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Intramolecular Cyclopropanation of Unsaturated Terminal Epoxides and Chlorohydrins

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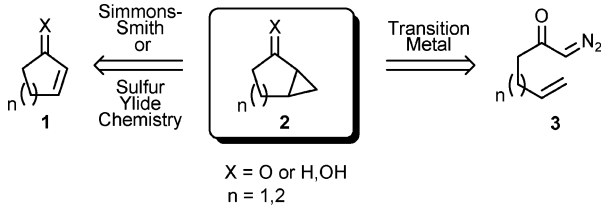
Abstract: Lithium 2,2,6,6-tetramethylpiperidide (LTMP)-induced intramolecular cyclopropanation of unsaturated terminal epoxides provides an efficient and completely stereoselective entry to bicyclo[3.1.0]hexan-2-ols and bicyclo[4.1.0]heptan-2-ols. Further elaboration of C-5 and C-6 stannyl-substituted bicyclo[3.1.0]-hexan-2-ols via Sn−Li exchange/electrophile trapping or Stille coupling generates a range of substituted bicyclic cyclopropanes. An alternative straightforward cyclopropanation protocol using a catalytic amount of 2,2,6,6-tetramethylpiperidine (TMP) allows for a convenient (1 g−7.5 kg) synthesis of bicyclo[3.1.0]-hexan-2-ol and other bicyclic adducts. The synthetic utility of this chemistry has been demonstrated in a concise asymmetric synthesis of (+)-β-cuparenone. The related unsaturated chlorohydrins also undergo intramolecular cyclopropanation via in situ epoxide formation.

Introduction

Cyclopropanes fused to normal-sized rings constitute important structural features widely found in natural products[1,2] as well as, increasingly, in pharmaceutical agents,[3] and their formation, especially in an enantioselective manner, has been an important research topic for many years.[4] Such bicyclic structures **2** can conventionally be accessed by carbene addition to a cycloalkene **1**, for example by Simmons−Smith[5] cyclopropanation or sulfur ylide chemistry[6] (Scheme 1). In general, oxygen-directed Simmons−Smith reactions[5b,c] generate bicyclic alcohols with excellent diastereoselectivity. However, utility of the latter in asymmetric synthesis is dependent on availability and enantiopurity of the cycloalkenol starting material. Following the pioneering work of Stork and Ficini,[7] the transition-metal-catalyzed intramolecular cyclopropanation of unsaturated α-diazocarbonyl compounds **3** is now also established as important methodology to access bicyclic cyclopropanes.[8] Recently, rhodium complexes have been developed to obtain high levels of asymmetric induction, but it remains the case that yields and enantioselectivities are highly susceptible to structural variation in the substrates.[9] Furthermore, α-diazocarbonyl compounds are typically synthesized in modest yields via one-carbon homologation of carboxylic acids using hazardous diazomethane and, once formed, possess limited stability.

Scheme 1. Construction of Bicyclo[3.1.0]hexane and Bicyclo[4.1.0]heptane Systems



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§ Rhodia Recherches.

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(2) A search of the Dictionary of Natural Products on CD-ROM (version 15: 1, July 2006, Chapman & Hall/CRC) for bicyclo[3.1.0]hexane and bicyclo-[4.1.0]heptane motifs gave 416 and 1978 hits, repectively.
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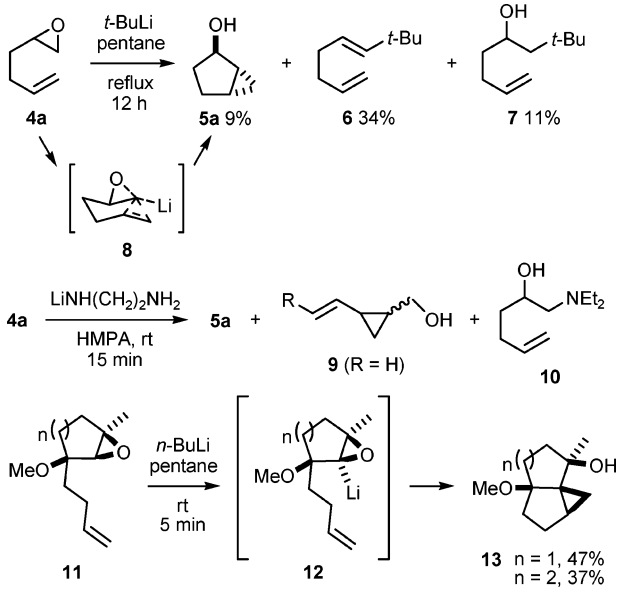
10.1021/ja0672932 CCC: $37.00

An unusual intramolecular cyclopropanation process was reported in 1967 by Crandall and Lin,[10] in which reaction of *t*-BuLi with 1,2-epoxy-5-hexene (**4a**) gave small amounts of *trans*-bicyclo[3.1.0]hexan-2-ol (**5a**) (9%), along with alkene **6** (34%) derived from reductive alkylation (reaction of the α-lithiated epoxide intermediate with more of the original organolithium base, followed by loss of Li_2O)[11] and alcohol **7** (11%) arising from direct nucleophilic ring-opening (Scheme 2). The completely stereocontrolled cyclopropanation of epoxide **4a** can be attributed to a chairlike transition state for the α-lithiated epoxide **8**, an electrophilic carbenoid,[12] in which $\pi_{alkene}/\sigma^*_{C-O}$ and $\sigma_{C-Li}/\pi^*_{alkene}$ interactions are important.[13] Although an interesting intramolecular cyclopropanation reaction, the low yield and competing side-reactions detracted from its further application in synthesis. Apparu and Barelle[14] later showed that the conversion of **4a** into **5a** was also possible using *N*-lithioethylenediamine in HMPA as solvent, although in this case the reaction was complicated by the concurrent formation of unwanted allylic cyclopropane **9** (R = H), likely arising from competing allylic deprotonation−cyclization,[15] and amino alcohol **10** (yields not reported). More recently, Mioskowski and co-workers reported organolithium-induced intramolecular cyclopropanation of fused α-alkoxy epoxides[11c,16] (e.g., **11** → **12** → **13**); however, modest yields were obtained due to competing reductive alkylation.

Scheme 2. Intramolecular Cyclopropanations via α-Lithiated Epoxides



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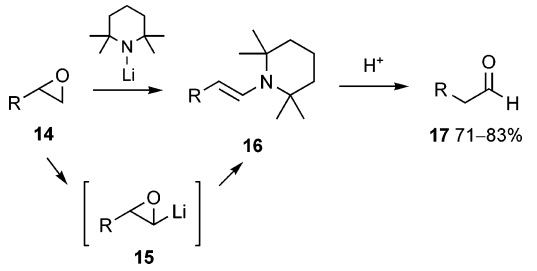
Arising out of the above observations and our interest in α-lithiated epoxides **15**,[17] we considered whether a more selective base might be used to provide more efficient access to bicyclic alcohols from terminal epoxides. Highly enantioenriched terminal epoxides have recently become readily available via Jacobsen hydrolytic kinetic resolution (HKR),[18] and expansion of the utility of such chiral building blocks would have special value for asymmetric synthesis. With these ideas in mind, we were attracted to the efficient lithium 2,2,6,6-tetramethylpiperidide (LTMP)-induced isomerization of terminal epoxides **14** to aldehydes **17**, reported in 1994 by Yamamoto and coworkers[19] (Scheme 3). Deuterium labeling studies conducted in that work indicated the reaction proceeds via a *trans*-α-lithiated epoxide **15**. Our further investigation into the reaction pathway revealed that lithiated epoxide **15** undergoes further reaction with LTMP (this time with the latter as nucleophile), followed by elimination of Li_2O to give an enamine **16**, which can be isolated or hydrolyzed to aldehyde **17**.[20]

Scheme 3. Isomerization of Terminal Epoxides to Aldehydes



Based on the ability of LTMP to effect clean lithiation of terminal epoxides (Scheme 3), we considered whether such a bulky lithium amide would be compatible with terminal epoxides bearing an alkene tether in the Crandall−Lin intramolecular cyclopropanation process. For such a reaction to be viable, allylic deprotonation[15] would have to be avoided/minimized and the α-lithiated epoxide would have to preferentially react with the tethered alkene, rather than with LTMP (which would result in enamine/aldehyde), or undergo dimerization.[21] In a preliminary examination of such chemistry, we have shown that this process can provide an efficient and highly stereoselective synthesis of functionalized bicyclic alcohols from unsaturated terminal epoxides and related chlorohydrin precursors.[22] In the present article, we provide a detailed account of the scope and limitations of this intramolecular cyclopropanation

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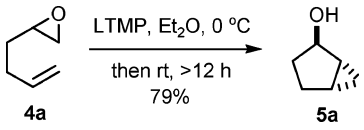
reaction, including its utility in the asymmetric synthesis of (+)-β-cuparenone, and further elaborations of tributylstannyl-substituted bicyclic alcohols. We also provide details of a conceptually new protocol using substoichiometric 2,2,6,6-tetramethylpiperidine (TMP), making large-scale syntheses of bicyclic alcohols more convenient and economically viable.

Results and Discussion

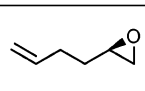
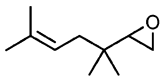
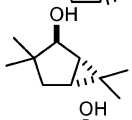
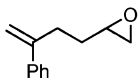
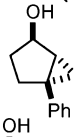
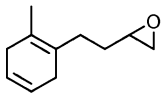
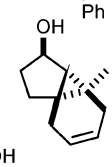
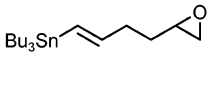
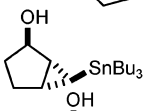
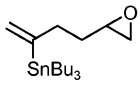
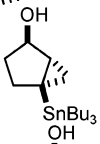
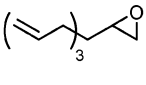
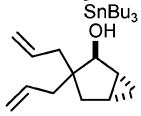
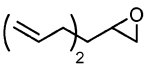
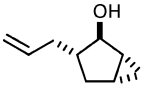
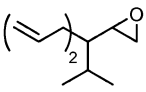
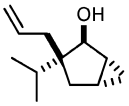
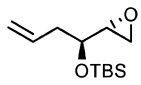
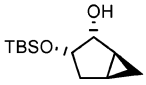
Due to the availability of 1,2-epoxy-5-hexene (**4a**) and its previous appearance in Crandall's work (Scheme 2), this simple unsaturated terminal epoxide was chosen for optimization of the LTMP-induced intramolecular cyclopropanation reaction.[23] The best conditions were initially determined to be slow (45−60 min) addition via cannula of LTMP (2 mmol, 2.0 equiv, 0.2 M in Et_2O) at 0 °C to a stirred solution of epoxide **4a** (1 mmol, 0.2 M in Et_2O) at 0 °C, followed by warming to room temperature over 12 h, which gave bicyclic alcohol **5a** in 79% yield (Scheme 4).

Scheme 4. LTMP-Induced Intramolecular Cyclopropanation



In order to examine the scope of the cyclopropanation chemistry, a variety of unsaturated terminal epoxides **4a**−**j** were synthesized and examined under the above cyclopropanation conditions (Table 1). Highly enantioenriched terminal epoxide ***R*-4a** (accessed via HKR[18d]) gave chiral bicyclic alcohol **(+)-5a** with no loss of enantiopurity (entry 1). This result confirms that the stereochemical outcome of the cyclopropanation is dictated by the epoxide stereocenter and that there is preservation of enantiointegrity in the reaction, making the methodology especially attractive for asymmetric synthesis. Alkyl substitution at the double bond or elsewhere in the tether was previously shown to be compatible with this chemistry,[22] and entry 2 provides an example containing both types. Note that, with more substituted alkenes such as this latter example, incomplete consumption of starting epoxide was observed in Et_2O, but this problem could be resolved using *t*-BuOMe[24] as solvent and subsequent examples in this article use *t*-BuOMe as solvent unless otherwise indicated. An α-substituted styrene underwent efficient cyclopropanation (entry 3), although the regioisomeric *trans*-β-substituted styrene gave an inseparable 1:2 mixture of the desired bicyclic cyclopropane and allylic cyclopropane **9** (R = Ph). Cyclopropanation involving a tetrasubstituted alkene proceeded smoothly, with possible complications arising from competitive doubly allylic deprotonation not being observed (entry 4). Epoxides bearing alkenylstannane substitution gave the corresponding bicyclic cyclopropylstannanes **5e** and **5f** (entries 5 and 6), which provides opportunities for further elaboration of the cyclopropyl moiety (vide infra). However, on treatment with LTMP the *trans*-vinylsilane corresponding to **4e** ($SnBu_3$ = $SiMe_3$) gave an inseparable mixture of the desired bicyclic cyclopropane and allylic cyclopropane **9** (R = $SiMe_3$),[23] and the *trans*-pinacolboronate corresponding to **4e** ($SnBu_3$ = $B(OCMe_2)_2$) underwent rapid decomposition. Intramolecular cyclopropanation of an epoxide bearing multiple alkene tethers was successful, to give potentially useful diallyl groups for further structural modification (entry 7). Two epoxides containing diastereotopic allyl groups proceeded to react in a highly diastereoselective manner to give cyclopropanes containing an additional stereocenter (entries 8 and 9). The stereocontrol can be rationalized by invoking the proposed chairlike transition state **8** (Scheme 2), in which the more sterically demanding group prefers to occupy a pseudo-equatorial position. The chemistry also proved viable even when a bulky group (TBSO) is forced to occupy the pseudoaxial position in the proposed chairlike transition state (entry 10).

Table 1. Synthesis of Bicyclo[3.1.0]hexan-2-ols **5**

Entry[a]	Epoxide **4a-j**	Cyclopropane **5**		Yield (%)[b]
1			**(+)-5a**	70[c]
2			**5b**	75
3			**5c**	80
4			**5d**	61
5			**5e**	68
6			**5f**	66
7			**5g**	84
8			**5h**	69
9			**5i**	82
10			**(+)-5j**	61

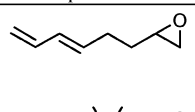
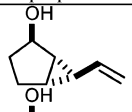
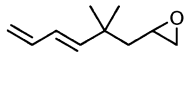
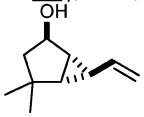
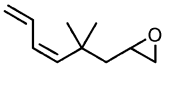
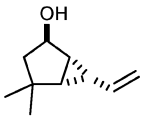
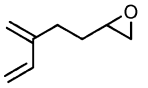
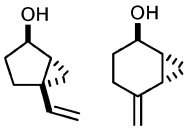
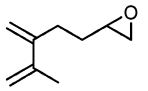
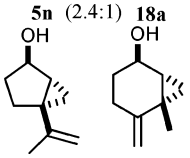
[a] *t*-BuOMe as solvent unless otherwise indicated. Reaction time 8−24 h. [b] Isolated yield. [c] Et_2O as solvent.

Intramolecular cyclopropanation of an epoxide bearing multiple alkene tethers was successful, to give potentially useful diallyl groups for further structural modification (entry 7). Two epoxides containing diastereotopic allyl groups proceeded to react in a highly diastereoselective manner to give cyclopropanes containing an additional stereocenter (entries 8 and 9). The stereocontrol can be rationalized by invoking the proposed chairlike transition state **8** (Scheme 2), in which the more sterically demanding group prefers to occupy a pseudo-equatorial position. The chemistry also proved viable even when a bulky group (TBSO) is forced to occupy the pseudoaxial position in the proposed chairlike transition state (entry 10).

As vinylcyclopropanes are useful synthetic intermediates,[25] we investigated carbenoid insertion into conjugated dienes with the aim of generating the corresponding vinylcyclopropane

(23) See Supporting Information for details.
(24) Kopka, I. E.; Fataftah, Z. A.; Rathke, M. W. *J. Org. Chem.* **1987**, *52*, 448−450.
(25) (a) Hudlicky, T.; Kutchan, T. M.; Naqvi, S. M. *Org. React.* **1985**, *33*, 247−335. (b) Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon: Oxford, 1992; Vol. 5, pp 899−970. (c) Oxgaard, J.; Wiest, O. *Eur. J. Org. Chem.* **2003**, 1454−1462. (d) Zuo, G.; Louie, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2277−2279.

Table 2. Terminal Epoxides Containing Conjugated Dienes

Entry[a]	Epoxide **4k-o**	Cyclopropane **5**	Yield (%)[b]
1		 **5k**	26[c]
2		 **5l**	75
3		 **5m**	78
4		 **5n** (2.4:1) **18a**	48
5		 **5o** (1.1:1) **18b**	69

[a] *t*-BuOMe as solvent. Reaction time 16−24 h. [b] Isolated yield. [c] Isolated as 1:1.5 mixture with allylic cyclopropane **9** (R = CH=CH_2).

adducts (Table 2). However, attempted cyclopropanation of epoxide **4k** produced a chromatographically inseparable 1:1.5 mixture (65%) of **5k** and allylic cyclopropane **9** (R = CH=CH_2) (Table 2, entry 1). The presence of the conjugated diene likely increases the acidity at the adjacent allylic position in epoxide **4k**, making deprotonation at that site competitive with α-lithiation of the epoxide (cf. **9** in Scheme 2). This issue could be overcome by full substitution at the allylic position. Thus, epoxides **4l** and **4m** were transformed in a stereospecific manner[12a] into the desired bicyclic vinylcyclopropanes **5l** and **5m** (entries 2 and 3). Unwanted allylic deprotonation was not observed with conjugated diene systems **4n** and **4o** (entries 4 and 5). However, in these latter cases the carbenoid insertion step was not regioselective, resulting in the formation of a chromatographically inseparable mixture of unsaturated five- and six-membered ring-fused cyclopropanes **5n/18a** (2.4:1) and **5o/18b** (1.1:1), respectively. In contrast, the *N*-*tert*-butylsulfonyl (Bus) aziridine corresponding to **4n** did undergo regioselective cyclopropanation to give **5n** (OH = NHBus).[26]

The results in entries 4 and 5 of Table 2 demonstrate that formation of cyclopropanes fused to six-membered rings is also possible, and this chemistry has been extended to trishomoallylic epoxides **19** (Figure 1), which allows access to *trans*-bicyclo[4.1.0]heptan-2-ols.[22] However, the chemistry could not be extended to give cyclopropanes fused to four- or seven-membered rings [epoxide **20** (Figure 1) underwent dimerization,[21] whereas decomposition was observed with epoxide **21**], or to intermolecular cyclopropanation,[27] or C−H insertion using epoxide **22**.

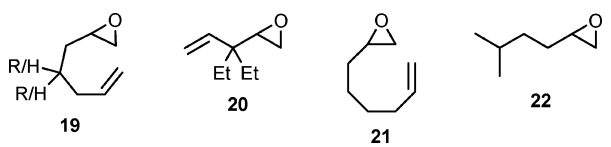
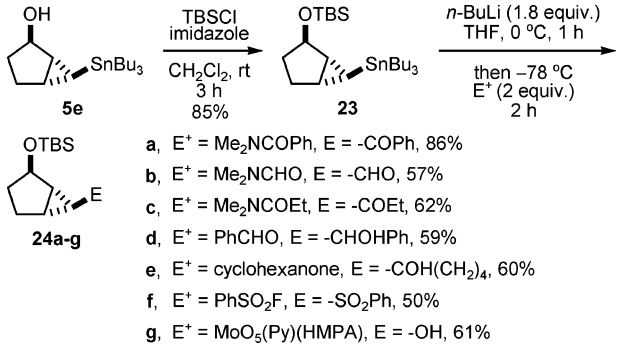


Figure 1. Other terminal epoxides studied with LTMP.

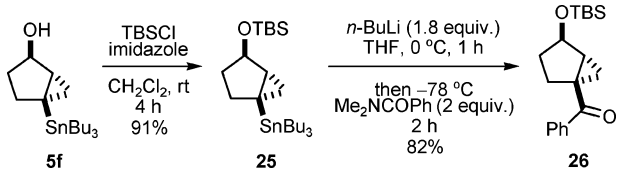
As terminal epoxides bearing carbonyl groups had earlier been found to be incompatible with the intramolecular cyclopropanation conditions, we considered methods to allow elaboration of the bicyclic alcohol products into more complex structures containing such functionality or other groups which may be sensitive to LTMP. The tributylstannyl-substituted bicyclic products **5e** and **5f** were considered to be suitable substrates, because cyclopropylstannanes are versatile synthetic intermediates capable of wide-ranging transformations, among which tin−lithium exchange/electrophile trapping and Stille cross-coupling chemistry are the most commonly utilized.[28] In order to avoid potential interference by the secondary hydroxy group of **5e** in this chemistry, it was first protected as the corresponding silyl ether **23** (Scheme 5).

Scheme 5. Electrophile Trapping of Cyclopropylstannane **23**



Tin−lithium exchange reactions are the most useful and widely studied transformations of cyclopropylstannanes, because the facile transmetallation with organolithium reagents at a wide range of temperatures (0 °C to −100 °C) renders such building blocks a convenient source of stereodefined cyclopropyllithiums.[28] Transmetallation of stannane **23** with *n*-BuLi followed by electrophile trapping was investigated and was found to allow rapid access to a diverse range of substituted cyclopropanes in satisfactory yields (Scheme 5). Stannane **25** was also trapped with *N*,*N*-dimethylbenzamide to give ketone **26** in 82% yield (Scheme 6).

Scheme 6. Electrophile Trapping of Cyclopropylstannane **25**

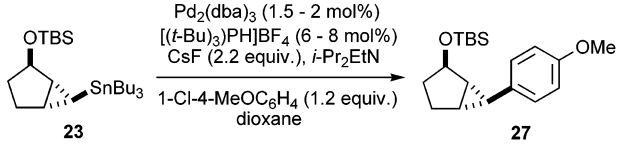


Stille cross-coupling reactions of cyclopropylstannanes with aryl halides or triflates are also potentially an attractive method for the preparation of diversely substituted cyclopropanes. However, most examples currently known provide coupled products in low to modest yields at best.[28] Recently, Fu and

(26) Hodgson, D. M.; Humphreys, P. G.; Ward, J. G. *Org. Lett.* **2006**, *8*, 995−998.
(27) (a) Olofson, R. A.; Dougherty, C. M. *J. Am. Chem. Soc.* **1973**, *95*, 581−582. (b) Dougherty, C. M.; Olofson, R. A. *Org. Synth. Coll. Vol. VI*, **1988**, 571−571.
(28) For a recent review, see: Rubina, M.; Gevorgyan, V. *Tetrahedron* **2004**, *60*, 3129−3159.

co-workers reported the use of Pd/P*t*-Bu_3 as a mild and general catalytic system for Stille coupling reactions of aryl chlorides and bromides.[29] The use of aryl chlorides are favored over bromides because the former are generally more readily available and stable, although prior to our work there were no examples of cross-coupling between cyclopropylstannanes and aryl chlorides. We briefly investigated the reaction of stannane **23** with *p*-chloroanisole under the conditions reported by Fu and co-workers, and also under microwave (75 W/110 °C) irradiation[23] (Scheme 7). Despite the incomplete consumption of starting material in both cases, good yields of coupled product **27** were obtained with respect to recovered starting cyclopropylstannane **23**. Under microwave conditions the reaction progress was considerably faster. This cross-coupling protocol provides an indirect solution to the incompatibility of the β-substituted styrene motif in the intramolecular cyclopropanation (vide supra).

Scheme 7. Stille Cross-Coupling of Cyclopropylstannane **23**



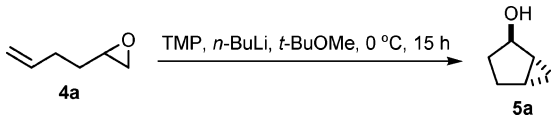
23 **27**

100 °C, 72 h, **27** 48% (86% based on recovered starting material)
75W/110 °C, 15 min, **27** 35% (95% based on recovered starting material)

Thus far, conversion of unsaturated terminal epoxides to bicyclic alcohols had been performed on relatively small scales (<1 g of epoxide), using 2 equiv of TMP.[30] However, this standard protocol is less favorable for large-scale syntheses from an economic and practical standpoint, since it involves the use of excess TMP and typically silica gel chromatography for purification. In order to demonstrate that such constraints can be circumvented, we have developed a straightforward protocol for the large-scale synthesis (up to multikilo quantities) of bicyclic alcohol **5a** using only a catalytic quantity of TMP. For this to be a viable concept, the amount of free organolithium available that could undergo an unwanted reaction with the epoxide[11] (cf. Scheme 2, **4a** → **5a**) must be kept to a minimum. We considered that slow addition of the organolithium to a mixture of the epoxide and a substoichiometric amount of TMP might fulfill this criterion, provided deprotonation of TMP and reaction of the so-generated LTMP with the epoxide (to regenerate TMP) were comparatively rapid steps.

The optimization studies involved slow (over 4 h) addition of *n*-BuLi to a stirred solution of epoxide **4a** (10 mmol) and TMP in *t*-BuOMe or hexane at 0 °C to −5 °C (Table 3). Initially, the use of 1 equiv of TMP and 2 equiv of *n*-BuLi gave bicyclic alcohol **5a** in 95% yield (entry 1). Similar yields were obtained with 0.5 equiv of TMP (entry 2), and then by also reducing the amount of *n*-BuLi to 1.1 equiv (entry 3). Further reduction of the amount of TMP (0.25 equiv) led to successively lower yields (entries 4−6), although 63% yield (GC) was still observed using 5 mol % TMP (entry 6). The conditions in entry 3 (0.5 equiv of TMP and 1.1 equiv of *n*-BuLi) gave the highest yield while using the most economical

Table 3. Intramolecular Cyclopropanation Catalytic in TMP



4a **5a**

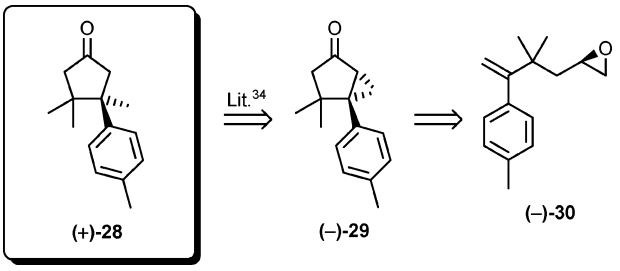
Entry[a]	TMP (equiv)	*n*-BuLi (equiv)	Yield (%)[b]
1	1	2	95
2	0.5	2	97
3[c]	0.5	1.1	95
4	0.25	1.1	85
5[d]	0.1	1.1	75[e]
6	0.05	1.1	63

[a] RLi was added dropwise to a stirred solution of **4a** (1 g, 10 mmol) and TMP in *t*-BuOMe (10 mL), unless otherwise indicated. After complete consumption of the epoxide, aqueous workup was performed using 3 N AcOH (1.6 equiv) to give crude **5a**. [b] GC yield with biphenyl as internal standard unless otherwise indicated. [c] *n*-HexylLi under these conditions gave **5a** (90%). [d] 50 mL of *t*-BuOMe used. [e] Isolated yield after column chromatography.

amounts of TMP and *n*-BuLi. The conversion of epoxide **4a** to bicyclic alcohol **5a** under this latter set of optimized conditions has been performed on numerous occasions and on various scales (1 g−7.5 kg), giving yields consistently in the range of 92−97%.[31]

In order to demonstrate the catalytic process, we focused on a synthesis of (+)-β-cuparenone **(+)-28** (Scheme 8). (+)-β-Cuparenone **(+)-28** is a sesquiterpene from the essential oil of *Mayur pankhi* and the liverwort *Mannia fragrans* and has been a popular target to illustrate new procedures for cyclopentanone construction and/or methods for juxtaposing quaternary centers.[32] (+)-β-Cuparenone **(+)-28** has previously been accessed from ketone **(+)-29** by reduction with lithium in liquid ammonia,[32c] and we anticipated ketone **(+)-29** could arise from intramolecular cyclopropanation of epoxide **(*R*)-30**; a synthesis of the latter therefore became our initial goal.

Scheme 8. Retrosynthesis of (+)-β-Cuparenone **(+)-32**

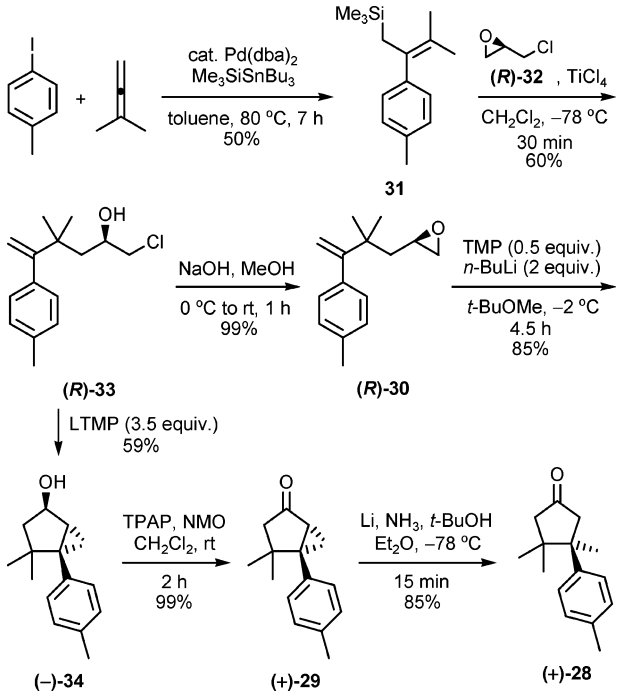


As a model for the TMP-catalyzed synthesis of (+)-β-cuparenone, we first studied intramolecular cyclopropanation of epoxide **4c** using substoichiometric TMP. Epoxide **4c** was converted to the secondary alcohol **5c** in 80% yield using 0.5 equiv of TMP and 2 equiv of *n*-BuLi; using 0.5 equiv of TMP and 1.1 equiv of *n*-BuLi, **5c** was obtained in 53% yield (58% yield brsm).

The synthesis of (+)-β-cuparenone commenced with commercially available 4-iodotoluene, $Bu_3SnSiMe_3$ and 3-methyl-1,2-butadiene, which underwent a $Pd(dba)_2$-catalyzed three-

(29) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343−6348.
(30) For an improved laboratory preparation of TMP, see: Kampmann, D.; Stuhlmüller, G.; Simon, R.; Cottet, F.; Leroux, F.; Schlosser, M. *Synthesis* **2005**, 1028−1029.
(31) Bio, M.; Brands, K. M. J.; Cleator, E. *PCT Int. Appl.* WO 2007015111, 2007.

***Scheme 9*.** Synthesis of (+)-β-Cuparenone **(+)-28**



component coupling reaction[33] to give allylsilane **31** in 50% yield (Scheme 9). A mixture of allylsilane **31** and (*R*)-epichlorohydrin (>99% ee) was then treated with $TiCl_4$[34] at −78 °C to give (*R*)-chlorohydrin **(*R*)-33** in 60% yield. Under similar conditions, the simple tetrasubstituted alkene (**31**, Me_3Si = H) only underwent partial dimerization, indicating a crucial role for the trimethylsilyl group. Ring-closure of **(*R*)-33** to give (*R*)-epoxide **(*R*)-30** was achieved in quantitative yield by treatment with NaOH in MeOH. Intramolecular cyclopropanation of terminal epoxide **(*R*)-30** under standard LTMP conditions proceeded smoothly to give the desired secondary alcohol **(−)-34**, in 72% yield. The chlorohydrin **(*R*)-33** could also be directly converted to cyclopropanol **(−)-34** (59%) using LTMP, presumably via in situ epoxide formation (Scheme 9). This latter protocol has been shown to be applicable to a range of unsaturated chlorohydrins directly accessed from unsaturated Grignard reagents and epichlorohydrin.[35] Significantly, using epoxide **(*R*)-30** with substoichiometric TMP (0.5 equiv) also proved viable, giving cyclopropanol **(−)-34** in 85% yield using 2 equiv of *n*-BuLi; even 1.1 equiv of *n*-BuLi with 0.5 equiv of TMP gave **(−)-34** in good yield (72%). Subsequent oxidation of alcohol **(−)-34** with catalytic TPAP and NMO afforded (99%) the known ketone **(+)-29**,[32c] which then underwent regioselective[36] reductive opening with lithium in liquid ammonia to give (*R*)-(+)-β-cuparenone **(+)-28** (85% yield, 97% ee by chiral GC).

Conclusion

We have developed intramolecular cyclopropanation of unsaturated terminal epoxides as a process for the synthesis of bicyclo[3.1.0]hexan-2-ols and bicyclo[4.1.0]heptan-2-ols. The methodology can be considered as a useful alternative to intramolecular cyclopropanation of unsaturated α-diazocarbonyl compounds. Indeed, the chemistry has already been applied to a range of 6-substituted bicyclo[3.1.0]hexan-2-ols as intermediates in the synthesis of fused pyrazole derivatives for the treatment of metabolic-related disorders.[3c,d] The ready availability of (highly enantioenriched) terminal epoxides and excellent stereocontrol in the carbenoid insertion process make this methodology especially attractive for asymmetric synthesis. Further elaboration at the cyclopropane of stannyl-substituted bicyclic alcohols can be achieved via tin−lithium exchange/electrophile trapping and Stille coupling. Modifications to the standard cyclopropanation conditions provide a protocol catalytic in terms of TMP for the conversion of **4a** to **5a** on a large scale (up to multikilo quantities). Concise syntheses of (−)-sabina ketone[22] and (+)-β-cuparenone **(+)-28** have been successfully developed employing this synthetic technology.

Experimental Section

A Typical Intramolecular Cyclopropanation, Using Unsaturated Terminal Epoxide 4c. *n*-BuLi (1.6 M in hexane, 1.3 mL, 2.0 mmol) was added to a stirred solution of 2,2,6,6-tetramethylpiperidine (0.34 mL, 2.00 mmol) in *t*-BuOMe (10 mL) at −78 °C. The pale yellow LTMP solution formed was stirred at rt for 15 min and cooled to 0 °C in an ice bath. To a stirred solution of terminal epoxide **4c** (174 mg, 1.00 mmol) in *t*-BuOMe (5 mL) at 0 °C was added the LTMP solution dropwise via cannula over 45−60 min. The resulting mixture was stirred at rt for 16 h, quenched with MeOH (0.5 mL), and concentrated. The residue was dry-loaded onto a small amount of silica and purified by chromatography on silica gel (30% Et_2O in petrol) to give the bicyclic alcohol **5c** (139 mg, 0.80 mmol, 80%) as a colorless oil, R_f = 0.2 (30% Et_2O in petrol); IR (film) 3346 (OH), 3060 (cyclopropane), 3028, 2933, 1603, 1498, 1447, 1326, 1166, 1107, 1031 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.76 (t, J = 4.8 Hz, 1H, H-6), 0.94 (dd, J = 5.2, 8.4 Hz, 1H, H-6′), 1.51−1.61 (m, 1H, H-4), 1.69 (s, 1H, OH), 1.73−1.78 (m, 2H, H-1, H-4′), 2.08 (dd, J = 8, 12.4 Hz, 1H, H-3), 2.29 (td, J = 8.4, 12.1 Hz, 1H, H-3′), 4.34 (d, J = 3.6 Hz, 1H, H-2), 7.17−7.32 (m, 5H, 5 × Ar−H); ^{13}C ($CDCl_3$, 100 MHz) δ 17.1 (C-6), 29.7 (C-3), 31.6 (C-4), 32.1 (C-5), 33.6 (C-1), 74.7 (C-2), 125.6 (Ar−C), 126.5 (Ar−C), 128.2 (Ar−C), 144.3 (Ar−C); MS (CI+) *m*/*z*: 157 ($[M - OH]^+$, 100%), 173 ($[M - H]^+$, 10%). HMRS: $[M - OH]^+$ found 157.1017, $C_{12}H_{13}$ requires 157.1017.

A Typical Electrophile Trapping of Stannane 23: With *N*,*N*-Dimethylbenzamide. *n*-BuLi (1.6 M in hexane, 1.4 mL, 2.2 mmol, 1.8 equiv) was added to a stirred solution of stannane **23** (501 mg, 1.00 mmol) in THF (6 mL) at 0 °C. After 1 h, the mixture was cooled to −78 °C, treated with a solution of *N*,*N*-dimethylbenzamide (298 mg, 2.00 mmol, 2.0 equiv) in THF (2 mL), and then stirred at the same temperature for a further 2 h. The resulting mixture was warmed to rt, dry-loaded onto a small amount of silica, and purified by chromatography on silica gel, followed by Kugelrohr distillation (70 °C and 0.07 mmbar) to give cyclopropane **24a** (273 mg, 0.86 mmol, 86%) as a white solid, R_f = 0.3 (5% Et_2O in petrol); mp = 57−58 °C; IR (film) 2930s, 2857s (C−H), 1668s (C=O), 1599m, 1582m, 1449s, 1401s, 1360s, 1267s, 1220s, 1168s, 1097s, 1034s cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.09 (s, 3H, $SiCH_3$), 0.10 (s, 3H, $SiCH_3$), 0.91 (s, 9H, $SiC(CH_3)_3$), 1.43−1.52 (m, 1H, H-3), 1.64 (dd, J = 8.4, 14.4 Hz, 1H, H-3′),

(32) For a review, see: (a) Pirrung, M. C.; Morehead, A. T., Jr.; Young, B. G. In *The Total Synthesis of Natural Products*; Goldsmith, D., Ed.; Wiley, New York, 2000; pp 196−199. For more recent syntheses of enantiomerically enriched β-cuparenone, see: (b) Castro, J.; Moyano, A.; Pericàs, M. A.; Riera, A.; Greene, A. E.; Alvarez-Larena, A.; Piniella, J. F. *J. Org. Chem.* **1996**, *61*, 9016−9020. (c) Aavula, B. R.; Cui, Q.; Mash, E. *Tetrahedron: Asymmetry* **2000**, *11*, 4681−4686. (d) Acherar, S.; Audran, G.; Cecchin, F.; Monti, H. *Tetrahedron* **2004**, *60*, 5907−5912.

(33) Wu, M. Y.; Yang, F. Y.; Cheng, C. H. *J. Org. Chem.* **1999**, *64*, 2471−2474.

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1.83 (dd, $J = 8.4$, 12.8 Hz, 1H, H-4), 2.11−2.24 (m, 3H, H-4′, H-5, H-6), 2.29 (t, $J = 2.8$ Hz, 1H, H-6), 4.37 (d, $J = 5.2$ Hz, 1H, H-2), 7.47 (t, $J = 8.0$ Hz, 2H, 2 × Ar−H), 7.56 (t, $J = 6.8$ Hz, 1H, Ar−H), 7.94 (d, $J = 8.4$ Hz, 2H, 2 × Ar−H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.7 ($SiCH_3$), −4.6 ($SiCH_3$), 18.2 (Si*C*$(CH_3)_3$), 25.5 (C-4), 25.9 (SiC-($CH_3)_3$), 26.7 (C-6), 31.8 (C-3), 32.2 (C-5), 38.1 (C-1), 74.3 (C-2), 127.9 (Ar−C), 128.4 (Ar−C), 133.0 (Ar−C), 138.0 (Ar−C), 198.8 (C=O); MS (CI+) *m*/*z*: 334.2 (MNH_4^+, 4%), 317.2 (MH^+, 100%), 259.1 (23%), 185.1 (20%), 131.1 (17%). Elemental analysis: found C, 72.08; H, 8.93. $C_{19}H_{28}O_2Si$ requires: C, 72.10; H, 8.92.

Large-Scale Catalytic Intramolecular Cyclopropanation of Epoxide 4a. *n*-BuLi (2.5 M in hexane, 89.6 mL, 224 mmol) was added slowly over 4 h to a stirred solution of epoxide **4a** (20.0 g, 204 mmol) and 2,2,6,6-tetramethylpiperidine (17.2 mL, 102 mmol) in *t*-BuOMe (200 mL) at 0 to −5 °C. The resulting mixture was stirred at 0 °C until complete consumption of the epoxide. The reaction mixture was quenched with 3 N AcOH (1.1 equiv). The layers were separated, the organic layer was washed with 3 N AcOH (0.5 equiv), and the combined aqueous layers were extracted with *t*-BuOMe (2 × 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to give bicyclic alcohol **5a** (19.2 g, 196 mmol, 96%) as a pale yellow oil (sufficiently pure for direct use). Alternatively, the product may be distilled (bp 63−65 °C at 15 mbar, lit.[37] 61−65 °C at 15 mbar). This procedure has been successfully performed on 7.5 kg of **4a**, $R_f = 0.2$ (30% Et_2O in petrol); IR (film) 3338bs (OH), 3036w, 3068w (cyclopropane), 2944s, 2869s (C−H), 1636m, 1466m, 1452m, 1330m, 1257w, 1178m, 1102m, 1045s, 1024m; ^{1}H NMR ($CDCl_3$, 400 MHz) δ −0.07−0.00 (m, 1H, H-6), 0.38−0.47 (m, 1H, H-6′), 1.27−1.37 (m, 2H, H-1, H-4′), 1.38−1.43 (m, 1H, H-5), 1.53 (dd, $J = 8.4$, 14.4 Hz, 1H, H-4), 1.65 (dd, $J = 8.0$, 12.4 Hz, 1H, H-3), 1.83 (s, 1H, OH), 1.87−1.98 (m, 1H, H-3′), 4.21 (d, $J = 4.8$ Hz, 1H, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 6.8 (C-6), 16.1 (C-5), 24.3 (C-1), 24.5 (C-3), 30.3 (C-4), 74.4 (C-2).

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Supporting Information Available: The full list of authors for ref 3a,b, experimental procedures and NMR spectra for compounds described in this article. This material is available free of charge via the Internet at http://pubs.acs.org.

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