A chiral auxiliary cleavable by ring-closing alkene metathesis — Efficient synthesis of chiral nonracemic cycloalkenes[1]

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Abstract: *p*-Menthane-3-carboxaldehyde is a readily available chiral auxiliary used to prepare cycloalkenes and heterocycles bearing a chiral tertiary or quaternary carbon of high enantiomeric purity. The auxiliary is available in both enantiomeric forms and is inexpensive and recyclable. It is cleaved by a ring-closing alkene metathesis reaction directly yielding the cycloalkene.

Key words: chiral auxiliary, cleavage reaction, cyclization, ring-closing alkene metathesis, enantioenriched cycloalkenes.

Résumé : Le *p*-menthane-3-carboxaldéhyde est utilisé comme auxiliaire chiral pour fabriquer des cycloalcènes et des hétérocycles contenant un centre carboné tertiaire ou quaternaire de pureté énantiomérique élevée. L'auxiliaire est disponible dans les deux séries énantiomériques et est peu dispendieux et recyclable. Il est clivé par une réaction de fermeture de cycle par métathèse d'alcènes menant directement au cycloalcène.

Mots clés : auxiliaire chiral, réaction de clivage, cyclisation, fermeture de cycle par métathèse d'alcènes, cycloalcènes énantioenrichis.

Introduction

Chiral auxiliaries are exceptionally useful tools in synthetic organic chemistry because many of them achieve high levels of asymmetric induction on a wide range of substrates (1). One inherent drawback to their use is the need to install and cleave the auxiliary, which adds two chemical steps to the synthesis of the target molecule. This disadvantage can, however, be minimized if one of these two steps consists of a chemical transformation that would have been carried out eventually as part of the synthetic plan. This is not the case for the majority of chiral auxiliaries found in the literature that are cleaved either by addition–elimination reactions on polarized π systems (e.g., hydride reduction of C=O functional groups) or by hydrolysis of acetal-like functionalities (1). In addition, while other auxiliary-specific cleaving reactions have been developed (e.g., ozonolysis of C=C bonds (2) or hydrogenolysis of benzylic groups (3)), there is still a need to widen the arsenal of available methods to cleave chiral auxiliaries.

In this report, we disclose the cleavage of a chiral auxiliary by ring-closing alkene metathesis (RCM) (4) to yield highly enantioenriched cycloalkenes. To the best of our knowledge, this constitutes the first example of a chiral auxiliary cleavable by a RCM reaction (5, 6). Using our strategy, the cleavage of the auxiliary becomes intrinsic to the synthetic strategy and does not add extra steps en route to the final target.

Synthesis of RCM precursors[3]

The sequence of reactions starts with the synthesis of allylic alcohols **7a**–**7e** from *p*-menthane-3-carboxaldehyde **3** (7). These allylic alcohols were prepared by one of three methods (Scheme 1 and Table 1).

Method A involves the $AlMe_3$-promoted addition of vinyllithium reagents **6a** to aldehyde **3** (8). In this manner, a mixture of diastereomeric allylic alcohols, which are easily separated by flash chromatography, is obtained with selectivities ranging from ca. 10:1 to more than 100:1, favouring the Felkin–Ahn adducts (i.e., **7** as illustrated). Method B involves the addition of vinylalanes **6b**, generated by the zirconium-catalyzed methylalumination of alkynes (9) to aldehyde **3**. In Method C, lithium acetylides **2** are added to aldehyde **3** in the presence of dry cerium trichloride to afford a mixture of diastereomeric propargylic alcohols **4** (10).

Received 19 October 2005. Accepted 13 December 2005. Published on the NRC Research Press Web site at http://canjchem.nrc.ca on 28 July 2006.

This article is dedicated to Dr. Alfred Bader for his precious contributions to the science of chemistry.

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[3]Supplementary data for this article are available on the journal Web site (http://canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5067. For more information on obtaining material refer to http://cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml.

 doi:10.1139/V06-095

Scheme 1.

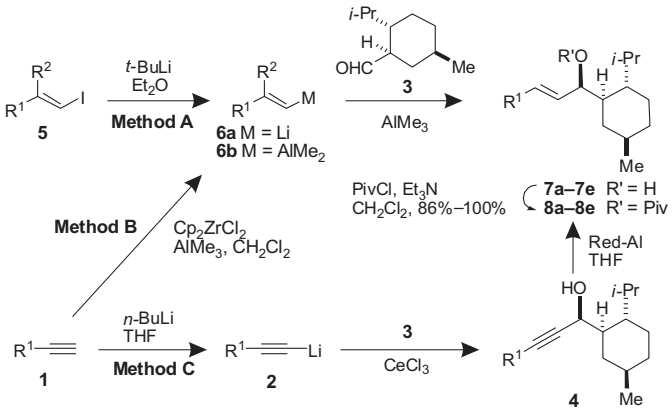


Table 1. Preparation of allylic alcohols **7a**–**7e** (cf. Scheme 1).

Entry	R1	R2	Compound	Yield of **7**[a] (%), (dr)
1	Bn	H	**7a**	64,[b] 170:1
2	$TBSOCH_2$	H	**7b**	43,[c] 3.5:1[d]
3	Bn	Me	**7c**	76,[e] 11:1
4	$TBSO(CH_2)_4$	Me	**7d**	68,[e] 11:1
5	$MOMOCH_2$	H	**7e**	37,[c] 3.1:1[d]

[a]Isolated yield of diastereomerically pure allylic alcohol **7**.
[b]Method A.
[c]Method C (yield of **7** over two steps).
[d]DR of **4** from the addition of **2** to **3**.
[e]Method B.

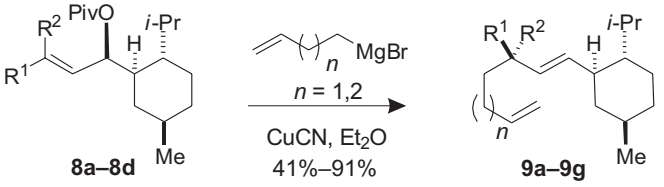
These propargylic alcohols are easily separated and converted to geometrically pure *E* allylic alcohols **7** by reduction with Red-Al. The alcohols **7a**–**7e** were then converted to the corresponding allylic pivalate esters **8a**–**8e** in excellent yields.

Cyanocuprates, derived from Grignard reagents, displaced the pivalate esters stereospecifically (anti to the leaving group with complete transfer of chirality) with 100% stereoselectivity (reaction on the conformer with minimized $A^{1,3}$ strain, yielding *E* alkenes) and with exclusive S_N2' regioselectivity (no S_N2 adduct detected by GC) (7, 11). Thus, cuprate adducts **9a**–**9g** (precursors to five- and six-membered rings for the subsequent RCM reactions) were prepared from pivalate esters **8a**–**8d** (Scheme 2). It should be noted that both absolute stereochemistries at the newly created chiral center in adducts **9** are accessible since both enantiomers of *p*-menthane-3-carboxaldehyde **3** are available, the double-bond geometry in **8** can be controlled, and the order of introduction of the different substituents on the new chiral center can be varied (7).

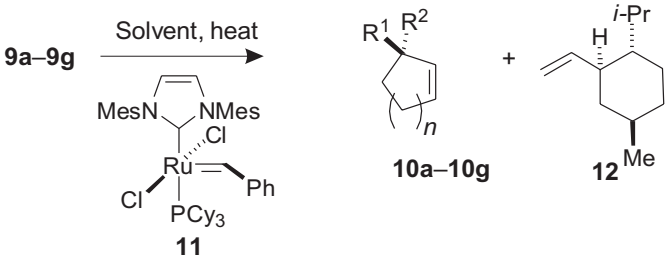
RCM reactions

After screening different ruthenium-based metathesis catalysts (see Supplementary data),[3] it was found that the formation of cycloalkenes **10** by a RCM reaction was best performed using the Grubbs–Nolan catalyst **11** (12) (Scheme 3). For precursors of five-membered rings bearing a tertiary carbon center (**9a** and **9c**) very mild conditions (**11** (1 mol%), CH_2Cl_2, 40 °C, 3 h) resulted in smooth transformation to cycloalkenes **10a** and **10c** (Table 2, entries 1 and

Scheme 2.



Scheme 3.



3). The only detectable (^{1}H NMR) products in the crude reaction mixtures were the cycloalkenes **10** and compound **12**.

Cyclization of precursors of six-membered rings bearing a tertiary carbon center (**9b** and **9d**) necessitated harsher conditions (**11** (10 mol%), $ClCH_2CH_2Cl$, 83 °C, 3 h) to avoid the formation of the corresponding dimers **13b** and **13d** by a competitive cross-metathesis reaction (Fig. 1). Under these conditions, the RCM reactions occurred smoothly to provide cycloalkenes **10b** and **10d** in good yields (Table 2, entries 2 and 4), with only trace amounts of **13** being detected.

Adducts **9e**–**9g**, bearing a quaternary carbon, presented a greater challenge. Minimizing the production of dimer **13** was crucial because when **13e** (derived from **9e**) was treated under RCM conditions (with or without an atmosphere of ethylene), no useful amount of **10e** could be obtained. Ultimately, it was found that higher dilution and temperatures were efficient in decreasing the amount of **13**. However, these conditions sometimes caused side-reactions, like the well-documented alkene isomerization (13), such that cycloalkenes **10e** and **10g** were contaminated with small amounts of inseparable alkene regioisomers **14e** and **14g**, respectively (Fig. 1).

Many strategies were tried to inhibit the formation of **14** (see Supplementary data),[3] but none gave reproducible results. Although the isomerization could not be completely suppressed, cycloalkene **10e** could be obtained in 79% yield as an acceptable 31:1 mixture of **10e** and **14e** by maintaining strictly anhydrous conditions and limiting the reaction time. In the same manner, **10g** was obtained in 70% yield as a 42:1 mixture of **10g** and **14g**. The fact that the RCM proceeds at all on substrates **9e** and **9g** is very satisfying, given the presence of an allylic quaternary center and a bulky menthyl fragment on each side of the *E* double bond (14).

It is perhaps not surprising, given the above results, that we have not yet succeeded in forming six-membered rings bearing a quaternary carbon. Compound **9f** afforded mostly dimer **13f** and degradation products under various conditions; RCM adduct **10f** was never observed, nor was by-product **12** (Table 2, entry 6).

The enantiomeric purity (determined by GC or HPLC analysis against racemic samples) of each RCM adduct was

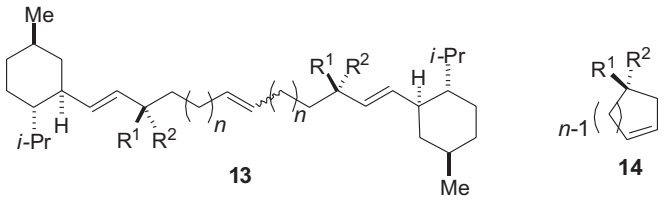
Table 2. Yields and enantiomeric ratios of cycloalkenes **10a**–**10g**.

Entry	9	R1	R2	*n*	10	Yield of **10** (%)[a]	er (%)
1	**9a**	Bn	H	1	**10a**	81	—[b]
2	**9b**	Bn	H	2	**10b**	84	>99:1[c]
3	**9c**	$TBSOCH_2$	H	1	**10c**	87	>98:2[d]
4	**9d**	$TBSOCH_2$	H	2	**10d**	73	>98:2[d]
5	**9**	Bn	Me	1	**10**	79[b]	97:3[e]
6	**9f**	Bn	Me	2	**10f**	0	—
7	**9g**	$TBSO(CH_2)_4$	Me	1	**10g**	70[b]	—[b]

Note: General conditions: **11** (1–10 mol%), CH_2Cl_2 or $ClCH_2CH_2Cl$ (0.01–0.002 mol/L), reflux, 3 h (see Supplementary data).[3]

[a]Isolated yield of **10** after flash chromatography.
[b]See text.
[c]Determined by HPLC analysis.
[d]Determined by GC analysis on the free alcohol.
[e]Determined by HPLC analysis on the allylic oxidation derivative.

Fig. 1. By-products from RCM reactions.



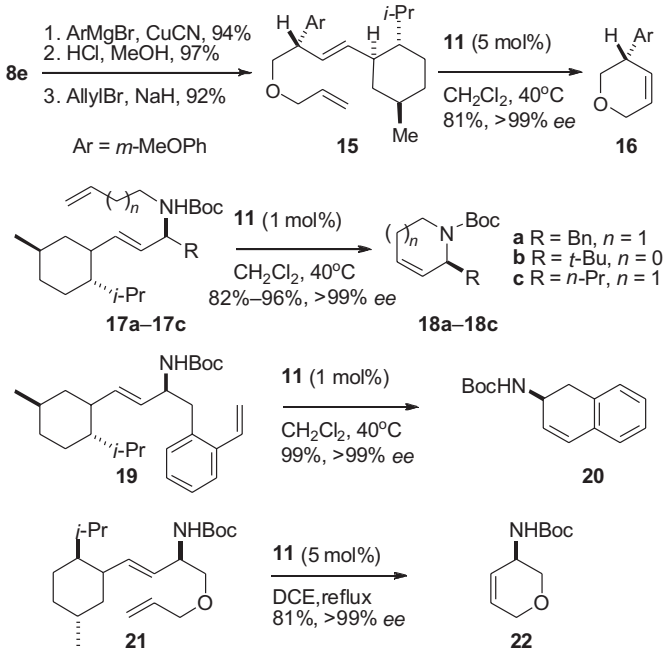
found to be excellent. For entries 1 and 7 of Table 2, we were unable to achieve complete resolution of the cycloalkene enantiomers, but their enantiomeric ratios are likely to be equally high. By-product **12** can be easily recovered by flash chromatography in yields of 70%–80% and, if desired, can be recycled back to aldehyde **3** by ozonolysis.

It is possible to envisage the application of our strategy to the preparation of a wide variety of highly enantioenriched cycloalkenes. Among the most interesting candidates, heterocycles are highly desirable (15). As an example, diene **15** (obtained in three steps from pivalate ester **8e**) was submitted to a RCM reaction to furnish dihydropyran **16** in 81% yield and >99% ee (as determined by HPLC analysis) (Scheme 4). *N*-Heterocycles, prepared by a different route (16), were also obtained by a similar RCM cleavage strategy as shown in Scheme 4. Dehydropiperidine **18a** and **18c**, pyrrolidine **18b**, and dihydroquinoline **20** were formed in excellent yield under much milder conditions (1 mol% catalyst in refluxing dichloromethane). Dihydropyran **22** required higher catalyst loading and higher temperature. We are currently embarked on the total synthesis of several alkaloids using this methodology.

Conclusion

We have achieved the first cleavage of a chiral auxiliary by a RCM reaction. This unprecedented method of cleavage has the merit of increasing the complexity of the substrate during the cleavage of the auxiliary, while not adding any extra steps to a synthetic plan aimed at synthesizing cycloalkenes. The sequence described herein allows the synthesis of enantioenriched cycloalkenes bearing a tertiary or quaternary chiral carbon in just four steps starting from readily available starting materials (vinyliodides or alkynes).

Scheme 4.



We are currently expanding the methodology to include more diverse and complex structures.

Acknowledgement

We thank the Natural Sciences and Engineering Research Council of Canada (NSERC), the ACS Petroleum Research Fund (Grant No. 36256-AC1), and the Université de Sherbrooke for financial support.

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