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Regiocontrolled Halohydroxylations of Bicyclic Vinylidenecyclopropanes: A Versatile Strategy for the Construction of Diverse Highly Functionalized Carbocyclic Scaffolds

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Abstract: Highly regioselective halohydroxylations of bicyclic vinylidenecyclopropanes that lead to four types of products **2**, **3**, **4**, and **6** were developed. The halohydroxylation reaction occurs at room temperature to give rise to ring-keeping products vinylbicyclo[(*n*+2).1.0]alkanols **2** in 55–90% yields with excellent regio- and diastereoselectivity; the reaction of bicyclic vinylidenecyclopropanes with 2.0 equiv of *N*-bromosuccinimide (NBS) at 100°C affords alkylidenebicyclo[(*n*+2).2.0]-alkanones **3** in 48–75% yields by means of further proximal cleavage of the cyclopropane ring. The structures of both types of compounds **2** and **3** have been elucidated by X-ray crystal diffraction. An interesting sequential reaction that consists of a couple electrophilic addition and elimination reactions was developed when the reaction of bicyclic vinylidenecyclopropanes with *N*-halosuccinimide (NXS; 3.0 equiv) was performed under the specified conditions to furnish a variety of divinyl ketones **4** by means of proximal cleavage of the cyclopropane ring. In addition, vinylidenecyclopropanes that bore one aryl group at the cyclopropyl ring reacted with NBS or I_2 at room temperature, thereby producing the corresponding divinyl ketones **4** in moderate to good yields with excellent *E* selectivity. Unexpectedly, 2-vinylic cyclohex-2-enols **6** were generated through a very different distal C–C bond cleavage of the cyclopropane due to the significant ring-size effect. Possible mechanisms are proposed on the basis of the obtained intermediates.

Keywords: allenes · carbocycles · reaction mechanisms · regioselectivity · small-ring systems

Introduction

The development of novel reactions with high selectivity for the construction of potentially useful compounds is a hot research topic in organic synthesis. Recently, we have witnessed robust growth in the development of efficient strategies that convert easily accessible starting materials to complex target molecules with high regio- and stereoselectivity. Vinylidenecyclopropanes[1] show unique reactivity in organic synthesis due to the presence of the cumulated C=C bonds adjacent to the highly strained cyclopropyl ring, and yet they are thermally stable.[2] An attractive but often troublesome feature of vinylidenecyclopropanes is their multiple reaction "points" that may lead to the formation of a variety of different products through various reaction pathways: regioselective addition to a cumulated C=C bond[3] and two types of ring openings of the cyclopropane (i.e., the proximal cleavage[4] and the distal cleavage).[5] In addition, for unsymmetrical vinylidenecyclopropanes, there is an additional issue of regio- and stereoselectivity. Thus, the control of regio- and stereoselectivity in reactions that involve vinylidenecyclopropanes is an attractive research topic in organic chemistry.

Halohydroxylations of C=C double bond are powerful methods for introducing the halogen and hydroxyl group into substrates by a single step.[6] During the past decade, the halohydroxylations of allenes[7] and cyclopropane derivatives[8] with defined regio- and stereoselectivity have been investigated in detail. However, reports on the halohydroxylation of vinylidenecyclopropanes are limited,[8e,f] probably due to the fact that their multiple reaction pathways are a

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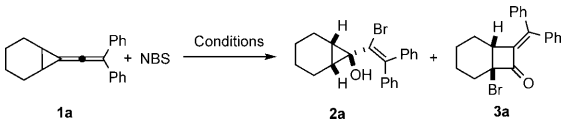
tremendous challenge to make this methodology synthetically attractive unless the regio- and stereoselectivity could be controlled in a highly efficient manner. In the context of our recent studies on the regio- and stereoselective chemistry of vinylidenecyclopropanes, we have developed several novel reactions of vinylidenecyclopropanes by means of controllable pathways to result in a diversity-oriented synthesis of different potentially useful compounds.[9] Stimulated by these interesting results, we turned our effort toward the highly selective halohydroxylations of vinylidenecyclopropanes. The reactivity of vinylidenecyclopropanes is unexpected in some respects. Herein, we report our detailed study on the highly regioselective halohydroxylations of vinylidenecyclopropanes that lead to a variety of vinylbicyclo[(*n*+2).1.0]alkanols **2** (*n* = 2, 3, 4, 8), alkylidenebicyclo[(*n*+2).2.0]alkanones **3** (*n* = 2, 3), divinyl ketones **4**, and 2-vinylic cyclohex-2-enols **6** in a highly selective manner as a function of the employed electrophiles, temperature, stoichiometry, and the substituent effects. The defined structural features of these bicyclic products not only often occur in natural products and biologically active compounds,[10] but also have been used as useful synthetic intermediates for the synthesis of other carbocyclic systems.[11] In addition, these unsymmetrical divinyl ketones are valuable building blocks for organic synthesis, which have been utilized in a wide range of reactions to prepare various ring systems,[12] including acid-catalyzed Nazarov cyclization that leads to cyclopentenones.[13]

Results and Discussion

The bromohydroxylation of vinylidenecyclopropane **1a** with *N*-bromosuccinimide (NBS; 2.0 equiv) was initially performed in aqueous DMSO (DMSO/H_2O = 4:1) at room temperature for 48 h, thereby affording the ring-keeping product 7-(1-bromo-2,2-diphenylvinyl)bicyclo[4.1.0]heptan-7-ol (**2a**) in 41% yield with an excellent diastereoselectivity; however, 52% of vinylidenecyclopropane **1a** was recovered (Table 1, entry 1). A screening of the ratio of the mixed solvent (DMSO/H_2O) showed that the amount of water in the system had significant effect on the yield of **2a**. When the reaction was carried out in aqueous DMSO (DMSO/H_2O = 80:1), the yield of product **2a** was efficiently improved to 87% (Table 1, entries 2–4). Although decreasing the amount of NBS led to a reduced yield, our further testing revealed that by using 1.5 equiv of NBS in aqueous DMSO (DMSO/H_2O = 80:1) at 40°C, an excellent yield of the product **2a** was observed (entries 5–7). To our surprise, the bromohydroxylation of vinylidenecyclopropane **1a** with 2.0 equiv of NBS at 70°C afforded **2a** in 51% yield together with an interesting product, 6-bromo-8-(diphenylmethylene)-bicyclo[4.2.0]octan-7-one (**3a**) in 18% yield (entry 8). The structure of **3a** was confirmed by X-ray crystallographic analysis of its (2,4-dinitrophenyl)hydrazine derivative **3a′** (Figure 1). The yield of product **3a** with a four-membered ring was improved to 75% when the reaction was conducted at 100°C (entry 9). However, the reaction at 120°C afforded **3a** in lower yield (entry 10).

Table 1. Optimization of the reaction conditions for the bromohydroxylation of **1a**.



1a **2a** **3a**

	NBS [equiv]	*T* [°C]	DMSO/H_2O	*t* [h]	Yield of **2a** [%]	Yield of **3a** [%]
1	2.0	RT	4:1	48	41[a]	–
2	2.0	RT	10:1	48	53[b]	–
3	2.0	RT	40:1	48	78	–
4	2.0	RT	80:1	48	87	–
5	1.3	RT	80:1	48	75	–
6	1.3	40	80:1	16	85	–
7	1.5	40	80:1	10	90	–
8	2.0	70	80:1	20	51	18
9	2.0	100	80:1	16	trace	75
10	2.0	120	80:1	12	–	64

[a] 52% of **1a** was recovered. [b] 43% of **1a** was recovered.

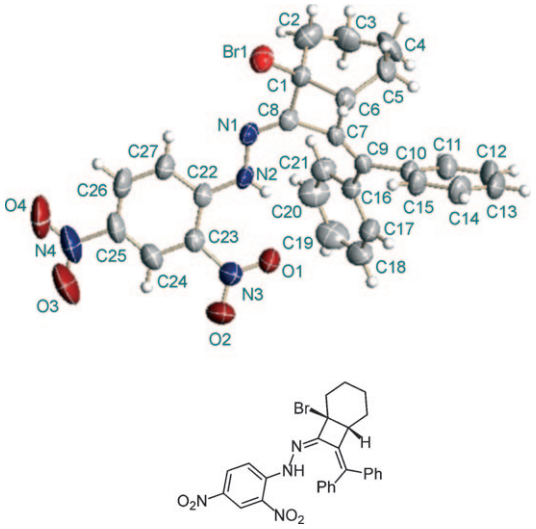
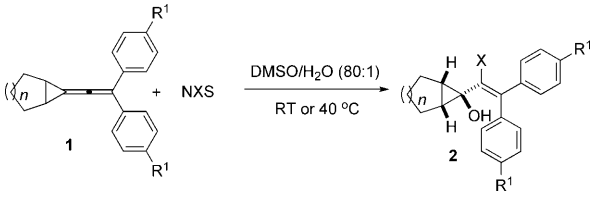


Figure 1. ORTEP representation of **3a′**.

Having established the optimized conditions for the synthesis of polysubstituted bicyclo[4.1.0]heptan-7-ol **2a**, we set out to explore the scope of this reaction. As shown in Table 2, the reaction of bicyclic vinylidenecyclopropanes **1a–d** with variation in ring size (*n* = 2, 3, 4, 8) proceeded smoothly, and gave a variety of multisubstituted vinylbicyclo[(*n*+2).1.0]alkanols **2a–d** in good to high yields with an excellent diastereoselectivity (Table 2, entries 1–4). Bicyclic vinylidenecyclopropanes **1** that bore a methyl group or chloro moiety on the aromatic rings (R^1) were accommodated (entries 5 and 6). On the other hand, reaction of **1a**,**b** and **1e** with *N*-iodosuccinimide (NIS) under similar conditions afforded the corresponding iodohydroxylation adducts **2g–i** in lower yields (entries 7–9). All of the products were characterized by spectroscopic methods, and **2e** was further confirmed by its X-ray crystallographic study (Figure 2).

Table 2. Synthesis of multisubstituted vinylbicyclo[(*n*+2).1.0]alkanols **2**.[a]



Entry	**1**		NXS	*t* [h]	*T* [°C]	Yield of **2** [%]
	R^1	*n*				
1	H	2 (**1a**)	NBS	10	40	90 (**2a**)
2	H	3 (**1b**)	NBS	14	40	81 (**2b**)
3	H	4 (**1c**)	NBS	12	40	84 (**2c**)
4	H	8 (**1d**)	NBS	10	40	71 (**2d**)
5	Cl	2 (**1e**)	NBS	14	40	87 (**2e**)
6	Me	2 (**1f**)	NBS	12	40	74 (**2f**)
7	H	2 (**1a**)	NIS	24	RT	62 (**2g**)
8	H	3 (**1b**)	NIS	15	RT	59 (**2h**)
9	Cl	2 (**1e**)	NIS	20	RT	55 (**2i**)

[a] The reaction was carried out using **1** (1.0 equiv) and NBS (1.5 equiv) or NIS (1.2 equiv) in DMSO/H_2O (80:1).

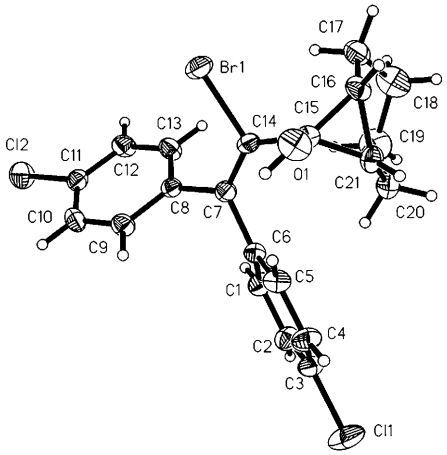
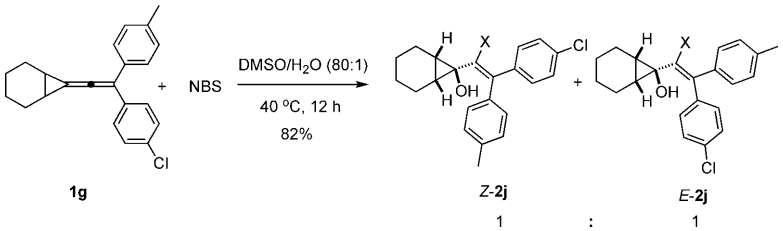


Figure 2. ORTEP representation of **2e**.

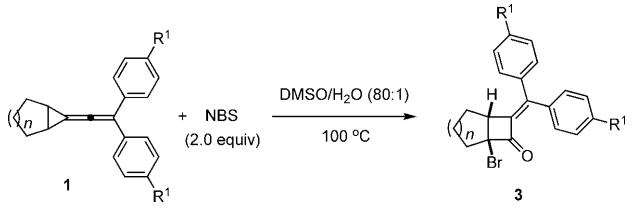
Further investigation showed that the bromohydroxylation of unsymmetrical substrate **1g** afforded **2j** as a mixture of *E*/*Z* isomers (1:1) in 82% yield as expected (Scheme 1).

We next turned our attention to the highly selective synthesis of a variety of alkylidenebicyclo[(*n*+2).2.0]alkanones **3**. The typical results summarized in Table 3 show that ring size had a significant effect on the outcome of this reaction. When a series of six- to seven-membered cycloalkane-fused



Scheme 1. Bromohydroxylation of unsymmetrical substrate **1g**.

Table 3. Synthesis of alkylidenebicyclo[(*n*+2).2.0]alkanones **3**.[a]

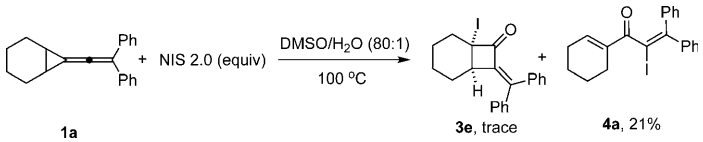


Entry	**1**		*t* [h]	Yield of **3** [%]
	R^1	*n*		
1	H	2 (**1a**)	20	75 (**3a**)
2	Me	2 (**1f**)	8	58 (**3b**)
3	H	3 (**1b**)	48	55 (**3c**)
4	Me	3 (**1h**)	30	48 (**3d**)
5	H	4 (**1c**)	10	–[b]

[a] The reaction was carried out using **1** (1.0 equiv) and NBS (2.0 equiv) in DMSO/H_2O (80:1). [b] The reaction was complicated.

vinylidenecyclopropanes were subjected to optimal reaction conditions, the desired alkylidenebicyclo[(*n*+2).2.0]-alkanones **3a–d** were formed in moderate to good yields (Table 3, entries 1–4). However, when cyclooctane-fused vinylidenecyclopropane **1c** was reacted with NBS under the same conditions, no desired product was obtained, and the reaction was complicated (entry 5).

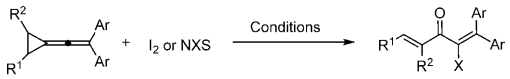
It was surprising but also quite exciting to observe a different reaction pattern when 2.0 equiv of NIS was used as the electrophile. The substituted methylene-6-iodobicyclo-[4.2.0]octan-7-one **3e** was only formed in a trace amount, whereas an unsymmetrical divinyl ketone **4a** was harvested in 21% yield (Scheme 2).



Scheme 2.

We then tried to optimize the reaction conditions to get a useful synthesis of these versatile building blocks. After treatment of bicyclic vinylidenecyclopropane **1a** with 3.0 equiv of NIS in aqueous DMSO (DMSO/H_2O = 80:1) at room temperature for 3 h, the resulting mixture was warmed to 85 °C for another 1 h with stirring. Then Et_3N (5.0 equiv) was added, and the mixture was stirred at 85 °C for 10 h. With a general workup, divinyl ketone **4a** could be obtained in 66% yield (Table 4, entry 1). To further explore the scope of this transformation, a variety of vinylidenecyclopropanes **1** were examined and the results are listed in Table 4. Bicyclic vinylidenecyclopropane

Table 4. Synthesis of various unsymmetrical divinyl ketones **4**.



1 **4**

X = I, Br

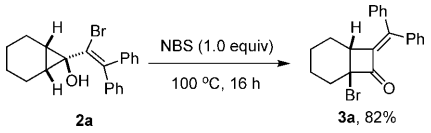
Entry	**1** Ar	R^1	R^2	X^+ [equiv]	*t* [h]	Yield of **4** [%]
1	Ph	$(CH_2)_4$ (**1a**)		NIS (3.0)	3/1/10[a]	66 (**4a**)
2	*p*-MeC_6H_4	$(CH_2)_4$ (**1f**)		NIS (3.0)	3/1/10[a]	58 (**4b**)
3	*p*-MeC_6H_4	$(CH_2)_5$ (**1h**)		NIS (3.0)	7[b]	60 (**4c**)
4	Ph	$(CH_2)_6$ (**1c**)		NIS (3.0)	6[b]	52 (**4d**)
5	Ph	$(CH_2)_6$ (**1c**)		NBS/NIS	12/10[c]	46 (**4e**)
6	Ph	Ph	H (**1i**)	I_2 (2.2)	48[d]	65 ((*E*)-**4f**)
7	*p*-MeC_6H_4	Ph	H (**1j**)	I_2 (2.2)	30[d]	71 ((*E*)-**4g**)
8	Ph	*p*-MeC_6H_4	H (**1k**)	I_2 (2.2)	48[d]	55 ((*E*)-**4h**)
9	Ph	*p*-ClC_6H_4	H (**1l**)	I_2 (2.2)	72[d]	60 ((*E*)-**4i**)
10	Ph	Ph	H (**1i**)	NBS (5.0)	96[e]	47 ((*E*)-**4j**)
11	Ph	*p*-ClC_6H_4	H (**1l**)	NBS (5.0)	96[e]	62 ((*E*)-**4k**)

[a] The reaction was carried out using 1.0 equiv of **1** with 3.0 equiv of NIS at room temperature in aqueous DMSO (DMSO/H_2O = 80:1). After being stirred for 3 h, the reaction mixture was heated to 85 °C for another 1 h with stirring. Then 5.0 equiv of Et_3N were added, and the mixture was stirred at 85 °C for another 10 h. [b] The reaction was carried out using **1** (1.0 equiv) and NIS (3.0 equiv) in aqueous DMSO (DMSO/H_2O = 80:1) at room temperature. [c] The reaction was carried out using **1** (1.0 equiv) and NBS (1.5 equiv) in aqueous DMSO (DMSO/H_2O = 80:1) at room temperature for 12 h, and then NIS (1.5 equiv) was added. The resulting mixture was stirred for another 10 h. [d] The reaction was carried out using **1** (1.0 equiv) and I_2 (2.2 equiv) in DMSO (analytical grade) at room temperature. [e] The reaction was carried out using **1** (1.0 equiv) and NBS (3.0 equiv) in DMSO (analytical grade) at room temperature. After being stirred for 48 h, another 2.0 equiv of NBS were added and the mixture was stirred for another 48 h.

1f (Ar = 4-MeC_6H_4) also readily participated in the reaction and gave 58% yield of the corresponding divinyl ketone compound **4b** (entry 2). Two substrates **1h** and **1c** were employed to examine the ring-size effect of the bicyclic group, and the desired products **4c** and **4d** were obtained in acceptable yields even at room temperature (entries 3 and 4). After treatment of **1c** with 1.5 equiv of NBS at room temperature for 12 h, 1.5 equiv of NIS was added for another 10 h with stirring to furnish the bromo-substituted divinyl ketone **4e** in 46% yield (entry 5). Furthermore, vinylidenecyclopropanes **1i–l** that bore one aryl group at the cyclopropyl ring were also investigated, thereby affording the corresponding divinyl ketones **4f–k** in 47–71% yields with an excellent *E* selectivity (entries 6–11).

To shed light on the reaction mechanism, attempts to isolate the intermediates were made. Initially, the relationship between the ring-keeping products **2** and ring-expansion products **3** was revealed by the fact that treatment of vinylbicyclo[(*n*+2).1.0]alkanol **2a** with NBS in DMSO/H_2O (80:1) at 100 °C successfully delivered the corresponding product **3a** in 82% yield (Scheme 3).

To our delight, intermediate **5a** could also be obtained in 68% yield from the electrophilic ring-opening reaction of vinylbicyclo[(*n*+2).1.0]alkanol **2g** with I^+. The structure of **5a** was determined by the X-ray diffraction study (Figure 3). In addition, treatment of **5a** at the specified temperature in the presence of Et_3N smoothly furnished **4a** in a good yield (Scheme 4).



2a **3a**, 82%

Scheme 3.

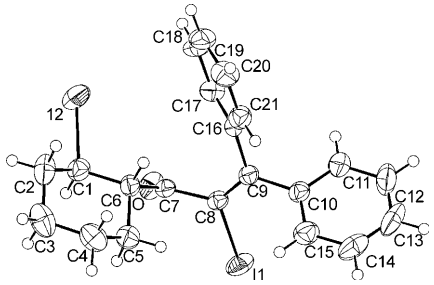
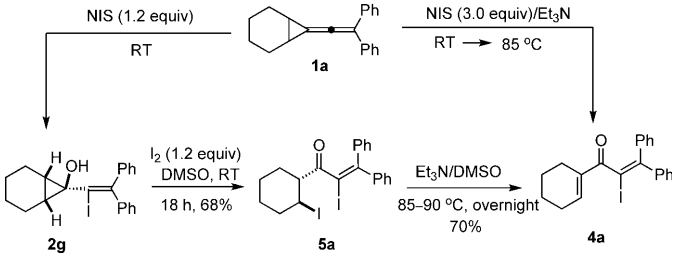


Figure 3. ORTEP representation of **5a**.

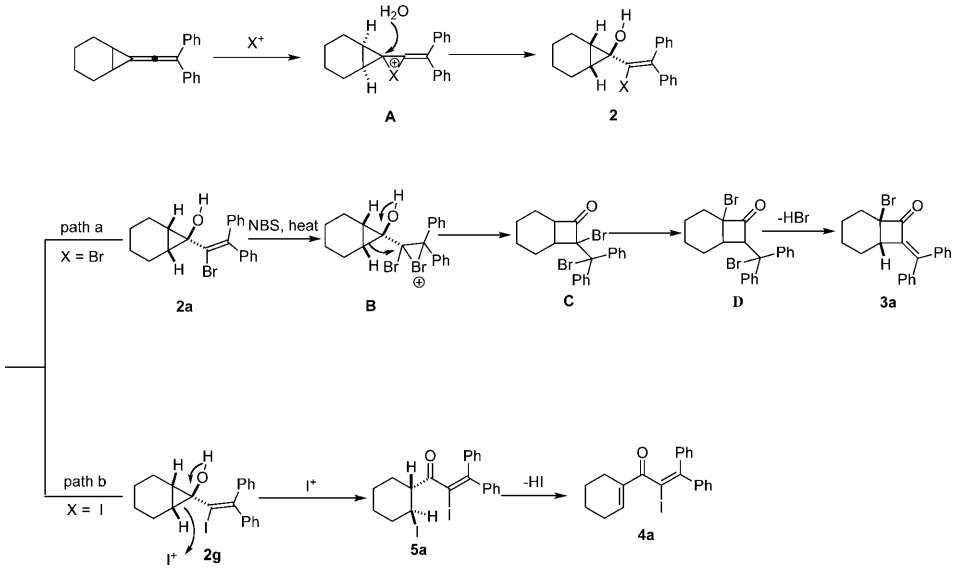


2g **5a** **4a**

Scheme 4.

On the basis of the obtained intermediates, a plausible reaction mechanism is proposed in Scheme 5. It begins with an electrophilic interaction of X^+ with the electron-rich C=C bond adjacent to the cyclopropane, thereby forming a three-membered cyclic halonium ion intermediate **A**, which is selectively attacked by H_2O from the less sterically hindered side to produce the ring-keeping halohydroxylation products **2** with excellent diastereoselectivity. With NBS at 100 °C, the addition of bromonium ion to the double bond induces a ring enlargement to give the dibromocyclobutanone **C**. Then a known rearrangement occurs with bromine atom migration mediated by HBr to afford **D**,[14] which undergoes an elimination reaction to furnish the ultimate product **3a** (Scheme 5, path a). However, in the presence of I^+, a different electrophilic ring-opening of **2g** occurs with high stereoselectivity to give the intermediate product **5a**, which is finally transformed to divinyl ketone **4a** through an elimination of HI (Scheme 5, path b).

Interestingly, when the reaction was extended to five-membered ring-fused vinylidenecyclopropane **1m**, an unexpected product 2-(1-bromo-2,2-diphenylvinyl)cyclohex-2-enol (**6a**) was obtained in 58% yield by means of a very dif-

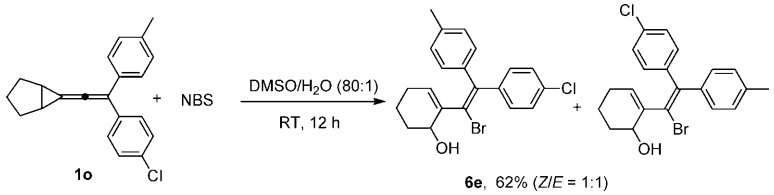


Scheme 5. Tentative mechanism for the selective synthesis of products **2**, **3**, and **4**.

ferent distal C–C bond cleavage of the cyclopropane ring due to the significant ring-size effect (Table 5, entry 1). Consequently, we examined the scope of the reaction for the synthesis of various 2-vinylic cyclohex-2-enols **6**. In one case, the bromohydroxylations of cyclopentane-fused vinylidenecyclopropane **1n** proceeded to afford the product **6b** smoothly in 69% yield (entry 2). In other cases, iodohydroxylations of **1m**,**n** proceeded faster to give the corresponding adducts **6c**,**d** in 52–60% yields (entries 3 and 4).

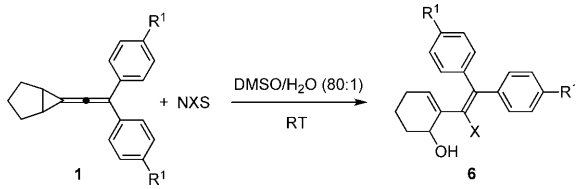
For unsymmetrical substrate **1o**, the reaction afforded **6e** as a mixture of 1:1 *E*/*Z* isomers in 62% yield (Scheme 6).

We reasoned that the presence of functional groups on the cyclopropane moiety may facilitate the selective cleavage of C–C bonds of the cyclopropane, thus delicately



Scheme 6. Bromohydroxylation of unsymmetrical substrate **1o**.

Table 5. Synthesis of 2-vinylic cyclohex-2-enols **6**.[a]

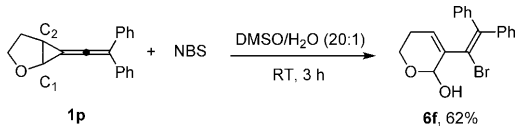


Entry	R^1 (**1**)	NXS	*t* [h]	Yield of **6** [%]
1	H (**1m**)	NBS	24	58 (**6a**)
2	Me (**1n**)	NBS	24	69 (**6b**)[b]
3	**1m**	NIS	4	52 (**6c**)
4	**1n**	NIS	4	60 (**6d**)

[a] Unless otherwise specified, the reaction was carried out using **1** (1.0 equiv) and NXS (1.3 equiv) in DMSO/H_2O (80:1). [b] 1.6 equiv of NBS were added.

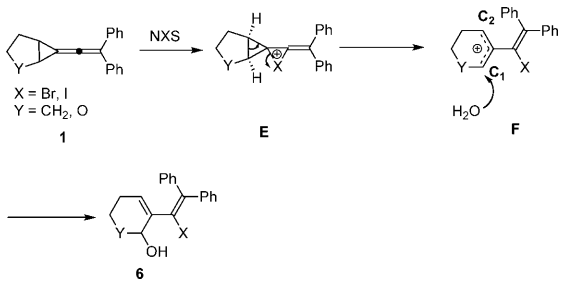
tuning the regioselectivity of the reaction. As a matter of fact, when using tetrahydrofuran-fused vinylidenecyclopropane **1p** as the substrate, 5,6-dihydro-2*H*-pyran-2-ol derivative **6f** was obtained in 62% yield with an excellent regioselectivity (Scheme 7).

The mechanism for the formation of ring-expansion products **6** through distal cleavage of the cyclopropane is proposed in Scheme 8. First, X^+ reacts with the electron-rich internal C=C bond adjacent to the cyclopropane to produce a three-membered cyclic halonium ion intermediate **E**, which undergoes a ring-opening process to



Scheme 7. Regioselective bromohydroxylation of vinylidenecyclopropane **1p**.

afford the six-membered ring cationic intermediate **F**, probably due to the strained nature of the bicyclo[3.1.0]hexane cationic intermediate. Then the cationic cyclic allylic intermediate **F** was subsequently attacked by H_2O to give **6**. It should be noted that the bromohydroxylation reaction of



Scheme 8. Tentative mechanism for the formation of ring-expansion products **6**.

substrate **1p** demonstrates an alkoxy group effect, which could be explained by its stabilization effect in the cationic allylic intermediate.

Conclusion

In summary, we have presented here a comprehensive study of the unique regiocontrolled halohydroxylation reaction of vinylidenecyclopropanes that provides direct synthetic access to a variety of bicyclic products, cyclohex-2-enols, and divinyl ketones in controllable ways, which may open up a new area for the control of selectivity in addition reactions of vinylidenecyclopropanes. Possible mechanisms are proposed on the basis of the obtained intermediates. Due to the easily accessible starting materials, simple reaction procedure, mild conditions, and the selective pathways, this reaction should be an appealing strategy in organic synthesis. Further studies on the synthetic application are currently ongoing.

Experimental Section

A typical procedure for the synthesis of compound 2a: Vinylidenecyclopropane **1a** (82 mg, 0.301 mmol) and DMSO/H_2O (80:1, 3 mL) were added sequentially to a reaction tube. Then NBS (81 mg, 0.455 mmol) was added and the mixture was stirred at 40 °C. After the reaction was complete as monitored by TLC, the resulting mixture was quenched with water (5 mL). The mixture was extracted with EtOAc (3×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Filtration, evaporation, and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 10:1) afforded **2a** (100 mg, 90 %). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.48 (d, J = 7.2 Hz, 2H), 7.20–7.42 (m, 8H), 3.17 (s, 1H), 1.77–2.00 (m, 2H), 0.88–1.54 (m, 7H), 0.06–0.28 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 19.2, 19.4, 21.2, 26.6, 29.0, 64.3, 126.9, 127.7, 127.8, 128.1, 128.2, 129.5, 130.3, 140.4, 143.9, 147.3 ppm; IR (neat): $\tilde{\nu}$ = 3364, 2925, 2854, 1491, 1446, 1075, 999, 760 cm^{-1}; MS (70 eV, EI): m/z: 368 [M^+]; HRMS (EI): m/z: calcd for $C_{21}H_{21}BrO$: 368.0776 [M^+]; found: 368.0770.

A typical procedure for the synthesis of compound 3a: Vinylidenecyclopropane **1a** (94 mg, 0.346 mmol), DMSO/H_2O (80:1, 3 mL), and NBS (123 mg, 0.691 mmol) were added sequentially to a reaction tube. Then the resulting mixture was stirred at 100 °C. After the reaction was complete as monitored by TLC, the resulting mixture was quenched with water (5 mL). The mixture was extracted with EtOAc (3×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Filtration, evaporation, and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 50:1) afforded **3a** (95 mg, 75 %). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.33–7.43 (m, 8H), 7.26–7.31 (m, 2H), 3.65 (t, J = 6.2 Hz, 1H), 2.20–2.28 (m, 1H), 2.06–2.16 (m, 1H), 1.65–1.75 (m, 2H), 1.50–1.62 (m, 1H), 1.36–1.46 (m, 2H), 1.20–1.31 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 17.9, 19.6, 22.4, 30.5, 47.7, 66.7, 128.1, 128.3, 128.4, 129.2, 129.5, 129.8, 137.5, 138.5, 141.9, 148.8, 193.5 ppm; IR (neat): $\tilde{\nu}$ = 2934, 1736, 1694, 1599, 1444, 1260, 734 cm^{-1}; MS (70 eV, EI): m/z: 366 [M^+]; HRMS (EI): m/z: calcd for $C_{21}H_{19}BrO$: 366.0619 [M^+]; found: 366.0614.

A typical procedure for the synthesis of compound 4a: Vinylidenecyclopropane **1a** (82 mg, 0.301 mmol), DMSO/H_2O (80:1, 3 mL), and NIS (203 mg, 0.902 mmol) were added sequentially to a reaction tube. After being stirred for 3 h, the reaction mixture was heated to 85 °C and stirred for another 1 h. Then Et_3N (5.0 equiv) was added, and the mixture was stirred at 85 °C for another 10 h. The resulting mixture was quenched with water (5 mL) and extracted with EtOAc (3×5 mL). The combined organic layers were washed with a saturated aqueous solution of $Na_2S_2O_3$ and dried over anhydrous Na_2SO_4. Filtration, evaporation, and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 50:1) afforded **4a** (83 mg, 66 %). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.29–7.43 (m, 5H), 7.16–7.23 (m, 3H), 7.02–7.07 (m, 2H), 6.85–6.90 (m, 1H), 1.95–2.08 (m, 4H), 1.31–1.42 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 21.3, 21.6, 23.2, 26.2, 97.2, 128.1, 128.2, 128.3, 129.0, 129.1, 136.5, 140.3, 143.7, 144.1, 152.7, 195.5 ppm; IR (neat): $\tilde{\nu}$ = 2924, 2858, 1638, 1625, 1491, 1443, 1268, 753, 696 cm^{-1}; MS (70 eV, EI): m/z: 414 [M^+]; HRMS (EI): m/z calcd for $C_{21}H_{19}IO$: 414.0481 [M^+]; found: 414.0485.

A typical procedure for the synthesis of compound 6a: Vinylidenecyclopropane **1m** (70 mg, 0.271 mmol), DMSO/H_2O (80:1, 3 mL), and NBS (62 mg, 0.348 mmol) were added sequentially to a reaction tube. Then the mixture was stirred at room temperature. After the reaction was complete as monitored by TLC, the resulting mixture was quenched with water (5 mL). The mixture was extracted with EtOAc (3×5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Filtration, evaporation, and column chromatography on silica gel (eluent: petroleum ether/ethyl acetate 10:1) afforded **6a** (56 mg, 58 %). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.23–7.38 (m, 7H), 7.12–7.23 (m, 3H), 5.74 (t, J = 3.8 Hz, 1H), 4.54 (t, J = 5.6 Hz, 1H), 2.09 (s, 1H), 1.76–1.94 (m, 3H), 1.58–1.76 (m, 2H), 1.45–1.58 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 18.4, 25.8, 30.8, 65.9, 123.5, 126.9, 127.3, 127.7, 128.0, 129.5, 129.7, 134.3, 139.9, 141.5, 143.1, 143.6 ppm; IR (neat): $\tilde{\nu}$ = 3415, 2930, 1491, 1443, 1030, 912, 760, 742 cm^{-1}; MS (70 eV, EI): m/z: 354 [M^+]; HRMS (EI): m/z calcd for $C_{20}H_{19}BrO$: 354.0619 [M^+]; found: 354.0626.

X-ray crystal data for 2e: $C_{21}H_{19}BrCl_2O$; M_r = 438.17; crystal system: monoclinic; space group: $P21/n$; final R indices ($I > 2\sigma(I)$): $R1$ = 0.0326, $wR2$ = 0.0657; R indices (all data): $R1$ = 0.0573, $wR2$ = 0.0682; a = 10.0629(3), b = 12.6575(3), c = 15.2116(5) Å; α = 90.00, β = 102.082(3), γ = 90.00°; V = 1894.60(10) Å^3, T = 293(2) K, Z = 4; $F(000)$ = 888; reflections collected/unique: 7978/3868 (R(int) = 0.0219); number of observations ($I > 2\sigma(I)$): 2514; parameters: 226.

X-ray crystal data for 3a′: $C_{27}H_{27}BrN_4O_4$; M_r = 551.44; crystal system: monoclinic; space group: $P21/c$; final R indices ($I > 2\sigma(I)$): $R1$ = 0.0444, $wR2$ = 0.1024; R indices (all data): $R1$ = 0.0783, $wR2$ = 0.1103; a = 11.9391(10), b = 13.8894(11), c = 16.1459(13) Å; α = 90.00, β = 110.4020(10), γ = 90.00°; V = 2509.5(4) Å^3, T = 293(2) K, Z = 4; $F(000)$ = 1136; reflections collected/unique: 13939/5178 (R(int) = 0.0425); number of observations ($I > 2\sigma(I)$): 3026; parameters: 338.

X-ray crystal data for 5a: $C_{21}H_{20}I_2O$; M_r = 542.17; crystal system: triclinic; space group: $P\bar{1}$; final R indices ($I > 2\sigma(I)$): $R1$ = 0.0274, $wR2$ = 0.0559; R indices (all data): $R1$ = 0.0433, $wR2$ = 0.0591; a = 9.4896(6), b = 9.7121(5), c = 11.4236(6) Å; α = 72.322(5), β = 78.215(5), γ = 85.356(5)°; V = 981.78(9) Å^3, T = 293(2) K, Z = 2; $F(000)$ = 520; reflections collected/unique: 7332/3590 (R(int) = 0.0221); number of observations ($I > 2\sigma(I)$): 2716; parameters: 217.

CCDC-785607 (**2e**), 785608 (**3a′**), and 785609 (**5a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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