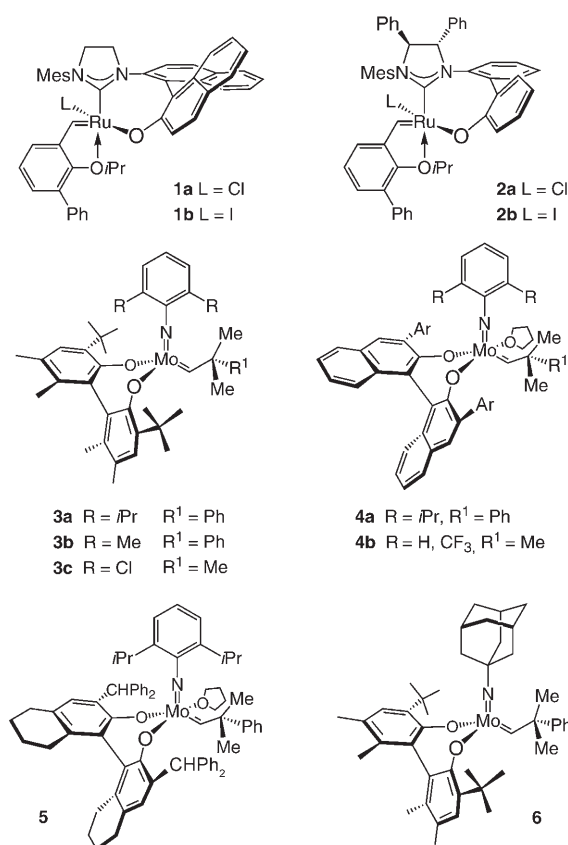


Efficient Enantioselective Synthesis of Piperidines through Catalytic Asymmetric Ring-Opening/Cross-Metathesis Reactions**

G. Alex Cortez, Richard R. Schrock, and Amir H. Hoveyda*

The remarkable influence of catalytic olefin metathesis is due to the availability of Mo- and Ru-based catalysts.^[1] One notable (and fortunate) aspect of these two classes of initiating alkylidenes and carbenes is that they are complementary in regards to functional-group tolerance.^[2] Unlike Mo alkylidenes, Ru carbenes promote transformations of substrates that bear a hydroxyl group; Mo-based systems, on the other hand, often retain their high activity in the presence of unhindered tertiary amines.^[1,2] Herein, we report a method for catalytic asymmetric ring-opening/cross-metathesis (AROM/CM)^[3] of unsaturated azabicycles; functionalized piperidines are formed in up to 98 % *ee* and with greater than 98 % *E* selectivity. With a few exceptions, high reactivity is observed only with Mo complexes. The present studies put forth the first catalytic AROM/CM protocol for enantioselective synthesis of N-containing heterocycles.^[4]

During the past several years, we have introduced chiral Ru^[5] (e.g., **1–2**; Scheme 1) and Mo-based (e.g., **3–6**) complexes^[2] that promote asymmetric ring-closing metathesis (ARCM)^[6,7] and ring-opening metathesis (AROM).^[8] In connection with catalytic AROM/CM, the majority of studies have involved reactions of *meso* norbornenes that deliver enantiomerically enriched cyclopentanes.^[3,8] One of the more noteworthy applications of these chiral complexes, however, relates to enantioselective synthesis of piperidines, components of numerous biologically active compounds.^[9] We have reported a catalytic AROM/CM protocol that yields functionalized pyrans in high enantiomeric purity (up to 98 % *ee*; > 98 % *E* selectivity in all cases).^[8c] To promote enantioselective reactions of the oxabicycles, we utilized Ru-based chiral complexes (**1–2**), which, however, often do not promote



Scheme 1. Chiral Mo- and Ru-based complexes used for various enantioselective olefin metathesis reactions. Ar = 2,4,6-*i*Pr₃C₆H₂, Mes = 2,4,6-Me₃C₆H₂.

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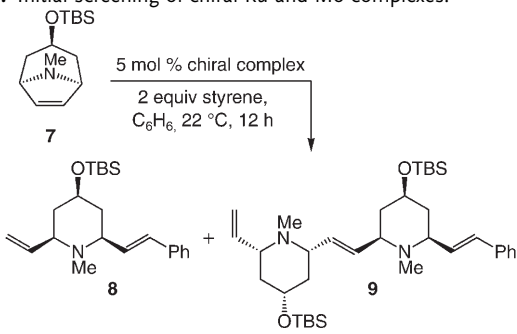
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reactions of N-containing substrates (see below for examples).

We first examined the ability of Ru and Mo complexes in initiating AROM/CM of azabicyclo **7** and styrene (Table 1). Since a number of biologically active agents^[10] contain 2,6-disubstituted *N*-methylpiperidines, we examined reactions that afford this type of heterocyclic structure.^[11] The results summarized in Table 1 illustrate that, presumably due to Lewis basic N→Ru chelation, Ru carbenes **1–2** are ineffective (< 2 % conversion). Even the parent achiral non-phosphine Ru carbene,^[12] which typically exhibits higher activity (vs. **1** and **2**) delivers 50 % conversion to **8** after 12 h.^[13] Only with two chiral Mo alkylidenes, dimethylphenylimido **3b** (Table 1, entry 5) and adamantylimido **6**^[14] (Table 1, entry 10), catalytic AROM/CM proceeds efficiently (> 98 % conv.). Whereas the reaction with arylimido **3b** generates *rac*-**8**, AROM/CM involving complex **6** leads to the desired trisubstituted

Table 1: Initial screening of chiral Ru and Mo complexes.^[a]


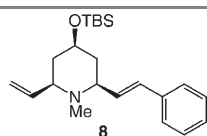
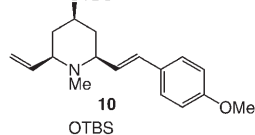
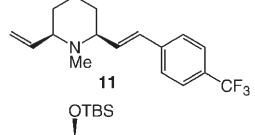
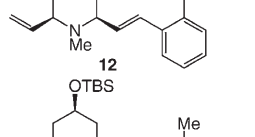
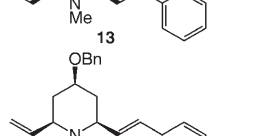
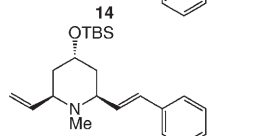
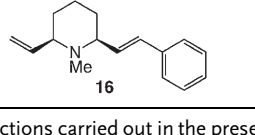
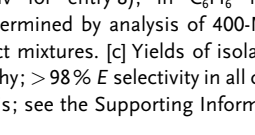
Entry	Chiral complex	Conv. [%] ^[b]	8:9 ^[b]	ee [%] ^[c]
1	1a	< 2	—	—
2	2a	< 2	—	—
3	2b	< 2	—	—
4	3a	< 2	—	—
5	3b	> 98	> 20:1	< 2 %
6	3c	< 2	—	—
7	4a	< 2	—	—
8	4b	< 2	—	—
9	5	< 2	—	—
10	6	> 98	2:1	94

[a] Reactions carried out under N₂. [b] Conversion and product ratios determined by analysis of 400-MHz ¹H NMR spectra of unpurified products; > 98 % *E* selectivity in all cases. [c] Determined by chiral HPLC analysis; see the Supporting Information for details.

piperidine in 94 % *ee* along with about 30 % of the homodimer **9** (see below for optimal conditions for minimal formation of **9**).^[15] It should be noted that in the absence of a cross partner, azabicyclo **7** is polymerized (22 °C, C₆H₆, 30 min). This finding points to the favorable reaction of the propagating alkylidene with styrene (vs. another azabicyclic substrate molecule) to afford Mo benzylidenes, which cleanly initiate a subsequent catalytic cycle.^[7a]

Chiral adamantylimido complex **6** promotes AROM/CM of a range of unsaturated *N*-Me-azabicycles in 64–95 % yield and 64–98 % *ee* (Table 2). Several points regarding the data in Table 2 are worthy of note: 1) To minimize formation of product-derived homodimer (see **9**, Table 1), reactions were carried out with 10 equivalents of cross partner (vs. two equivalents in Table 1); transformations proceed to greater than 98 % conversion within one hour (vs. 12 h in Table 1), affording the desired products without detectable amounts of the by-product (< 2 % by ¹H NMR analysis). Thus, as shown in entry 1 of Table 2, piperidine **8** is isolated in 95 % yield and 94 % *ee*. 2) Mo-catalyzed AROM/CM of different cross partners takes place with varying enantioselectivities, depending on their steric and electronic attributes. Catalytic AROM/CM with electron-rich *p*-methoxystyrene (Table 2, entry 2) proceeds in 89 % *ee* (92 % yield), whereas reaction of electron-deficient *p*-trifluoromethylstyrene (entry 3) is less enantioselective (64 % *ee* and 88 % yield). Although initial studies indicate that the electron-deficient olefin reacts at a lower rate (e.g., > 90 % conv. for *p*-methoxystyrene vs. 54 % conv. for *p*-trifluorostyrene with two equivalents of cross partner after 4 h), a precise mechanistic rationale regarding this selectivity trend, which is in contrast to AROM/CM of

Table 2: Catalytic enantioselective synthesis of *N*-methylpiperidines promoted by chiral Mo complex **6**.^[a]

Entry	Product	Conv. [%] ^[b]	Yield [%] ^[c]	ee [%] ^[d]
1		> 98	95	94
2		> 98	92	89
3		> 98	88	64
4		> 98	86	88
5		> 98	91	98
6		> 98	86	96
7		> 98	90	85
8		> 98	64	80

[a] Reactions carried out in the presence of 5 mol % **6**, 10 equiv of styrene (2 equiv for entry 8), in C₆H₆ for 1 h, at 22 °C and under N₂. [b] Determined by analysis of 400-MHz ¹H NMR spectra of unpurified product mixtures. [c] Yields of isolated product after silica gel chromatography; > 98 % *E* selectivity in all cases. [d] Determined by chiral HPLC analysis; see the Supporting Information for details.

meso norbornenes^[7a] and thus unexpected, is unclear at the present time. As illustrated in entries 4–5 of Table 2, sterically more hindered styrenes, including *o*-methylstyrene, readily undergo highly enantioselective catalytic AROM/CM.

The derived unsaturated azabicyclo bearing a benzyl ether substituent (vs. an OTBS group; Table 2, entry 6), and the diastereomeric silyl ether (leading to **15**), undergo reaction with equally high efficiency and enantioselectivity. Mo-catalyzed AROM/CM furnishes access to 2,6-disubstituted piperidine **16** in 80 % *ee* and 64 % yield of isolated product (Table 2, entry 8).

Chiral complex **6** promotes AROM/CM of unsaturated azabicycles that bear carbamate groups, including the popular and easily removable *N*-Cbz unit (Table 3). Cbz-protected

Table 3: Catalytic enantioselective synthesis of carbamate-protected piperidines promoted by chiral Mo complex **6** and Ru complex **1a**.^[a]

Entry	Product	Chiral complex; mol %	Conv. [%] ^[b]	<i>t</i> [h]	Yield [%] ^[c]	<i>ee</i> [%] ^[d]
1		6 ; 10	> 98	12	93	90
2		6 ; 10	70	12	65	80
3		6 ; 10	> 98	12	92	86
4		6 ; 10	85	24	80	85
5		6 ; 10	70	24	60	80
6		6 ; 10	83	24	80	82
7		1a ; 10	91	24	70	–90 ^[e]
8		6 ; 5	78	24	72	90
9		1a ; 10	90	24	66	–94 ^[e]

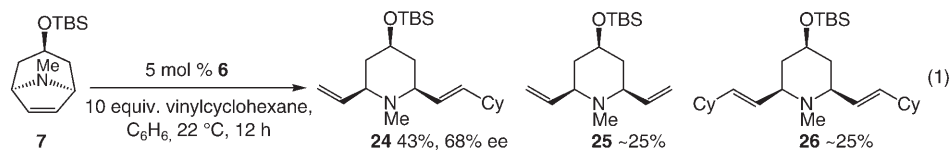
[a] Reactions carried out with 10 equiv of styrene in C₆H₆ for entries 1–6 and 8, and 20 equiv of styrene without solvent for entries 7 and 9; all reactions performed at 22 °C, under N₂. [b] Determined by analysis of 400-MHz ¹H NMR spectra of unpurified product mixtures. [c] Yields of isolated product after silica gel chromatography; > 98% *E* selectivity in all cases. [d] Determined by chiral HPLC analysis; see the Supporting Information for details. [e] The negative *ee* values indicate that the specific isomers shown in Scheme 1 for **1a** and **6** afford opposite product enantiomers. Cbz = benzyloxycarbonyl.

piperidines **17–20** and **22** (Table 3, entries 1–4 and 6) can be synthesized in 65–93% yield and 80–90% *ee*. Similarly, ethyl carbamates **21** and **23** (entries 5 and 8) are generated in 80% and 90% *ee*, respectively (60 and 72% yields of isolated product). Ru carbenes **1–2**,^[5] as well as the parent achiral complex, do not readily initiate the AROM/CM reactions shown in Table 3 (≤ 20% conv. in 24 h). There are two exceptions: the transformations shown in entries 7 and 9, involving an unsaturated azabicyclooctane that lacks a C4 substituent, proceed to greater than 90% conversion (24 h) in the presence of 10 mol % **1a**. These Ru-catalyzed processes, which must be

carried out in the absence of solvent for high conversion (<10% conv. otherwise), deliver **22** and **23** in 90% and 94% *ee* and 70% and 66% yield, respectively. Unlike AROM/CM of oxabicycles,^[5b] reactions are significantly less efficient with Ru carbene **2a**^[5b] (30% conv. and 42% *ee* for **22** and 40% conv. and 56% *ee* for **23**). The higher reactivity of unsubstituted azabicycles with chiral carbene **1a** may be due to reduced steric repulsion involved with transformations of substrates lacking a siloxy or alkoxy substituent.^[16]

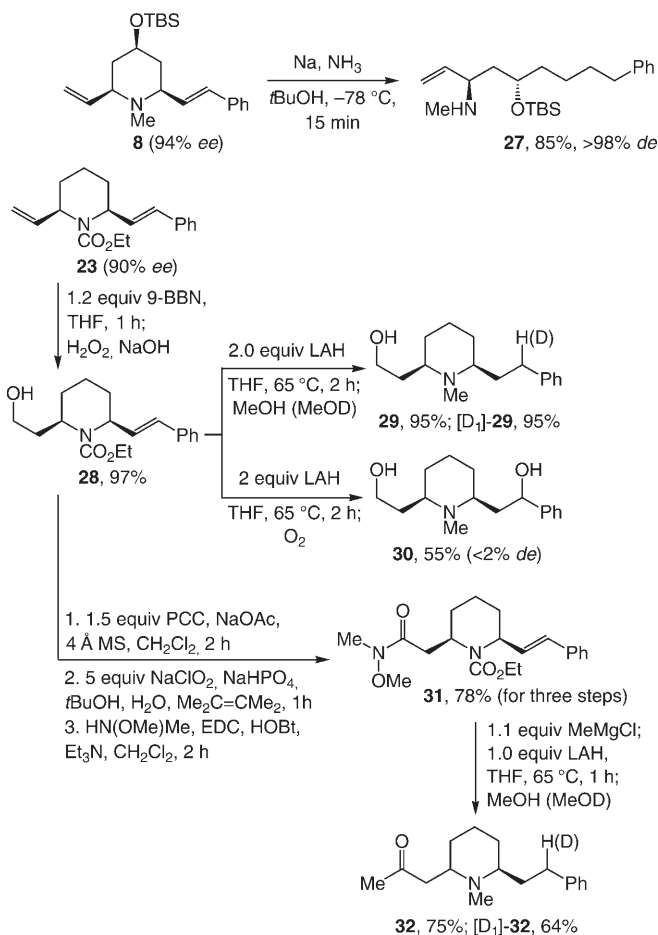
One important point regarding the AROM/CM reactions described above is whether such transformations are reversible, since azabicycles are less strained than the previously examined norbornenes.^[7a] Our investigations indicate that Mo-catalyzed reactions in Table 2 (*N*-methyl-substituted substrates) are under kinetic control. For instance, subjection of pure **14** (Table 2, entry 6; 96% *ee*) to the reaction conditions (5 mol % **6**, 10 equiv styrene, C₆H₆, 22 °C, 12 h) furnishes less than 2% of the corresponding *meso* azabicyclooctane and leads to recovery of piperidine in 96% *ee*. In contrast, certain reactions shown in Table 3 can, at least to a limited extent, be reversible. For example, subjection of pure **20** (85% *ee*) to the reaction conditions leads to the formation of about 20% of the corresponding *meso* Cbz carbamate; Cbz-protected piperidine is recovered in 85% *ee*. Such reversibility accounts for incomplete conversions, shown in Table 3. A similar observation is made with Cbz amide **22** in the presence of Ru carbene **1a**: the achiral substrate is isolated in 15% yield after 24 h (10 mol % **1a**, 20 equiv styrene, neat, 22 °C) along with recovered **22** (82% *ee*).

Another noteworthy issue relates to reactions of aliphatic cross partners. As has been noted previously,^[8b] the relatively rapid rate of homodimerization of non-aromatic olefins results in the formation of the exceptionally reactive^[8a] methylenecyclobutane complex, which often promotes less selective reactions [e.g., **24** in 66% *ee* and 43% yield, Eq. (1)]. As the example in Equation (1) illustrates, reaction of the Mo alkylidene intermediate derived from AROM may proceed through a metallacyclobutane that affords an achiral divinylpiperidine (e.g., **25**). Moreover, the well-established ability of aliphatic alkenes to undergo cross-metathesis (e.g., the homodimerization mentioned above) faster than styrenyl alkenes leads to reaction of the desired chiral products (e.g., **24**) with another equivalent of a cross partner and the



generation of a nonchiral piperidine (e.g., **26**). Such complications with aliphatic substrates are endemic to olefin metathesis^[8b,17] and not particular to this class of catalysts.^[8c] The above considerations suggest that future research must focus on designing catalytic transformations involving non-styrenyl cross partners that are more immune to homodimerization.^[18]

The unsaturated side chains at the C2 and C6 atoms of piperidines provide opportunities for functionalization of enantiomerically enriched N-containing heterocycles; noteworthy examples are provided in Scheme 2. The phenyl-substituted allylic amine of **8** is cleaved with Na/NH₃ (15 min, –78 °C) and the resulting styrenyl olefin is site-selectively



Scheme 2. Representative functionalizations of enantiomerically enriched piperidines obtained through Mo-catalyzed AROM/CM reactions. TBS = *tert*-butyldimethylsilyl; 9-BBN = 9-borabicyclo-[3.3.1]nonane; LAH = LiAlH₄; PCC = pyridinium chlorochromate; EDC = 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide; HOBT = 1-hydroxybenzotriazole.

reduced to afford terminally unsaturated amino ether **27** as a single diastereomer and in 85 % yield of isolated product. Site-selective hydroboration of enantiomerically enriched **23**, obtained through Mo- or Ru-catalyzed AROM/CM, leads to the formation of primary alcohol **28**. Treatment of **28** with lithium aluminum hydride at 65 °C (THF) delivers **29** through reduction of the carbamate and a rare process: directed regioselective hydroalumination of the styrenyl alkene.^[19] When the above multistep transformation is quenched with MeOD, [D₁]-**29** is obtained in 95 % yield and as a single regioisomer (by 400-MHz NMR analysis; > 98 % deuterium incorporation). When the reaction is quenched with dry O₂, diol **30** is isolated in 55 % yield as a single regioisomer

(>98 %) but as an equal mixture of diastereomers.^[20] The primary carbinol of **28** can be oxidized with PCC and then NaClO₂ to afford the corresponding carboxylic acid; subsequent treatment with HN(OMe)Me and EDC delivers **31** in 78 % overall yield (from **28**). Treatment of **31** with MeMgCl, followed by carbamate reduction and quenching with methanol, constitutes a one-pot conversion to saturated β-amino ketone **32** in 75 % yield. Similar to the formation of [D₁]-**29**, when the alkylation, reduction, hydroalumination sequence is terminated by quenching with MeOD, [D₁]-**32** is obtained in 64 % yield.^[21]

The studies described herein underline the crucial position of high-oxidation-state olefin metathesis catalysts and point to important future directions in new catalyst and method development. Investigations along these lines are in progress.

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- [16] Molecular models indicate that substrates bearing an *exo* heteroatom substituent (substrate corresponding to **20**) can cause the amide group to be situated in a manner that hinders approach of the bulky Ru carbene from the *exo* face of the cyclic olefin.
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