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Intramolecular Simmons−Smith Cyclopropanation. Studies into the Reactivity of Alkyl-Substituted Zinc Carbenoids, Effect of Directing Groups and Synthesis of Bicyclo[*n*.1.0]alkanes

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Abstract: An intramolecular Simmons−Smith (IMSS) cyclopropanation has been developed, providing a novel method for the construction of substituted bicycloalkanes. First, functionalized *gem*-diiodoalkanes containing allylic alcohols were prepared in high yield. Then the intramolecular cyclization to form different ring sizes was investigated and proved to be successful for the synthesis of bicyclo[3.1.0]hexanes and bicyclo[4.1.0]heptanes. Larger chain lengths led to terminal alkene-containing products. Analysis of the product distribution for the different ring sizes and under various reaction conditions provided insight into the reactivity of substituted zinc carbenoids, and by the appropriate choice of conditions cyclopropanation could be promoted over alternative reaction pathways. Next the ability of allylic groups to promote the IMSS reaction by directing the zinc carbenoid was examined for the formation of bicycloheptanes. A scale of 'directing-ability' for these allylic groups has been rationalized, with an OMOM directing group providing the greatest enhancement in formation of the bicycle. Finally, the scope of the cyclization in forming substituted bicyclo[3.1.0]hexanes was explored. Substitution on the alkene and at the allylic position was well tolerated, providing the bicyclic products in high yields. Additionally, the IMSS reaction allowed a highly diastereoselective synthesis of a 5−3−5 fused tricycloalkane. These studies will have implications for the use of substituted carbenoids in cyclopropanation reactions and for directed cyclopropanation reactions as well as in the synthesis of substituted bicycloalkanes.

Introduction

The intramolecular cyclopropanation of suitably functionalized substrates affords bicyclic [*n*.1.0] ring systems.[1] The defined structural features of these bicyclic systems make them desirable synthetic targets for application as conformationally restricted biological probes.[2] In addition they offer potential as synthetic intermediates, due to the strained nature of the cyclopropane ring, and may participate in a wide range of ring-opening reactions.[3] The methods available to achieve intramolecular cyclopropanation have expanded greatly in recent years.[4−8] In particular, the transition metal-catalyzed decomposition of diazo compounds followed by intramolecular alkene insertion is well established (Figure 1).[4] Notable recent methods include the metal-catalyzed cycloisomerization of enynes using transition metal catalysts,[5] organocatalytic Michael-initiated ring closure,[6] the cyclization of lithiated epoxides,[7] and others.[8] Here we report

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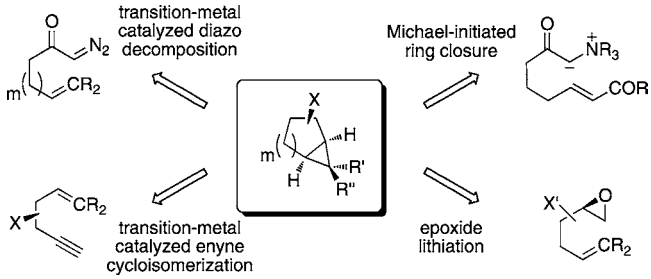

Figure 1. Intramolecular cyclopropanation methods for the formation of [*n*.1.0] bicycles.

our studies into an intramolecular Simmons−Smith (IMSS) cyclopropanation.

The Simmons−Smith cyclopropanation remains one of the most powerful methods to form cyclopropanes stereospecifically.[9] Since the original reports in the late 1950s,[10] the reaction has been subject to several important modifications.[11−14] These include the use of diethyl zinc to generate the required carbenoid as reported by Furukawa,[12] which provided simpler reaction procedures and allowed the use of noncoordinating solvents. The structures of carbenoids formed from CH_2I_2 are well-understood, following NMR studies and crystal structures of the carbenoid complexed with diethers and bipyridines.[13] Additionally, more reactive zinc carbenoid species are now available.[14] Variants of this reaction have been exploited in the synthesis of numerous complex structures and natural products,[15] employing diastereo- and enantioselective methods.[1,16,17] Furthermore, the Simmons−Smith reaction and the carbenoid reagents have been the subject of several theoretical investigations.[18]

Despite the extensive studies that the Simmons−Smith cyclopropanation has attracted, an intramolecular version of the reaction, involving an alkyl diiodide containing a pendant alkene, has not previously been reported.[19] Moreover, to date there are only limited examples of the use of alkyl-substituted carbenoids to form trisubstituted cyclopropanes in an intermolecular manner.[20,21] We previously reported such an intermolecular reaction between allylic alcohols and substituted alkyl diiodides to generate trisubstituted cyclopropanes with excellent yields and stereocontrol (eq 1).[20e] We envisaged developing an *intra*molecular Simmons−Smith cyclopropanation reaction, to access bicyclic structures not easily available by other methods and to examine the reactivity of the substituted zinc-carbenoids (eq 2).

Here we describe our studies into the feasibility and development of an intramolecular Simmons−Smith cyclopropanation, which resulted in the successful synthesis of [3.1.0] and [4.1.0] bicycloalkanes. Salient features also include the synthesis of

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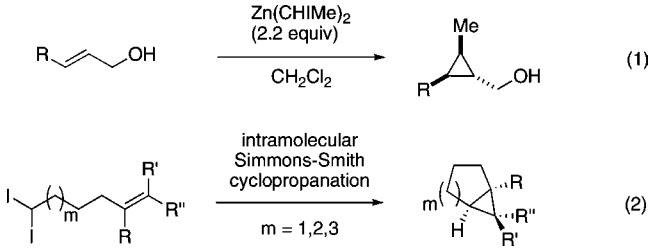
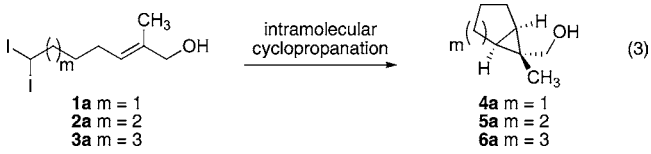
(21) For the formation of tri-substituted cyclopropanes using other functionalized carbenoids see: (a) For carbenoids formed from haloforms to deliver halogens: Kim, H. Y.; Lurain, A. E.; García-García, P.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 13138–13139. (b) Beaulieu, L.-P. B.; Zimmer, L. E.; Charette, A. B. *Chem.—Eur. J.* **2009**, *15*, 11829–11832. (c) For bis-zinc carbenoids formed from haloforms to afford cyclopropylzincs: Charette, A. B.; Gagnon, A.; Fournier, J.-F. *J. Am. Chem. Soc.* **2002**, *124*, 386–387. (d) Fournier, J.-F.; Mathieu, S.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 13140–13141. (e) Zimmer, L. E.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 15624–15626.



functionalized *gem*-diiodoalkanes, and the promotion of the IMSS over competing reaction pathways through the choice of reaction conditions and of allylic groups. Furthermore, the substitution requirements of the alkene have been examined, leading to the synthesis of several bicyclo[3.1.0]hexanes and to a diastereoselective synthesis of a substituted tricycloalkane.

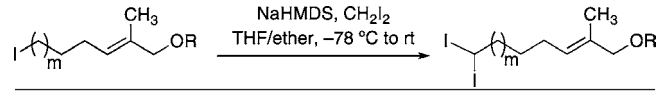
Results and Discussion

Preparation of Intramolecular Cyclopropanation Substrates: Synthesis of *gem*-Diiodoalkanes. We intended to examine the intramolecular cyclopropanation using allylic alcohol-containing diiodides **1a**−**3a** of varying chain lengths (eq 3). This reaction would then form meso products **4a**−**6a**, a structural type that, although relatively simple, would not be easy to access by other cyclopropanation methods. In this transformation the relative stereochemistry of the cyclopropane would be controlled exclusively by the double bond geometry.



The first barrier to the investigation was the preparation of these functionalized *gem*-diiodoalkanes. Although several methods are available for the preparation of *gem*-diiodides,[22] they often suffer from poor yields or limited functional group tolerance. We planned to access the required diiodides by the alkylation of diiodomethane,[23] using our recently developed conditions for the alkylation of the sodium anion of diiodomethane with primary alkyl iodides.[24] Here, we applied our optimal conditions (5 equiv NaHMDS/CH_2I_2, −78 °C) to the corresponding iodides **7b**, **8b**, and **9b** of different chain lengths to form *gem*-diiodides **1b**, **2b**, and **3b** in excellent yields, containing THP-protected allylic alcohols (Table 1 entries 1−3).[25] Under these conditions complete consumption of the primary iodides was reliably achieved, enabling further investigation without the presence of the otherwise inseparable starting material. We chose to protect the allylic alcohol with the THP group for the ease of subsequent deprotection, which was indeed removed in high yields to afford the desired *gem*-diiodide-containing allylic alcohols **1a**−**3a** (Scheme 1). With these substrates in hand we could investigate their performance in an intramolecular cyclopropanation reaction.

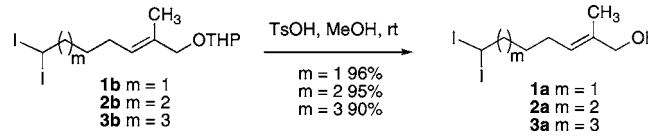
Table 1. Preparation of Functionalized *gem*-Diiodoalkanes As Substrates for Intramolecular Simmons−Smith Cyclopropanation



entry	iodide	*m*	OR	yield (%)[a]	diiodide
1	**7b**	1	OTHP	89	**1b**[b]
2	**8b**	2	OTHP	94	**2b**
3	**9b**	3	OTHP	95	**3b**
4	**8c**	2	OBn	92	**2c**
5	**8d**	2	OMe	95	**2d**
6	**8e**	2	$OCONMe_2$	77	**2e**
7	**8f**	2	OMOM	90	**2f**
8	**8g**	2	OMEM	90	**2g**
9	**8h**	2	OTIPS	94	**2h**
10	**8i**	2	H	77	**2i**

[a] Yield of isolated product. [b] Reference 25.

Scheme 1. Synthesis of Allylic Alcohol-Containing *gem*-Diiodoalkanes



For studies described later in this paper we required a range of *gem*-diiodoalkanes containing various groups at the allylic position. Consequently, *gem*-diiodides **2c**−**i** were prepared in good to excellent yields from iodides **8c**−**i** (Table 1, entries 4−10).[25] The conditions proved to be compatible with allylic benzyl and methyl ethers, acetals, carbamates, and TIPS ethers, extending the scope and functional group tolerance for this transformation. Further examples of the preparation by this method of functionalized *gem*-diiodides as substrates for the IMSS reaction are described in a later section of this paper (see Synthesis of Bicyclo[3.1.0]hexanes).

Intramolecular Simmons−Smith: Effect of Ring Size. In 1964 Simmons and Smith reported that alkyl diiodides gave low levels of cyclopropanation in an intermolecular reaction,[26] and to date there remain relatively few examples of alkyl-substituted zinc carbenoids in cyclopropanation reactions.[20] This is in part due to the additional carbenoid decomposition pathways that are available in these cases[27] on top of those that occur with the unsubstituted carbenoid.[13c,f,28] Also, substituted ethylzinc carbenoids have also been shown to undergo migration of the ethyl group to generate secondary alkyl zinc reagents.[29] As a consequence of these alternative reaction pathways, an excess of the diiodide is required to achieve high yields in the *inter*molecular processes.[30]

We first examined the feasibility of the IMSS reaction with the different chain-length diiodides **1a**−**3a**, aiming to form

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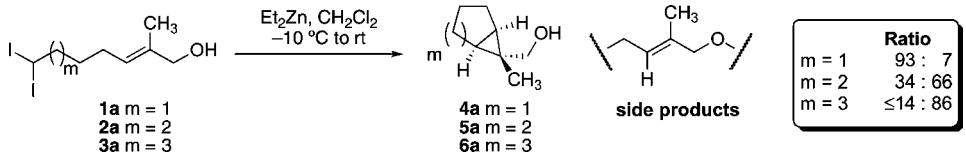
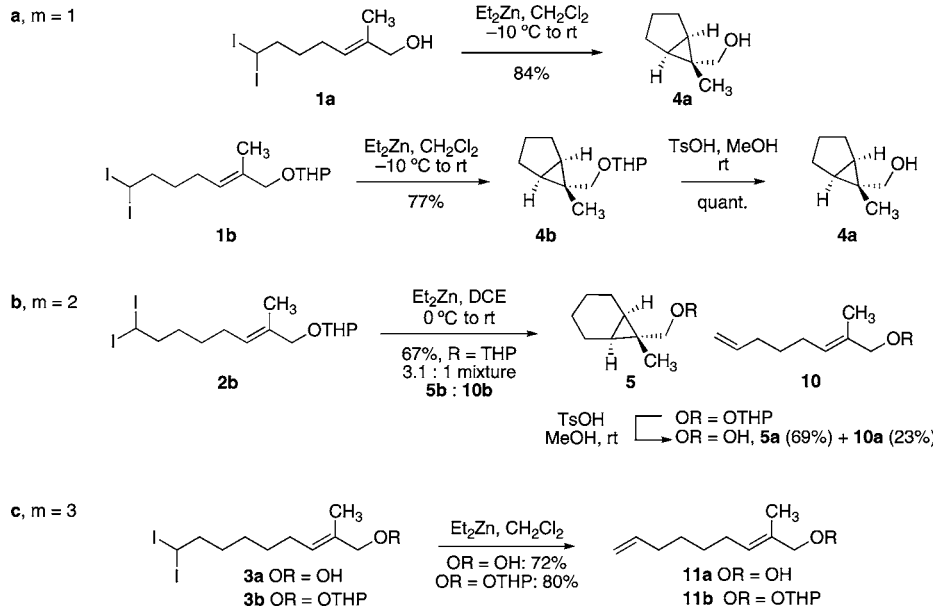
Scheme 2. Ratios of Cyclopropane Product to Side Products Obtained with Increasing Ring Sizes



Scheme 3. Formation of [3.1.0] and [4.1.0] Bicycloalkanes by Intramolecular Simmons–Smith Cyclopropanation and Terminal Alkene Side Products on Increasing the Chain Length



[3.1.0], [4.1.0], and [5.1.0] bicycloalkanes. Preliminary investigations showed that treating the allylic alcohol-containing diiodides with one equivalent of Et_2Zn returned the diiodide starting material unchanged, indicating stability of the diiodide to the EtZn-alkoxide formed. Excess diethylzinc was employed to ensure a uniform reacting species was formed, as the iodoalkyl(ethyl)zinc carbenoid,[30] and the use of 4 equiv ensured complete consumption of the diiodides. Aware that decomposition of the carbenoid by non-cyclopropanation pathways may form various side products, we measured the ratio of the bicyclic product to all other products in the crude mixture.[31] Pleasingly, under standard cyclopropanation conditions the bicyclic product appeared to be formed in all cases (Scheme 2). However, on increasing the chain length to form 6- and then 7-membered rings, the formation of other products became dominant.

High conversions to the bicycloalkane were observed by applying 4 equiv of diethylzinc to diiodide **1a** in the formation of bicyclo[3.1.0]hexane **4a** (Scheme 3a). The cyclopropane-containing product was isolated in high yield, which constitutes the first example of the desired intramolecular Simmons–Smith cyclopropanation reaction. Applying these conditions to the THP-protected allylic alcohol **1b** also led to a successful cyclopropanation to afford **4b** in good yield. Deprotection of the THP group provided alcohol **4a** with a yield over the two steps comparable to that obtained by performing these reactions in the reverse order.

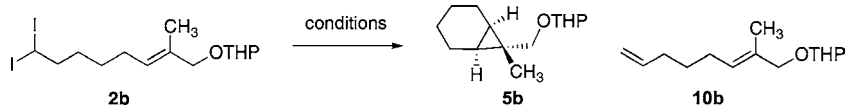
Employing allylic alcohol **2a** with an extended chain length ($m = 2$) to form a bicyclic compound containing a 6-membered ring gave a complex mixture of products with the desired [4.1.0] bicycle constituting only 34% of the mixture. Early optimization of this reaction showed it to be independent of temperature and gave similar results using CH_2Cl_2 or DCE as the reaction solvent. Further investigations with this system did not lead to improvement in selectivity for cyclopropanation. In all cases the complex mixture of products prevented isolation of the individual components. Somewhat surprisingly, applying similar conditions to diiodide **2b** carrying the THP-protected alcohol led to a significant improvement in the proportion of the cyclopropane product formed, 66% of the mixture. Furthermore in this case, a 3.1:1 mixture of cyclopropane **5b** and terminal alkene **10b** could be isolated in 67% yield (Scheme 3b).[32] Removal of the THP group from the mixture allowed separation of the structural isomers, providing the deprotected alcohol **5a** in a 46% yield

(30) Our previously reported conditions (ref 20e) for the intermolecular cyclopropanation with alkyl-substituted carbenoids employed 4.4 equiv of the alkyl diiodide and 2.2 equiv of Et_2Zn to generate the bis-iodoalkyl zinc reagent. In this intramolecular case the bis-iodoalkyl reagent could not be employed in order to ensure a uniform reacting species: reaction with one-half of the reagent would generate the iodoalkylzinc iodide which would undergo the IMSS reaction with different selectivity. The use of excess Et_2Zn will favor the equilibrium towards the ethyl(iodoalkyl)zinc carbenoid (see ref 13c).

(31) For Scheme 2: Ratio determined by ^1H NMR based on the ratios of the integration of the remaining olefinic proton (assumed to be present in all non-cyclopropanation products) against the integration of the CH_2OH or cyclopropane C–*H* signals in the bicyclic product as appropriate. For Table 2: as above using the integration of the C*H*HO signals of **5b** (δ 3.38 (d, $J = 10.0$ Hz, 1H)) and the alkene CH signal for **10b** (δ 5.79 (ddt, $J = 17.0, 10.3, 6.7$ Hz, 1H)). For Table 3: as above using the integration of the cyclopropane CH signal of **5** ($\delta \sim 3$ 0.65 (m, 2H)).

(32) A pure reference sample of THP-protected bicyclohexane **5b** was obtained by dihydroxylation of the mixture of **5b** and **10b** (OsO_4, NMO, acetone/H_2O). The relative stereochemistry of compound **5b** about the cyclopropane ring was confirmed by NOESY correlations between the cyclopropane CH and CH_2OTHP, which were absent between the cyclopropane CH and the methyl CH_3.

Table 2. Optimization of Reaction Conditions for the Intramolecular Cyclopropanation of Diiodide **2b**



2b **5b** **10b**

entry[a]	Zn reagent[b]	temperature	solvent	conv. (%)	bicycle (%)[c]	alkene (%)[c]
1[d]	Et_2Zn	0 °C to rt[e]	CH_2Cl_2	100	66	16
2	Et_2Zn	0 °C to rt[e]	DCE	100	66	16
3	Et_2Zn	0 °C to rt[e]	hexane	100	52	28
4	Et_2Zn	0 °C to rt[e]	toluene	100	39	41
5	Et_2Zn	0 °C to rt[e]	ether	100	25	47[f]
6	Et_2Zn	0 °C to rt[e]	CH_2Cl_2[g]	100	63	18
7	Et_2Zn	0 °C to rt[e]	CH_2Cl_2[h]	100	45	24
8[i]	EtZnI	0 °C to rt[e]	CH_2Cl_2	100	55	33
9[i]	$EtZnOCH_2CF_3$	0 °C to rt[e]	CH_2Cl_2	68	11	55
10[i]	$EtZnO_2CCF_3$	0 °C to rt[e]	CH_2Cl_2	∼10	−	−
11	Et_2Zn (0.6 equiv)	0 °C to rt[e]	CH_2Cl_2	74	53	18
12	Et_2Zn	−40 to 0 °C	CH_2Cl_2	100	72	12
13[j]	**Et_2Zn**	**0 °C**	**CH_2Cl_2**	**100**	**72**	**12**
14	Et_2Zn	rt	CH_2Cl_2	100	63	20

[a] Reaction performed on 0.1-mmol scale, 5 h reaction time. [b] Addition of 4 equiv (unless otherwise stated) of zinc reagent to solution of diiodide (0.05 M). [c] Proportion of crude reaction mixture as determined by ^{1}H NMR (see ref 31). [d] An identical result was obtained on reversing the order of addition of reagents. [e] Addition at 0 °C then warmed to rt. [f] Primary iodide **9b** formed (∼5%). [g] Ether additive (8 equiv). [h] NMP additive (4 equiv). [i] Reverse addition procedure. [j] A 5.3:1 mixture of **5b**:**10b** was isolated in 73% yield on a 0.35 mmol scale.

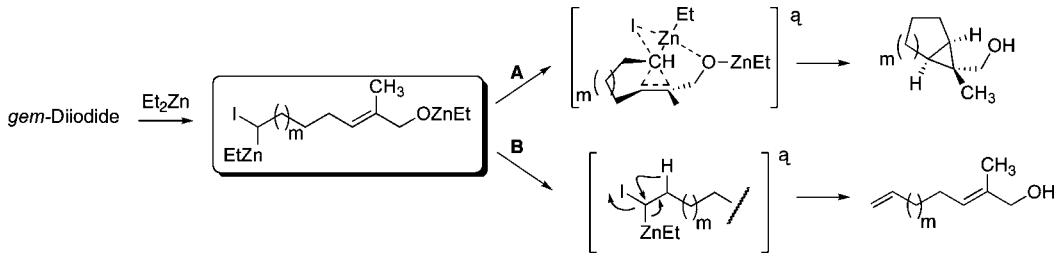


Figure 2. Transition states for the formation of bicycles and side products.

over the two steps from **2b** (Scheme 3). Terminal alkene **10a** was also isolated, confirming this as the major side product formed in both cases with OH or OTHP groups.

Due to the poor kinetics of 7-membered-ring formation, a low level of cyclization to the [5.1.0] system was obtained from diiodide **3a**. Terminal alkene **11a** was formed as the major product and isolated in 72% yield (Scheme 3c). In this case performing the reaction with diiodide **3b**, containing the THP-protecting group, did not lead to an enhancement in the proportion of the bicycle formed, and again the terminal alkene (**11b**) was isolated in high yield.

The above results suggest two major reaction pathways are operative for the intermediate Zn carbenoid. To achieve the desired cyclopropanation requires the complex to fold up on itself to adopt a butterfly-type transition state (Figure 2, path A).[18a] This is more easily adopted in the case of smaller rings due to the lower entropic constraints. The second major pathway leads to the terminal alkene by rearrangement of the carbenoid intermediate via a hydride shift with the loss of EtZnI (Figure 2, path B).[26,27,33]

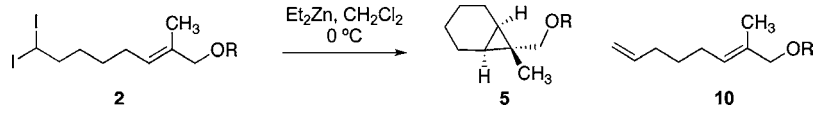
IMSS Reaction Conditions. The study into the ring sizes showed that for [3.1.0] bicycles the IMSS reaction is the favored pathway of the carbenoid intermediate, whereas for [5.1.0] bicycles the formation of the terminal alkene is favored. Therefore, we explored the reaction to form [4.1.0] bicycles, which formed both products in more similar amounts. We aimed to promote the cyclopropanation over other reaction pathways for this system by the choice of reaction conditions, as well as to study the reactivity of the zinc carbenoids. We chose to optimize the reaction using THP-protected alcohol **2b**, focusing particularly on minimizing the formation of terminal alkene **10b** (formed as the major side product and difficult to separate from the bicyclic product).

Initially, we examined the effect of the solvent on the amount of bicycloalkane **5b** and terminal alkene **10b** formed, with CH_2Cl_2 or DCE proving to be similar and superior to other solvents tested (Table 2, entries 1 and 2). Moving from hexane to toluene and ether gave progressively increasing amounts of the terminal alkene product with the corresponding decrease in formation of the bicycle (entries 3−5). When diethyl ether was used as the solvent, the formation of **10b** was favored. In addition 5% of primary iodide **9b** was formed, corresponding to protonation of the carbenoid in the quench, after a 5-h reaction time. The coordinating solvent stabilized the carbenoid, reducing its reactivity, but also reduced the tendency to coordinate with the THP group to promote cyclopropanation. Coordinating additives to the dichloromethane solvent (ether or NMP) also gave poorer results in terms of formation of the bicycle (entries 6 and 7).

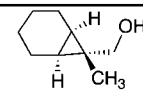
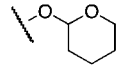
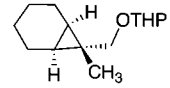
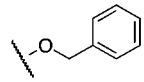
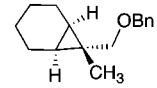
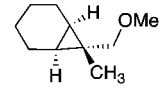
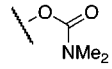
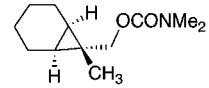
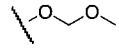
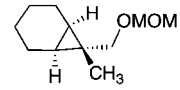
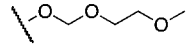
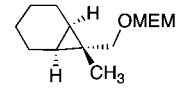
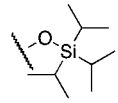
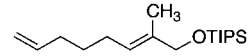
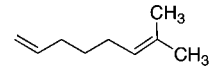
Increasing the reactivity of the carbenoid by using the Simmons−Smith reagent and the trifluoroethanol-zinc carbenoid gave progressively less of the cyclized product (entries 8 and 9). These more electrophilic carbenoids must increase the rate

(33) Other minor products observed include the vinyl iodide due to elimination of HI from the diiodide. The chain-extended compound was observed, resulting from migration of the ethyl group.

Table 3. Effect of Allylic Directing Groups on the Intramolecular Cyclopropanation of Diiodide **2**



2 **5** **10**

entry[a]	diiodide		bicycle (%)[b]	alkene (%)[b]	major product[c]	
1	**2a**		35[d]	19		**5a**
2[e]	**2b**		72	12		**5b**
3	**2c**		78[f]	3		**5c**
4[g]	**2d**		75	10		**5d**
5	**2e**		53[h]	31		**5e**
6	**2f**		89[i]	2		**5f**
7	**2g**		65[d,j]	26		**5g**
8	**2h**		19	66[k]		**10h**
9[g]	**2i**		18	75		**10i**

[a] Reaction performed using 4 equiv Et_2Zn over a 5-h reaction time, 0.05 M. [b] Proportion of crude reaction mixture as determined by ^1H NMR (see ref 31). [c] Major product observed in crude reaction mixture. [d] Products could not be isolated from mixture by flash chromatography. [e] Entry as for Table 2, entry 13. [f] Bicycloalkane **5c** isolated in 70% yield. [g] Reaction performed in CD_2Cl_2 to allow direct analysis of the crude mixture due to volatility of products. [h] A 1.8:1 mixture of **5e**: **10e** was isolated in 78% yield. [i] Bicycloalkane **5f** isolated in 83%. [j] Bicycloalkane **5g** was isolated in 48% yield over two steps following treatment of the crude mixture with dihydroxylating conditions. [k] Alkene **10h** was isolated in 58% yield.

of formation of the terminal alkene to a greater extent than the rate of the IMSS reaction is increased. These results suggest that the use of less electrophilic carbenoids will be advantageous in the formation of trisubstituted cyclopropanes using alkyl-substituted carbenoids. The more electron-deficient zinc reagents also displayed a decreased propensity to undergo alkyl exchange with the diiodide, as evidenced by the lower conversions (entries 8−10). Attempts to form the bis-iodoalkylzinc species also gave reduced amounts of the cyclized product and incomplete conversion (entry 11). However, formation of **5b** was improved by lowering the temperature (entries 12−14). Performing the reaction at 0 °C provided the optimal conditions and a convenient procedure.

Effect of Allylic 'Directing' Groups. It is well-known that zinc carbenoids can be directed by Lewis basic groups, often in the context of facial selectivity.[34] It was apparent from our results with diiodides **2a**/**2b** that the nature of the allylic group (OH vs OTHP) affected the rate of the IMSS reaction by acting as a directing group. On the other hand, we assumed that the rate of the hydride-shift would be largely independent of the allylic groups. This prompted us to investigate the effect of directing groups on this reaction to influence the reaction pathway.

(34) (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370. (b) Charette, A. B.; Marcoux, J.-F. *Synlett* **1995**, 1197–1207.

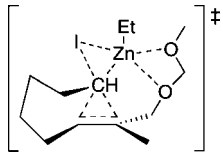


Figure 3. Proposed transition state for the OMOM directing group.

We have previously shown that in some circumstances an OBn group provides a more effective directing group than an OH group.[34b] As a wider comparison of directing groups has not been undertaken, we were keen to assess the ability of other groups to promote the IMSS reaction. We assumed that the OTHP group provided a better product ratio than the hydroxy group due to improved coordination to the zinc carbenoid, lowering the entropic cost of adopting the butterfly transition state. We envisioned that alternative directing groups could further improve the product distribution in favor of the bicyclic product.

Several *gem*-diiodoalkanes were synthesized, bearing a variety of directing groups (Table 1), and were subjected to our optimized IMSS conditions. Initially the substrate bearing the benzyl ether (**2c**) was tested (Table 3, entry 3), which gave a significant improvement in the product ratio in favor of the bicyclic product (**5c**), compared to results from the OH or OTHP examples (entries 1 and 2). In particular the amount of the alkene product formed was very low, which allowed bicycle **5c** to be isolated cleanly in 70% yield. The methyl ether gave results similar to those of the OTHP example (entry 4).

We hoped that the use of more Lewis basic groups would further improve the proportion of the intermediate carbenoid that undergoes the IMSS reaction. However, the dimethyl carbamate of substrate **2e** was a poor directing group, with the bicyclic product and the terminal alkene formed in similar amounts. This highlighted the two competing effects of the allylic groups: favorable coordination to the carbenoid can lower the $\Delta S^{\ddagger}$ of the cyclopropanation, however, the carbamate has an electron-withdrawing effect leading to a more electron-poor olefin that is less reactive toward the electrophilic carbenoid.[18a]

We next examined other acetals to offer greater ease of introduction and removal of the directing group. Indeed the introduction of an OMOM group proved to be the most effective directing group in this study (entry 6). Analysis of the crude product mixture displayed that the desired bicycle was formed almost exclusively (89% of the mixture), with other side products only formed in very small amounts. The MOM-containing bicyclic product was then isolated in 83% yield. This significant improvement is presumably due to the second oxygen group being well located to coordinate the Zn atom of the carbenoid, increasing the rate of the IMSS over those of other reaction pathways (Figure 3). This improvement over the THP group which also has a well-located acetal oxygen atom is likely because the THP example will lead to diastereomeric transition states which may not favor cyclopropanation equally, or due to being constrained in a ring, preventing an efficient coordination. Although the MEM group, containing an additional ether oxygen, may have been expected to increase coordination and hence the degree of cyclopropanation, it proved to be a poor directing group. This is presumably due to coordination of zinc species to the OCH_2CH_2O unit of the MEM group, which was not conducive to cyclopropanation (entry 7).

Conversely, using diiodide **2h** containing an OTIPS group gave the terminal alkene as the major product, which was isolated in 58% yield (entry 8). The bicycle was formed in low levels due to the adverse steric and electronic effects of the large silyl group causing unfavorable interactions in the transition state and preventing coordination of the oxygen atom to the zinc carbenoid. For comparison alkyl diiodide **2i** (OR = H) was prepared, and although **2i** contains the most electron-rich double bond, the level of cyclopropanation is very low in the absence of a directing group, comparable to that obtained with the OTIPS example.

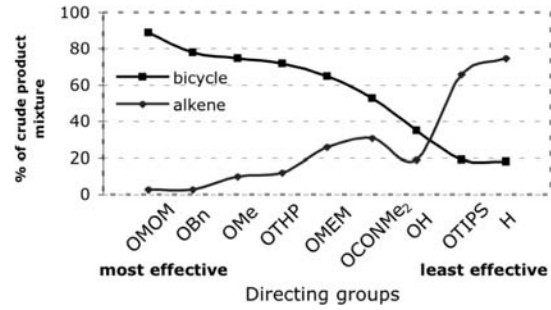


Figure 4. Directing group effects: proportion of **5**/**10** formed with different allylic directing groups.

Placing these results in order of the amount of bicyclic product formed provides a scale of the ability of allylic groups to promote the IMSS reaction over alternative reaction pathways (Figure 4). The OMOM group provided the most effective enhancement of the IMSS reaction, followed by the OBn, OMe, and OTHP groups. At the other end, the diiodides containing the OTIPS group and no directing group favor the formation of the alkene side product.

Plotting these values highlights that for the hydroxy group formation of the two major products accounts for an unusually small amount of the total material. This is presumably due to other reactions occurring involving the hydroxy group (e.g., etherification) which must be particularly favorable at this ring size.

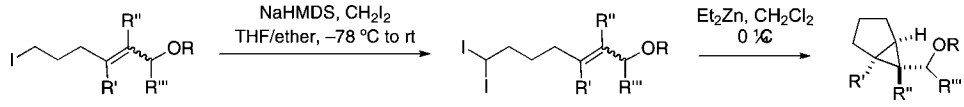
Synthesis of Bicyclo[3.1.0]hexanes. Having established the optimal reaction conditions for the IMSS reaction and that the OMOM group acts as the more efficient directing group, we next chose to examine the structural requirements on the alkene and at the allylic position through the synthesis of substituted bicyclohexanes. Pleasingly, in all cases the *gem*-diiodides were successfully employed in the IMSS reaction to access the corresponding bicyclohexanes (Table 4).

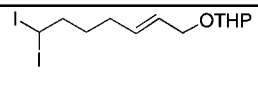
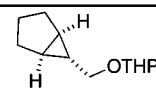
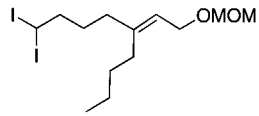
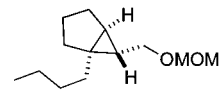
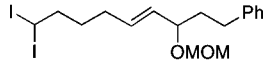
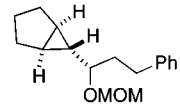
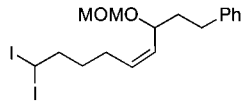
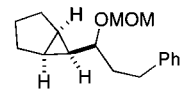
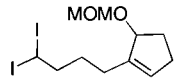
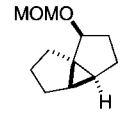
First we prepared diioide **12** containing a *trans*-disubstituted alkene. Applying our optimal conditions provided the corresponding bicyclohexane in good yield (entry 1). We showed in the synthesis of **4a/b** that the alkene could be trisubstituted with a substituent at the α-position. Introducing a substituent on the alkene at the β-position of the alkene in diiodide **14** was also successful, leading to bicyclohexane **15** in good yield. Next we prepared diiodide **16** with substitution at the allylic position. This substrate afforded bicyclohexane **17** in high yield, perhaps aided by the additional substituent orientating the directing group toward the reacting centers. The corresponding *cis*-alkene **18** of the same substrate was also prepared, leading to the

(35) For other routes to similar products and their reactivities see: (a) Nishii, Y.; Fujiwara, A.; Wakasugi, K.; Miki, M.; Yanagi, K.; Tanabe, Y. *Chem. Lett.* **2002**, 30–31. (b) Kang, S. H.; Jun, H. S. *Bull. Korean Chem. Soc.* **1992**, *13*, 227–229.

(36) Major diastereoisomers assigned on the basis of NOE studies and the chemical shifts of the C*H*O protons; *endo*-isomer: δ 4.28 (t, J = 8.0 Hz), *exo*-isomer: δ 4.11 (d, J = 4.6 Hz) (ratio 16:1 *endo*:*exo*). See Supporting Information for further information on the NMR studies on this compound. For analogous examples see: (a) Ohira, S. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1902–1907. (b) Friedrich, E. C.; De Lucca, G. *J. Org. Chem.* **1983**, *48*, 4563–4567. (c) Freeman, P. K.; Grostic, M. F.; Raymond, F. A. *J. Org. Chem.* **1965**, *30*, 771–777.

Table 4. Preparation of Bicyclo[3.1.0]hexanes by Intramolecular Simmons−Smith Cyclopropanation



entry	diiodide	yield[a]	bicyclohexane	yield[b]
1[c]		87%		73%
	12		**13**	
2		99%		79%
	14		**15**	
3		90%		83%
	16		**17**	
4		95%		81%
	18		**19**	
5		82%		81% (94:6 d.r)[d]
	20		**21**	

[a] Isolated yield of diiodide from corresponding primary iodide. [b] Isolated yield of bicyclohexane. [c] OTHP group used as directing group due to volatility of the low-molecular weight MOM-protected products. [d] By ^{1}H NMR (ref 36).

diastereoisomeric compound **19**, obtained in essentially the same yield as the *trans*-isomer. This confirmed that the IMSS reaction proceeds with complete retention of the double bond stereochemistry.

We were keen to combine the directing effect to promote the cyclopropanation with a facially selective reaction. We felt this could provide access to well-defined tricyclic systems.[35] Therefore, diiodide **20** was prepared in high yield and submitted to the optimal IMSS conditions. Pleasingly 5−3−5 fused tricycloalkane **21** was obtained in good yield and in excellent diastereoselectivity (dr = 16:1) as the *endo*-isomer, corresponding to the carbenoid being directed by the OMOM group.[36]

Conclusion

We have described the first intramolecular Simmons−Smith cyclopropanation reaction involving an alkyl diiodide with a pendant alkene, which is successful for the synthesis of [3.1.0] and [4.1.0] bicycloalkanes. On forming bicyclo[4.1.0]alkanes a terminal alkene product resulting from a hydride shift of the intermediate carbenoid becomes significant. For larger ring sizes this alkene product becomes dominant. We have examined conditions to promote the IMSS reaction over the alternative reaction pathways. Performing the reaction at 0 °C and forming the iodoalkyl(ethyl)zinc carbenoid are optimal. We have also shown that the nature of the allylic directing group has a large influence on the product distribution. The OMOM group provides significantly improved conversion to the bicyclic product. On the other hand the presence of a TIPS group under identical reaction conditions leads to the formation of the alkene product in high yield. In addition these conditions have been used to construct several substituted bicyclo[3.1.0]hexanes in high yields. This was extended to the synthesis of a 5−3−5 fused tricycloalkane with high yield and diastereoselectivity. These studies will have implications for cyclopropanation reactions involving the use of substituted carbenoids and for directed cyclopropanation reactions.

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Supporting Information Available: Experimental procedures, compound characterization data and NMR spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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