Asymmetric Catalysis

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

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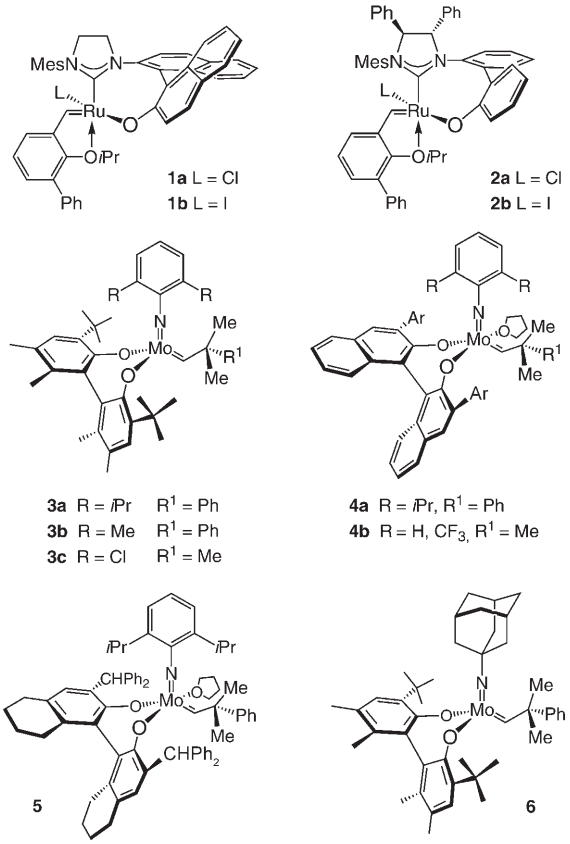
The remarkable influence of catalytic olefin metathesis is due to the availability of Mo- and Ru-based catalysts.[1] One notable (and fortunate) aspect of these two classes of initiating alkylidenes and carbenes is that they are complementary in regards to functional-group tolerance.[2] Unlike Mo alkylidenes, 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 reactions of N-containing substrates (see below for examples).



Scheme 1. Chiral Mo- and Ru-based complexes used for various enantioselective olefin metathesis reactions. Ar = 2,4,6-$iPr_3C_6H_2$, Mes = 2,4,6-$Me_3C_6H_2$.

We first examined the ability of Ru and Mo complexes in initiating AROM/CM of azabicycle **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

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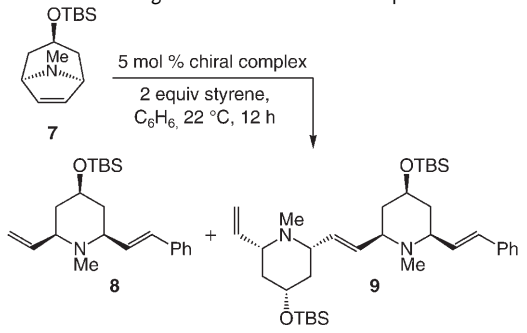
Table 1: Initial screening of chiral Ru and Mo complexes.[a]



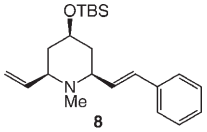
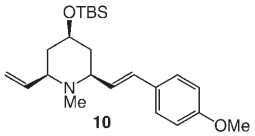
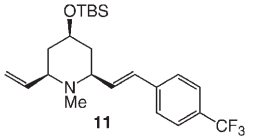
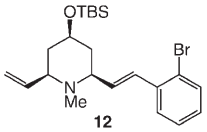
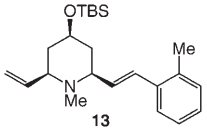
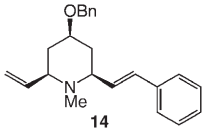
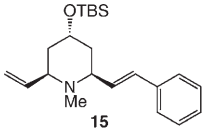
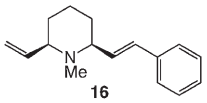
Entry	Chiral complex	Conv. [%][b]	**8**:**9**[b]	*ee* [%][c]
1	**1a**	< 2	–	–
2	**2a**	< 2	–	–
3	**2b**	< 2	–	–
4	**3a**	< 2	–	–
5	**3b**	> 98	> 20:1	< 2%
6	**3c**	< 2	–	–
7	**4a**	< 2	–	–
8	**4b**	< 2	–	–
9	**5**	< 2	–	–
10	**6**	> 98	2:1	94

[a] Reactions carried out under N_2. [b] Conversion and product ratios determined by analysis of 400-MHz ^{1}H 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, azabicycle **7** is polymerized (22°C, C_6H_6, 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 ^{1}H 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	 **8**	> 98	95	94
2	 **10**	> 98	92	89
3	 **11**	> 98	88	64
4	 **12**	> 98	86	88
5	 **13**	> 98	91	98
6	 **14**	> 98	86	96
7	 **15**	> 98	90	85
8	 **16**	> 98	64	80

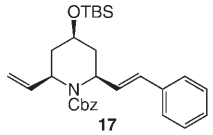
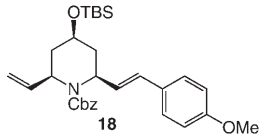
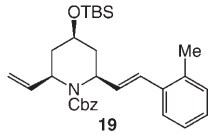
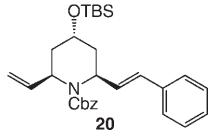
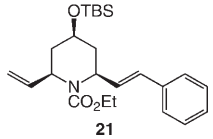
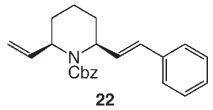
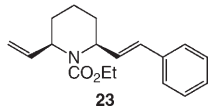
[a] Reactions carried out in the presence of 5 mol% **6**, 10 equiv of styrene (2 equiv for entry 8), in C_6H_6 for 1 h, at 22°C and under N_2. [b] Determined by analysis of 400-MHz ^{1}H NMR spectra of unpurified product mixtures. [c] Yields of isolated product after silica gel chromatography; > 98% *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 enantioslective catalytic AROCM/CM.

The derived unsaturated azabicycle 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]

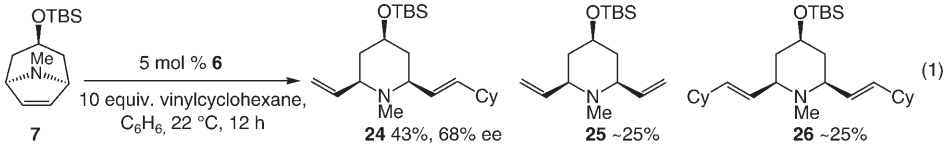
Entry	Product	Chiral complex; mol%	Conv. [%][b]	*t* [h]	Yield [%][c]	*ee* [%][d]
1	 **17**	**6**; 10	>98	12	93	90
2	 **18**	**6**; 10	70	12	65	80
3	 **19**	**6**; 10	>98	12	92	86
4	 **20**	**6**; 10	85	24	80	85
5	 **21**	**6**; 10	70	24	60	80
6	 **22**	**6**; 10	83	24	80	82
7		**1a**; 10	91	24	70	−90[e]
8	 **23**	**6**; 5	78	24	72	90
9		**1a**; 10	90	24	66	−94[e]

[a] Reactions carried out with 10 equiv of styrene in C_6H_6 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 N_2. [b] Determined by analysis of 400-MHz ^{1}H 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 azabicycle 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]

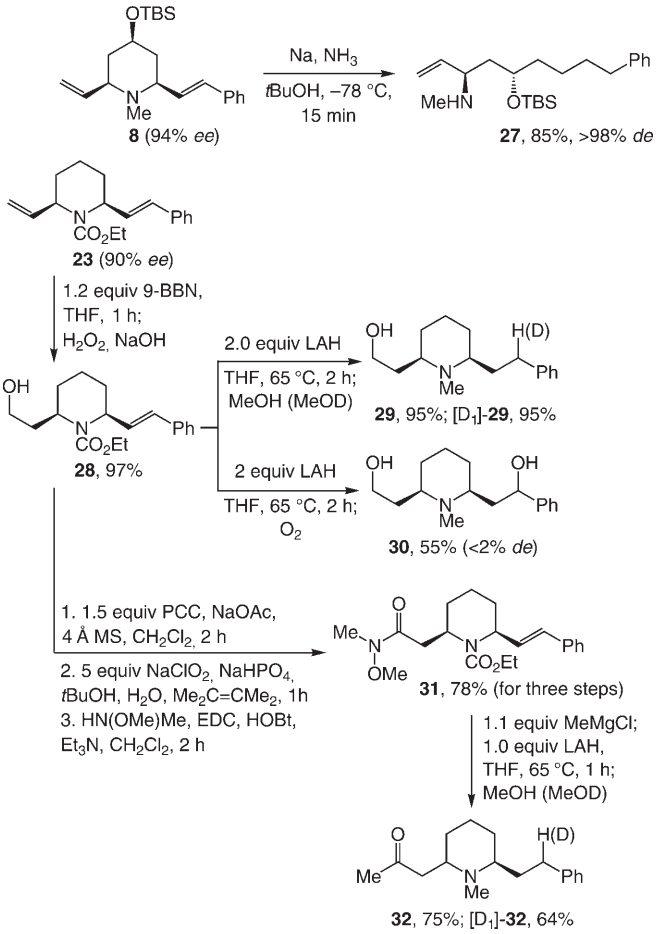
One important point regarding the AROM/CM reactions described above is whether such transformations are reversible, since azabicycles are less strained than the previously examined norbornenes.[7a] Our investigations indicate that Mo-catalyzed reactions in Table 2 (*N*-methyl-substituted substrates) 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, C_6H_6, 22 °C, 12 h) furnishes less than 2% of the corresponding *meso* azabicycle 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] methylidene 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 divinylpiperidene (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]



(1)

The unsaturated side chains at the C2 and C6 atoms of piperidines provide opportunities for functionalization of enantiomerically enriched N-containing heterocyles; noteworthy examples are provided in Scheme 2. The phenyl-substituted allylic amine of **8** is cleaved with Na/NH_3 (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 = $LiAlH_4$; 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, [D_1]-**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 O_2, 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 $NaClO_2$ 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 [D_1]-**29**, when the alkylation, reduction, hydroalumination sequence is terminated by quenching with MeOD, [D_1]-**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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[10] For example, see: a) R. W. Bates, K. Sa-Ei, *Tetrahedron Lett.* **2002**, *43*, 5957 – 5958; b) F. X. Felpin, J. Lebreton, *Tetrahedron* **2004**, *60*, 10127 – 10153.

[11] For applications of catalytic olefin metathesis (non-asymmetric) to total synthesis of piperidine-containing natural products, see: a) S. Randl, S. Blechert, *J. Org. Chem.* **2003**, *68*, 8879 – 8882; b) P. Rückert, P. H. Deshmukh, S. Blechert, *Tetrahedron Lett.* **2006**, *47*, 7977 – 7981.

[12] S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168 – 8179.

[13] Attempts to circumvent N–Ru complexation through protonation of the substrate's Lewis basic amine resulted in substrate decomposition (presumably due to cleavage of the allylic C–N bond).

[14] W. C. P. Tsang, J. A. Jernelius, G. A. Cortez, G. S. Weatherhead, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2003**, *125*, 2591 – 2596.

[15] Formation of **9** is likely due to the reaction of the Mo alkylidene generated through AROM/CM (before $\{L_nMo{=}C\}$ is converted to a terminal olefin) and another molecule of **7** (vs. reaction with styrene to afford **8**).

[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.

[17] A. K. Chatterjee, T.-L. Choi, D. P. Sanders, R. H. Grubbs, *J. Am. Chem. Soc.* **2003**, *125*, 11360 – 11370.

[18] For example, see: R. E. Giudici, A. H. Hoveyda, *J. Am. Chem. Soc.* **2007**, *129*, 3824 – 3825.

[19] Preliminary experiments indicate that hydroalumination of **28** is directed by the hydroxyl (vs. the amine) group. Thus, subjection of piperidine **23** to the same reaction conditions only results in carbamate reduction, and the corresponding pyrans bearing the primary alcohol undergo hydroalumination. For a review of substrate-directed reactions, see: a) A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307 – 1360; for examples of hydroxyl-directed hydraoluminations, see: b) H. W. Thompson, E. McPherson, *J. Org. Chem.* **1977**, *42*, 3350 – 3352; c) R. B. Gammill, P. M. Gold, S. A. Mizak, *J. Am. Chem. Soc.* **1980**, *102*, 3095 – 3100; d) K. Koch, J. H. Smitrovich, *Tetrahedron Lett.* **1994**, *35*, 1137 – 1140; for amine-directed hydroaluminations, see: e) A. P. Marchand, R. W. Allen, *Tetrahedron Lett.* **1975**, *16*, 67 – 70; f) J. Szmsuzkovicz, J. H. Musser, L. G. Lurian, *Tetrahedron Lett.* **1978**, *19*, 1411 – 1412; g) W. Granitzer, A. Stutz, *Tetrahedron Lett.* **1979**, *20*, 3145 – 3148.

[20] In addition, primary alcohol **28** is obtained in 45% yield. Formation of **28** is not due to the presence of adventitious moisture. When the reaction (O_2 quench) is worked up with MeOD, $[D_1]$-**28** is generated as the exclusive by-product. A portion of the alkylaluminum intermediate might exist in a less reactive oligomeric form.

[21] As reported previously, β-amino ketones such as **31** are subject to facile epimerization, presumably through an elimination/intramolecular conjugate addition process; see: R. W. Bates, K. Sa-Ei, *Tetrahedron* **2002**, *58*, 5957 – 5978.

