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COMMUNICATION

Study on the coupling of acyclic esters with alkenes – the synthesis of 2-(2-hydroxyalkyl)cyclopropanols *via* cascade cyclization using allylsamarium bromide†

Yawei Tu,[a] Liejin Zhou,[a] Ruifeng Yin,[a] Xin Lv,*[a] Robert A. Flowers II,[b] Kimberly A. Choquette,[b] Huili Liu,[a] Qingsheng Niu[a] and Xiaoxia Wang*[a]

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The radical cyclization between aliphatic acyclic esters and alkenes was achieved unprecedentedly in the presence of allylsamarium bromide with HMPA and H_2O as additives. The cascade radical cyclization–ring-opening–anionic cyclization allowed facile and efficient access to 2-(2-hydroxyalkyl)cyclopropanols from readily available materials.

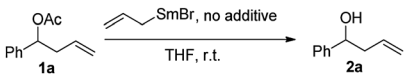
Carbonyl–alkene (ketyl–olefin) coupling[1] promoted by SmI_2 has found broad applications as the key step in the construction of a range of important intermediates. In contrast, ester–alkene radical cyclizations received little attention until 2009, when the Procter group first reported that the radical intermediates, formed during lactone reduction with SmI_2–H_2O, underwent addition to alkenes.[2] The success of ester–alkene radial cyclization was based on the unusual radical anions formed by electron transfer from Sm(II) to the ester carbonyl.[2] Cyclization cascades were also possible when two unsaturated carbon–carbon bonds were present in the starting cyclic diester and thus led to the formation of two rings and four stereocenters with excellent stereocontrol.[3] Very recently, the Procter group also reported that the cascade radical reactions of unsaturated Meldrum's acid derivatives allowed complex carbocyclic motifs to be assembled in a single step.[4] Nevertheless, the ester–alkene coupling is at present only limited to cyclic esters (lactones). Although the reduction of unactivated alkyl esters using SmI_2–H_2O–Et_3N has been reported for the first time in 2011, the coupling between aliphatic acyclic esters and alkenes remains a challenge since it was noticed that the optimal conditions for the efficient reduction of lactones and cyclic 1,3-esters with SmI_2–H_2O did not promote the reduction of aliphatic acyclic esters.[5]

AllylSmBr is known as a traditional C-nucleophilic reagent used for allylation reaction.[6] Its potential to act as a single-electron-transfer (SET) agent has not received much attention until very recently.[7] Zhang and co-workers reported that allylSmBr acted as a nucleophile and a SET reagent simultaneously when it reacted with γ-halo-α,β-unsaturated carbonyl compounds.[7a] And we unexpectedly found that 3-aryl-1,2,4-benzotrizines could be generated from 1,1-bis(benzotriazo1-1-yl)-methylarenes by treatment of allylSmBr *via* cascade reductive debenzotriazoylation and radical rearrangement.[7b] The divalent samarium in allylSmBr can rationally account for its SET reactivity. The potential of allylSmBr to act as a good SET agent is worth studying since it is an organometallic divalent samarium agent and may exhibit unique advantages.

In this communication, we wish to report the allylSmBr promoted ester–alkene radical cyclization of the aliphatic esters of homoallylic alcohols. It provided a facile and diastereoselective synthesis of 2-(2-hydroxyalkyl)-cyclopropanols from readily available materials.

During the preliminary investigation, homoallylic alcohol acetate **1a** was employed as the model substrate. However, by treatment of **1a** with 2.2 equiv. of allylSmBr in THF, 1-phenylbut-3-en-1-ol **2a** was obtained in 86% yield (Scheme 1).

We proposed that **2a** might be liberated from **1a** by the nucleophilic allylation of the ester moiety. Thus, allylSmBr acted as a nucleophilic agent in this case. Effective measures should be taken to inhibit the nucleophilicity of allylSmBr and enhance its SET ability. Illuminated by the fact that the addition of HMPA could increase the reducing ability of SmI_2, 10 equiv. of HMPA was utilized as an additive.[8] However, it was surprising to find that complex reaction mixtures resulted from the addition of HMPA (for details, see Table S1, ESI†). Nevertheless, these results did identify that the addition of HMPA was able to hinder the nucleophilicity of allylSmBr, observed through the suppressed formation of **2a**. Also, increasing the amount of allylSmBr and HMPA did not change this result significantly. Gratifyingly, with HMPA (10 equiv.) and water (0.5 equiv.) as the co-additives, allylSmBr did afford **3a** in 55% yield. The reaction failed to occur when



Scheme 1 The reaction of **1a** with allylSmBr without additives.

[a] *Zhejiang Key Laboratory for Reactive Chemistry on Solid Surfaces, College of Chemistry and Life Sciences, Zhejiang Normal University, Jinhua 321004, People's Republic of China. E-mail: wangxiaoxia@zjnu.cn, lvxin@zjnu.cn*
[b] *Department of Chemistry, Lehigh University, Bethlehem, PA 18015, USA*

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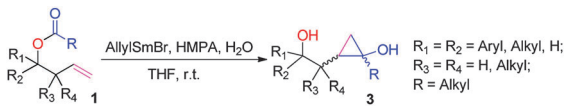
water alone was used as the additive. The result improved further by using a slightly larger amount of additives. However, further increase in the amount of the promoters hardly brought about any change. To our delight, the combination of allylSmBr (2.2 equiv.), HMPA (10 equiv.) and H_2O (1.0 equiv.) afforded satisfactory efficiency (73% yield). The use of excess H_2O seemed to be unfavorable for this reaction. In fact, no desired **3a** was detected when 3.0 equiv. of water was utilized as the co-additive.

With these optimized reaction conditions in hand, the scope of the reaction was explored, and the results are summarized in Table 1.

As shown in Table 1, both the 1-aryl and 1-alkyl homoallylic alcohol esters underwent the cascade ester–alkene radical cyclization smoothly and the desired 2-(2-hydroxyalkyl)cyclopropanols **3** were prepared in moderate to excellent yields. Generally, 1-alkyl homoallylic acetates afforded better yields of **3** than 1-aryl homoallyl esters.

Table 1 The allylSmBr–HMPA–H_2O promoted cascade synthesis of various 2-(2-hydroxyalkyl)cyclopropanols[a]



Entry	R^1	R^2	R^3	R^4	R	Substrate	Product	Yield[b] (dr)[c]
1	C_6H_5	H	H	H	Me	**1a**	**3a**	73% (1.5 : 1)
2	4-$CH_3C_6H_4$	H	H	H	Me	**1b**	**3b**	73% (2.1 : 1)
3	4-$MeOC_6H_4$	H	H	H	Me	**1c**	**3c**	90% (1.6 : 1)
4	2-$MeOC_6H_4$	H	H	H	Me	**1d**	**3d**	55% (2.3 : 1)
5	3,4-$(MeO)_2C_6H_3$	H	H	H	Me	**1e**	**3e**	39% (1.7 : 1)
6	4-FC_6H_4	H	H	H	Me	**1f**	**3f**	77% (2.2 : 1)
7	4-ClC_6H_4	H	H	H	Me	**1g**	**3g**	40% (3.8 : 1)
8	4-BrC_6H_4	H	H	H	Me	**1h**	**3h**	39% (3.0 : 1)
9	*n*-Pr	H	H	H	Me	**1i**	**3i**	67% (1.4 : 1)
10	*i*-Pr	H	H	H	Me	**1j**	**3j**	86% (1.6 : 1)
11	Cyclopropyl	H	H	H	Me	**1k**	**3k**	88% (6.7 : 1)
12	$-(CH_2)_5-$		H	H	Me	**1l**	**3l**	90% (0.7 : 1)
13	C_6H_5	H	Me	Me	Me	**1m**	**3m**	82% (3.2 : 1)
14	2-Furyl	H	H	H	Me	**1n**	**3n**	51% (0.7 : 1)
15	C_6H_5	H	H	H	Et	**1o**	**3o**	57% (1.1 : 1)
16	4-$CH_3C_6H_4$	H	H	H	*i*-Pr	**1p**	**3p**	65% (0.5 : 1)
17	C_6H_5	Me	H	H	Me	**1q**	**3q**	56% (1.5 : 1)

[a] Reaction conditions: a mixture of substrate **1** (1 mmol), allylSmBr (2.2 eq.), HMPA (10 eq.) and H_2O (1 eq.) in dry THF (20 mL) was stirred at rt for 3 h under N_2. [b] Isolated yield. [c] The molar ratio of *cis* : *trans* based on isolated yields.

It was worth pointing out that the reaction exhibited high stereoselectivity and only two pairs (the *cis*- and *trans*-) of diastereoisomers were obtained despite the theoretical existence of four pairs (three stereocenters) of diastereoisomers for 2-(2-hydroxyalkyl)cyclopropanols **3**. The ratios of the *cis*- and *trans*-isomers range from 6.7 : 1 (Table 1, entry 11) to 0.5 : 1 (Table 1, entry 16). In most cases, the *cis*-isomer was isolated as the major product, however, the reaction of **1l**, **1n** and **1p** afforded the *trans*-isomer as the major product (Table 1, entries 12, 14 and 16).

Acetate **1l** derived from the tertiary alcohol could also successfully give the 2-(2-hydroxyalkyl)-cyclopropanol in excellent yield (Table 1, entry 12). The cascade process seemed not to be affected by the steric hindrance on the 2-position (Table 1, entry 13) and was also applicable to the acetates derived from cyclic ketone and heteroaromatic aldehyde (Table 1, entries 12 and 14). Besides acetates, other aliphatic esters of the homoallylic alcohols also worked (Table 1, entries 15 and 16). The homoallylic ester derived from acetophenone (**1q**), however, afforded four pairs of diastereoisomers and showed poor stereoselectivity (see ESI†).

The structure of **3m** (both the *cis*- and *trans*-isomers) was ascertained unambiguously by the X-ray crystal diffraction analysis (Fig. 1).

The reaction of **1h** bearing *p*-Br on the phenyl ring afforded **1a** in 28% yield and also trace amounts of product **3a** in addition to **3h** (Scheme 2). The unexpected formation of **1a** and **3a** resulting from debromination indicated the powerful reducing ability of the allylSmBr–HMPA–H_2O system.

The reaction of allylic ester **1r** and substrate **1t** with the unsaturation nearer or farer than the homoallylic position, however, resulted in deprotection of the acetyl group (Scheme 3). Deprotection of esters with other Sm(II) species was also known[9] and the mechanism for the deprotection here should be analogous. Although the ester–alkene coupling seems to be limited only to the homoallylic esters, it did show high regioselectivity when substrate **1s** was examined, where the appropriately located C=C bond reacted smoothly while the other remained intact (Scheme 3).

In view of the above experiments and the previous reports,[2,3,10] a probable single electron transfer (SET) mechanism for the allylSmBr-promoted cascade intramolecular cyclopropanation was proposed as shown in Scheme 4. The coordination of samarium in **VII** is essential to ensure the high diastereoselectivity.

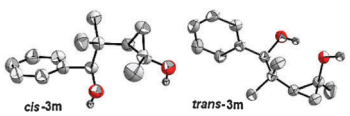
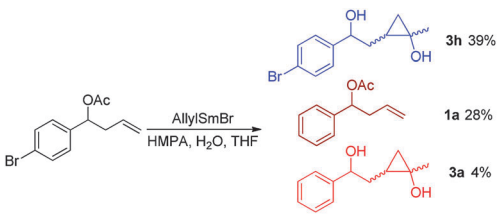
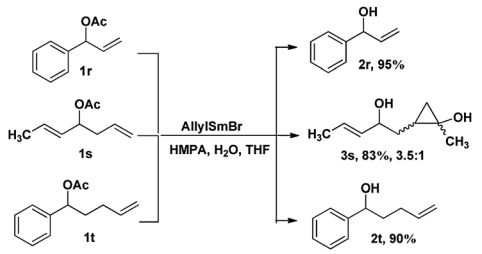


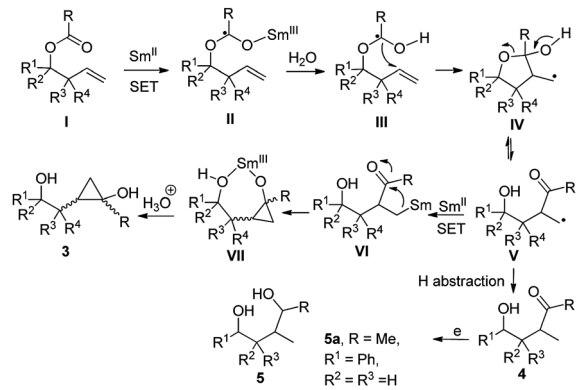
Fig. 1 The X-ray crystal structure of **3m**.



Scheme 2 The reaction of **1h** under the optimized conditions.



Scheme 3 The reactions of the substrates with different location of the C=C bond.



Scheme 4 A probable mechanism.

In the case of substrate **1q** (R^1 = Ph, R^2 = Me), steric hindrance may occur and the formation of **VII** was thus not as favored, accounting for the poor stereoselectivity observed therein.

The proposed mechanism could further be rationalized by the isolation of by-product **5a** (Scheme 4). Compound **4**, however, could not be obtained by either decreasing the amount of reducing agent or introducing 1,4-cyclohexadiene[11] as the H-donor, indicating a very high efficiency for the transformation of **V** into **VI**.

The reductive potentials of allylSmBr and allylSmBr–HMPA in THF were determined using cyclic voltammetry (see ESI†).[12] The addition of HMPA shifts the reductive peak potential approximately 760 mV to more negative values, indicating that HMPA enhances the reducing ability of allylSmBr significantly. Redox potentials can be estimated from the oxidation and reduction peaks of the quasi-reversible voltammograms of Sm-allylBr and were found to be -1.84 ± 0.01 V in THF. For Sm-allylBr–HMPA the potential was found to be -2.60 ± 0.01 V. These values are close (but not identical) to those determined for $SmBr_2$ and $SmBr_2$–HMPA.[13]

In summary, we have achieved the first example of aliphatic acyclic ester–alkene radical cyclization promoted by allylSmBr with HMPA and H_2O as the co-additives. The additives were found to have inhibited the nucleophilicity and enhanced the SET ability of allylSmBr. Besides, the reaction provides a facile and diastereoselective synthesis of *cis*-2-(2-hydroxyalkyl)cyclopropanols[14] from the readily available homoallyl esters.

Further investigation of the reductive species present in the allylSmBr–HMPA system, the exact role of HMPA and H_2O, the use of various additives to tune the SET ability and more synthetic applications of the allylsamarium–additive system is currently underway and will be reported in due course.

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