared to **1a**).

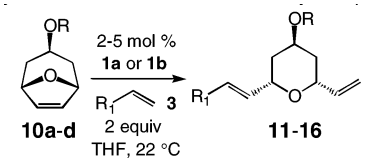
We prepared chiral complex **1b** as a light brown powder by treatment of **1a** with NaI (THF, 70 °C). Formation of **1b** is indicated by the presence of a signal corresponding to a new Ru carbene in the ^{1}H NMR spectrum (Ru=C*H* at 15.57 ppm vs 16.04 ppm for **1a**); an X-ray structure of **1b** has been obtained (see above). Subsequent studies indicate that, although **1b** is less active than **1a**, it effectively initiates AROM/CM. Importantly, as illustrated in eq 1 (**2d**→**4d**), Ru−iodide **1b** promotes AROM/CM of **2d** with styrene in significantly higher asymmetric induction compared to chloride complex **1a** (84 vs 46% ee). We have established that, as the data in entries 2, 4, 6, and 8 of Table 2 illustrate (see below also), the ability of **1b** to effect AROM/CM of oxabicyclic alcohol **2a** with higher (often substantially) enantioselectivity extends to most other olefin partners; only in reactions shown in entries 9 and 10 is the enantioselectivity not enhanced with complex **1b**.



(1)

As indicated by the data in Table 1, enantioselectivities can vary significantly as a result of a small structural modification within a substrate. Accordingly, to establish the generality of this class of Ru-catalyzed transformations, we examined the AROM/CM of exo alcohol **10a** and its derived ethers (Table 3); catalytic transformations of tertiary alcohol **17** were also investigated (Table 4). Ru-catalyzed AROM/CM of the exo alcohol and ethers **10a**−**d** proceed efficiently in the presence of 2 mol % **1a** and electron-rich (entries 1, 3, 5, and 11, Table 3) or electron-deficient styrenes (entry 7) as well as aliphatic terminal olefins (entry 9). Nonetheless, enantioselectivity levels are lower than those observed in reactions of endo alcohol **2a** and its derived ethers (Tables 1 and 2). However, as also shown in Table 3, with these exo-substituted alcohols and ethers, Ru−iodide **1b** promotes AROM/CM with significantly higher asymmetric induction (entries 2, 4, 6, 8, 10, and 12). Similar observations are made in the case of transformations of tertiary alcohol **17** (Table 4). In nearly all cases, the chiral complex **1b** elevates the catalytic AROM/CM protocol from a method that delivers 2,6-disubstituted pyrans with moderate levels of optical purity (≤90% ee) to one that allows access to the same heterocyclic structures often in >90% ee.

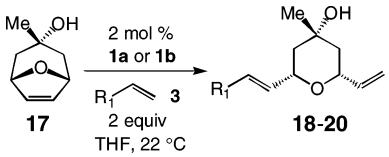
Table 3. Ru-Catalyzed AROM/CM of **10** Promoted by Complexes **1a**−**b**



entry		R	R_1 (olefin)	catalyst; mol (%)	time (h); conversion (%)[a]	product[b]	yield (%)[c]	recycled catalyst yield (%)[c]	ee (%)[d]
1	H	**10a**	Ph	**1a**; 2	3; >98	**11**	60	56	69
2[e]	H	**10a**	Ph	**1b**; 5	3; >98	**11**	**85**	74	**83**
3	Bn	**10b**	Ph	**1a**; 2	6; >98	**12**	87	77	79
4	Bn	**10b**	Ph	**1b**; 5	36; >98	**12**	**85**	67	**90**
5	Bn	**10b**	*p*-OMeC$_6$H$_4$	**1a**; 2	3; >98	**13**[f]	74	<5	66
6	Bn	**10b**	*p*-OMeC$_6$H$_4$	**1b**; 5	5; >98	**13**	**79**	83	**92**
7	Bn	**10b**	*p*-CF$_3$C$_6$H$_4$	**1a**; 2	3; >98	**14**	87	<5	73
8[e]	Bn	**10b**	*p*-CF$_3$C$_6$H$_4$	**1b**; 5	5; 98	**14**	**98**	22	**91**
9	Bn	**10b**	Cy	**1a**; 5	15; 98	**15**	52	75	70
10[e]	Bn	**10b**	Cy	**1b**; 5	2; >98	**15**	**61**	71	**81**
11	TBS	**10b**	Ph	**1a**; 5	3; >98	**16**	75	56	63
12[e]	TBS	**10b**	Ph	**1b**; 5	3; >98	**16**	**91**	31	**93**

[a−d] See Table 1. [e] Reactions run neat. [f] *E*:Z = 9:1.

Table 4. Ru-Catalyzed AROM/CM of Tertiary Alcohol **17**



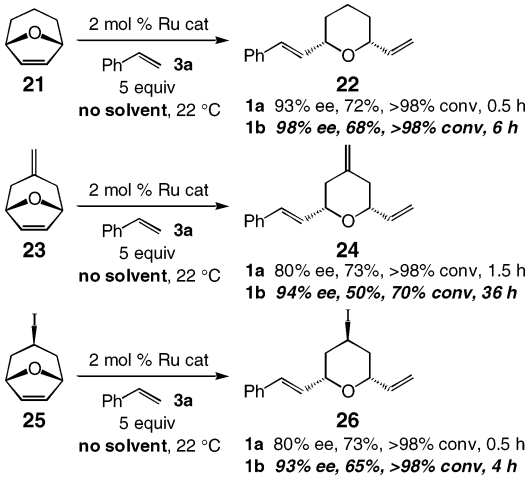
entry	R_1		catalyst	time (h); conversion (%)[a]	product[b]	yield (%)[c]	recycled catalyst yield (%)[c]	ee (%)[d]
1	Ph	**3a**	**1a**	3; >98	**18**	78	60	71
2	Ph	**3a**	**1b**	48; 86	**18**	**58**	<5	**92**
3	*p*-OMeC$_6$H$_4$	**3b**	**1a**	2; >98	**19**	72	55	68
4	*p*-OMeC$_6$H$_4$	**3b**	**1b**	48; >98	**19**	**60**	<5	**88**
5	*p*-CF$_3$C$_6$H$_4$	**3c**	**1a**	3; >98	**20**	75	58	74
6	*p*-CF$_3$C$_6$H$_4$	**3c**	**1b**	48; 86	**20**	**60**	<5	**92**

[a−d] See Table 1.

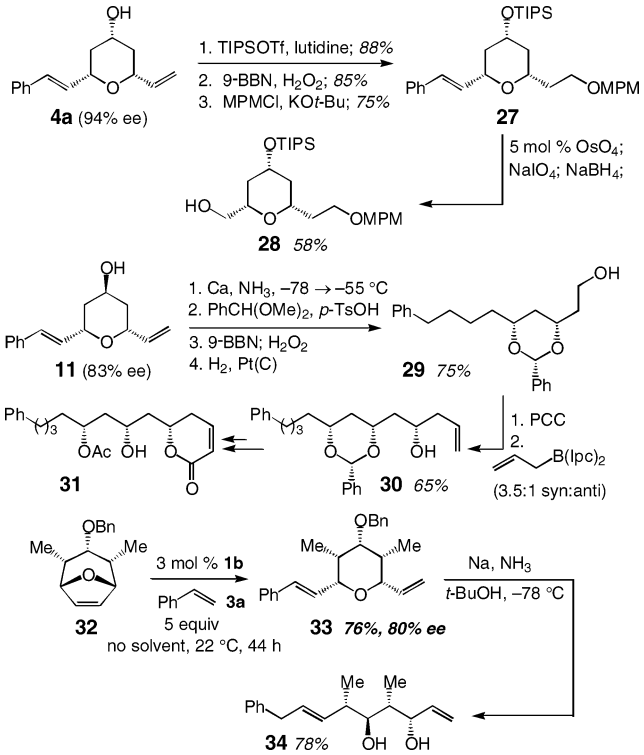
Several additional attributes of the Ru-catalyzed method are worthy of note: (1) Chiral Mo-based complexes[1] readily promote polymerization reactions, under a variety of conditions, with the representative substrates examined in Tables 1−4. (2) Reactions can be carried out in commercial-grade, undistilled THF. (3) In many instances, when reactions are carried out in solvent (e.g., Table 4), the yield of recovered **1b** is lower than that of **1a**. This is likely because the less reactive complex **1b** requires longer reaction times, which lead to the release of substantially larger amounts of the active Ru carbene; previous studies show that, with this class of chiral catalysts, the active Ru complex does not return to the styrene ether ligand.[2b] Consistent with the above proposal, when reactions are run neat, conditions that require shorter times (Table 3), the yield of recovered **1b** is typically increased. (4) Chiral catalyst **1a** can be isolated after each reaction and reused for up to five cycles to promote highly enantioselective metathesis reactions (see Supporting Information for details).

That Ru-catalyzed AROM/CM can be run neat becomes a particularly notable advantage with substrates that do not easily undergo reaction in solution. For example, whereas the reactions in Scheme 1 proceed to <2% conversion after 24 h in solution

Scheme 1. Ru-Catalyzed AROM/CM of Less Reactive Substrates in the Absence of Solvent (<2% Conversion in Solution)



Scheme 2. Representative Functionalizations of AROM/CM Products



with 2 mol % **1a**, in the absence of solvent, oxabicycles **21**, **23**, and **25** readily undergo AROM/CM to afford **22**, **24**, and **26**[14] in <2 h in 93, 80, and 80% ee, respectively. Furthermore, when the less reactive **1b** is used (2 mol %), >98% conversion is achieved in longer reaction times but with notably higher enantioselectivity (98, 94, and 93%, respectively).[15]

Optically enriched pyrans obtained through the present catalytic protocol can be functionalized with excellent regioselectivity in a variety of ways. The sequence illustrated in Scheme 2 involving the conversion of **4a** to primary alcohol **28**, an intermediate synthesized previously in the course of a total synthesis of leucascandrolide,[16] is one case in point. In addition to enantioselective synthesis of pyrans, the Ru-catalyzed protocol provides access to highly functionalized *acyclic* building blocks that can be used in the synthesis of biologically active compounds. Two representative cases are depicted in Scheme 2. Dissolving metal reduction of **11** and functionalization of the resulting *syn*-1,3-diol lead to homoallylic alcohol **30** (via **29**), an intermediate employed in a recent asymmetric synthesis of natural product **31**.[17] The fully functionalized pyran **33**, obtained in 80% ee (9:1 *E*:*Z*) by Ru-catalyzed AROM/CM of **32** with styrene (neat) can be converted to optically enriched diol **34**, a synthon for the total synthesis of natural polypropionates,[18] as a single diastereomer and olefin regio- and stereoisomer.

Future studies will include the synthesis and development of more effective chiral Ru catalysts for olefin metathesis, examination of the mechanism of these and related catalytic asymmetric processes, as well as applications of the newly developed protocols to total synthesis of complex molecules.

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Supporting Information Available: Experimental procedures and spectral and analytical data for reaction products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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