ACCOUNTS
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Stereoselective Construction of Quaternary Carbon Stereocenters via a Semipinacol Rearrangement Strategy

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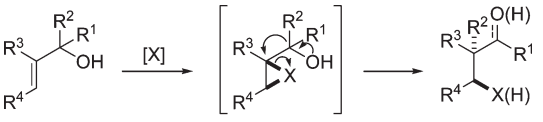
CONSPECTUS

Quaternary carbon stereocenters are found in a broad range of organic compounds, including important bioactive natural products and medicinal agents. Given their ubiquity and the significant synthetic challenges they present, quaternary carbon stereocenters have long attracted great interest from synthetic organic chemists. Numerous efforts have been devoted to their construction, leading to a spectrum of strategies for creating stereogenic quaternary carbon centers. In this context, the semipinacol rearrangement has proven successful. In this extension of the pinacol rearrangement, the 1,2-carbon-to-carbon migration in a 1,2-diol has been expanded to include leaving groups other than the hydroxyl group.



X = O, NTs, NPhth, F^+, Cl^+, Br^+, I^+, H^+

Over the past decade, our laboratory has explored the semipinacol rearrangement strategy for the stereoselective construction of quaternary carbon stereocenters. We have investigated various substrates, including 2,3-epoxy alcohols (also termed α-hydroxy epoxides), 2,3-aziridino alcohols, and allylic alcohols. Several promoters that effect the semipinacol rearrangement have been identified, including Lewis acids based on Al, Sm, B, Zn, and Ti for the rearrangement of α-hydroxy epoxides and 2,3-aziridino alcohols; cationic halogen species for the rearrangement of allylic alcohols; and cinchona alkaloids and chiral phosphoric acid for the asymmetric semipinacol rearrangement. Our research efforts have led to a series of valuable synthetic methods, including (1) a tandem semipinacol rearrangement and Meerwein–Ponndorf–Verley reduction, (2) a tandem semipinacol rearrangement and Tishchenko reaction, (3) a tandem semipinacol rearrangement with either an allylation or a propargylation, (4) a tandem semipinacol rearrangement and Schmidt reaction, (5) a semipinacol rearrangement of 2,3-aziridino alcohols, (6) a semipinacol rearrangement of allylic alcohols induced by halogen cation, (7) a tandem aziridination and semipinacol rearrangement of allylic alcohols, and (8) asymmetric semipinacol rearrangements with chiral organic catalysts. One hallmark of these reactions is the creation of stereogenic quaternary carbon centers with high levels of stereocontrol. In this Account, we describe the development of these synthetically useful methodologies and their successful application to the total syntheses of natural products.

Our results demonstrate that the semipinacol rearrangement of carefully designed substrates constitutes an efficient approach to the stereoselective construction of quaternary carbon centers. These reactions have produced a broad array of useful compounds that lend themselves to further elaboration. Furthermore, the total synthesis of a series of alkaloids, with significant bioactivity and intriguing molecular architecture, was achieved through these semipinacol rearrangement strategies, highlighting their synthetic value.

1. Introduction

Quaternary carbon stereocenters, that is, carbon centers with four different non-hydrogen substituents, are present in a wide variety of organic compounds. The construction of such quaternary carbon centers, with high levels of stereocontrol, remains a significant challenge in organic synthesis, despite tremendous efforts having been devoted to this area. The stereoselective construction of quaternary carbon stereocenters has been the subject of several excellent review articles.[1] In most cases, a stereogenic quaternary carbon scarcely appears as the sole stereocenter in an organic molecule, but instead coexists with other chiral centers, forming architectures with multiple stereocenters. The construction of such a quaternary carbon, with

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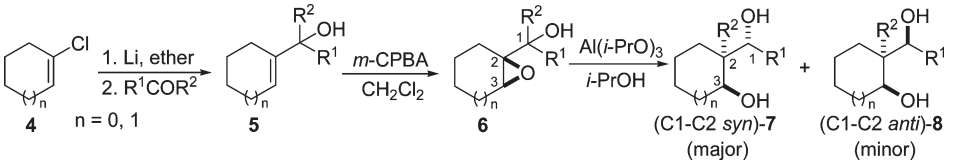
TABLE 1. Rearrangement of α-Hydroxy Epoxides with Al(*i*-PrO)$_3$[a]



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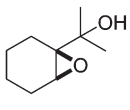
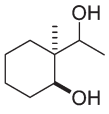
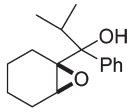
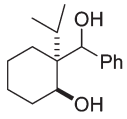
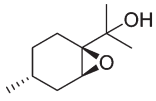
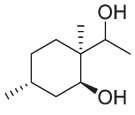
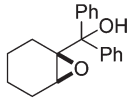
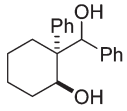
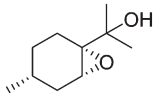
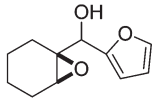
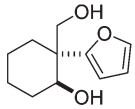
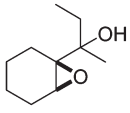
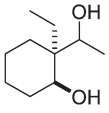
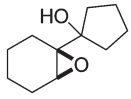
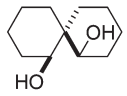
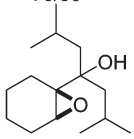
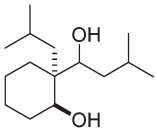
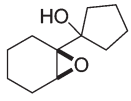
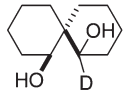
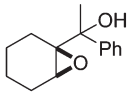
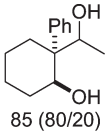
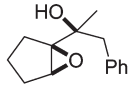
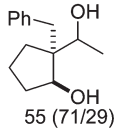
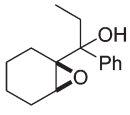
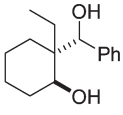
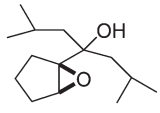
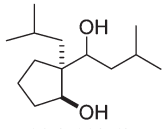
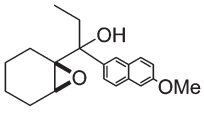
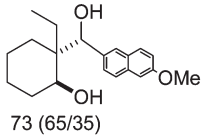
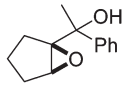
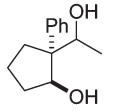
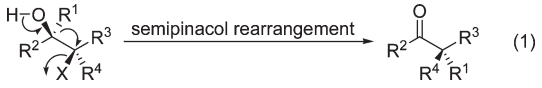
1		 26 (>98/<1)	9	 87/13	 95 (73/27)
2		 25 (>98/<1)	10		 91 (80/20)
3		–	11[a]	 80/20	 54 (91/9)
4	 70/30	 43 (91/9)	12		 98 (>98/<1)
5		 53 (>98/<1)	13		 88 (>98/<1)
6	 70/30	 85 (80/20)	14		 55 (71/29)
7	 61/39	 98 (72/28)	15		 86 (>98/<1)
8	 75/25	 73 (65/35)	16	 80/20	 42 (>98/<1)

[a]The 91/9 refers to a ratio of C2-C3 *anti* isomer to the *syn*.

simultaneous stereocontrol over other coexisting stereocenters, is an even more challenging task, since both enantioselectivity and diastereoselectivity need to be considered in the case of an asymmetric synthesis. The semipinacol rearrangement, a variant of the pinacol rearrangement, has become a well-established reaction that allows the rapid synthesis of relatively complex architectures comprising multiple stereocenters, with one being quaternary.

In contrast to the original definition, which describes a rearrangement involving a 1,2-carbon-to-carbon migration

toward the secondary center of a tertiary, secondary 1,2-diol with the loss of water, the semipinacol rearrangement has now been extended to include rearrangements involving leaving groups other than the hydroxyl group (eq 1). Two review articles contributed by Coveney[2] and Snape[3] have documented the advances of the modern seminacol rearrangement, with the latter focusing on the rearrangements of α-hydroxy epoxides and their synthetic applications. Early contributions from Suzuki, Tsuchihashi, and co-workers,[4] Marson et al.,[5] and recent efforts by other groups[6] have reported the application of the semipinacol rearrangement to certain epoxides for the creation of stereogenic quaternary carbon centers. Despite these achievements, however, we have further developed the power and scope of such transformations with our continuous efforts.

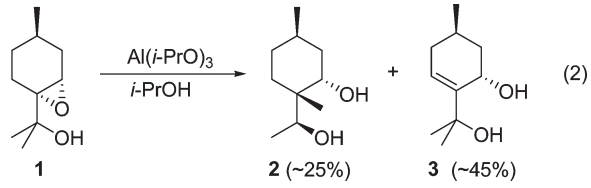


(1)

By encompassing the construction of quaternary carbon stereocenters with high efficiency and stereocontrol, we have studied the semipinacol rearrangements of α-hydroxy epoxides, 2,3-aziridino alcohols, and allylic alcohols under the influence of a range of promoters. This has laid the foundation for a series of synthetic methodologies unique to the creation of quaternary carbon stereocenters. More importantly, these reactions have been applied to the total syntheses of a number of interesting natural products. These efforts and findings comprise the major focus of this Account.

2. Diastereoselective Construction of Quaternary Carbon Stereocenters via the Semipinacol Rearrangement of α-Hydroxy Epoxides

During the course of our studies toward the total synthesis of didemnaketals, a group of marine natural products isolated from the ascidian *Didemnum* sp. possessing inhibitive activity toward HIV-1 protease, we serendipitously observed that the optically active α-hydroxy epoxide **1**, upon treatment with 2 equiv of aluminum isoproxide (Al(*i*-PrO)$_3$) in isopropyl alcohol, delivered 1,3-diol **2** bearing a quaternary stereocenter at C2 as a major byproduct, in an effort to prepare allylic diol **3** as a synthetic intermediate (eq 2).[7] Presumably, the formation of 2-quaternary 1,3-diol **2** results from a tandem reaction sequence, involving an initial semipinacol rearrangement of the α-hydroxy epoxide **1** and a subsequent Meerwein–Ponndorf–Verley reduction. The 2-quaternary 1,3-diol units are synthetically valuable for a wide range of bioactive natural products and spirocyclic compounds for chiral ligands in asymmetric catalysis.[8] These potentials, coupled with the long-standing challenge in constructing quaternary carbon stereocenters, inspired us to study this reaction in depth. This discovery became the starting point for all our subsequent studies toward the stereoselective construction of quaternary carbon centers via semipinacol rearrangement strategy.



(2)

The reductive rearrangement of enantioenriched α-hydroxy epoxide **1** was extended to a range of racemic analogues derived from the corresponding cycloalkenyl alcohols **5** (Table 1).[9] Upon treatment with Al(*i*-PrO)$_3$, under the standard conditions (2 equiv of Al(*i*-PrO)$_3$, refluxing temperature of 2-propanol or THF, 4–8 h), the epoxides **6** underwent a smooth reductive rearrangement to produce 1,3-diols **7** and **8** in good yield. A key strength to this methodology is the stereoselective construction of three carbon stereocenters, with one being quaternary, simultaneously in one simple operation. The stereochemical outcome of the reaction indicates the following: (1) the carbon-to-carbon migration occurs in an anti orientation relative to the cleaved C–O bond (except entries 7 and 8), which is consistent with the general observations in related semipinacol rearrangements promoted by other Lewis acids, such as $TiCl_4$,[10] $BF_3 \cdot OEt_2$,[4] and $SnCl_4$;[5] and (2) the hydride transfer to the latent C1 keto group proceeds through a pathway in favor of diastereomer **7**, with C1–OH in an α-configuration, as the major product. The stereoselectivity of this overall transformation was further supported by using deuterated Al(*i*-PrO)$_3$ (Table 1, entry 13). Based on the stereooutcome of this reductive rearrangement and the deuteration experiment, a possible mechanism was proposed (Scheme 1). Evidently, the Al(*i*-PrO)$_3$ in this transformation serves a dual role as both a Lewis acid to promote the semipinacol rearrangement and as reducing agent for hydride transfer. Of the two possible pathways for hydride transfer, path A is more favorable in terms of steric hindrance versus path B, which affords the C1–C2 *syn* diastereomer **7** as the major product.

In addition to the tandem reductive rearrangement mediated by Al(*i*-PrO)$_3$, a catalytic amount of $ZnBr_2$ (2–8 mol %) was observed to catalyze the semipinacol rearrangement of α-hydroxy epoxides **6** to afford α-quaternary β-hydroxy ketones with good to excellent diastereoselectivity

SCHEME 1. Proposed Mechanism for the Reductive Rearrangement of α-Hydroxy Epoxides with Al(*i*-PrO)$_3$

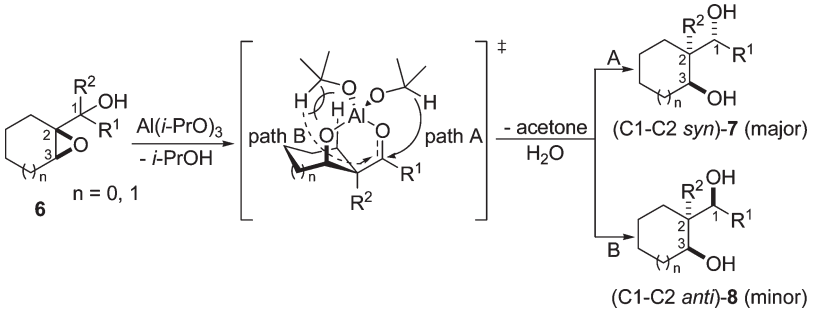
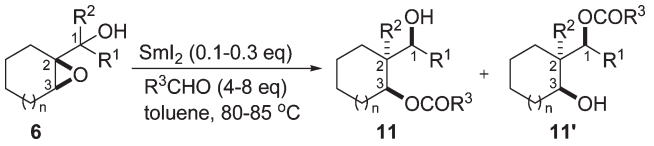
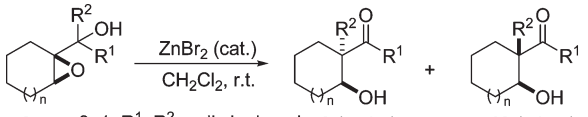


TABLE 2. Sm-Catalyzed Tandem Semipinacol Rearrangement/Tishchenko Reaction of α-Hydroxy Epoxides



entry	*n*	*syn*:*anti* of **6**	R^1	R^2	R^3	SmI_2 (equiv)	yield (%)	**11**:**11′**
1	1		Ph	Ph	Ph	0.1	95	100:0
2	1	70:30	Me	Ph	Ph	0.15	96	100:0
3	1	61:39	Et	Ph	Ph	0.15	92	100:0
4	1	87:13	*i*Pr	Ph	Ph	0.2	92	100:0
5	1	56:44	Allyl	Ph	Ph	0.3	70	100:0
6	1	100:0	Bn	Ph	Ph	0.3	95	0:100
7	1	79:21	*n*Bu	Ph	Ph	0.3	78	100:0
8	0	70:30	Bn	Ph	Ph	0.3	88	44:56
9	0	80:20	Me	Ph	*p*-ClC_6H_4	0.3	85	74:26
10	1	60:40	Me	2-thiophenyl	*p*-ClC_6H_4	0.25	83	0:100
11	1	91:9	Me	cyclopropyl	*p*-ClC_6H_4	0.3	78	93:7

(eq 3).[11] A similar result had been reported by Marson et al., but 2 equiv of $SnCl_4$ was employed.[5]

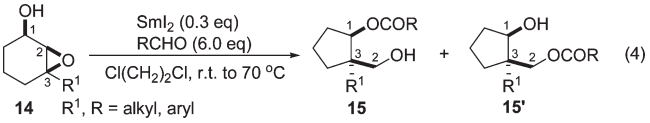


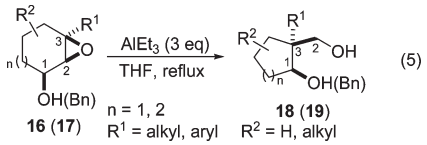
(3)

The main limitation of the Al(*i*-PrO)$_3$ mediated diastereoselective semipinacol rearrangement of α-hydroxy epoxides is the requirement for at least 1 equiv of Lewis acid, and also the stereocontrol is not always perfect. This prompted us to explore alternative promoters. After some trial and error, we discovered that a catalytic amount of SmI_2 (0.1−0.3 equiv), in combination with an excess amount of aromatic aldehyde, could efficiently promote a novel tandem semipinacol rearrangement/Tishchenko reaction of tertiary α-hydroxy epoxide **6** to form 2-quaternary 1,3-diol monoesters **11** and/or **11′**, with complete diastereocontrol (Table 2).[12] This reaction exhibited perfect stereoconvergence, since both diastereomers of the α-hydroxy epoxide **6** afforded the same diastereopure product **11** and/or **11′**, which gave the same 1,3-diol upon methanolysis with NaOH/MeOH. In addition, it is noteworthy that the opposite stereochemistry was observed at C1 in comparison to the products of the process mediated by Al(*i*-PrO)$_3$. Thus, SmI_2 and Al(*i*-PrO)$_3$ offered complementary diastereocontrol over centers C1 and C2 in the tandem reactions. This is a very important result and is not an easily achievable task in stereoselective organic synthesis.

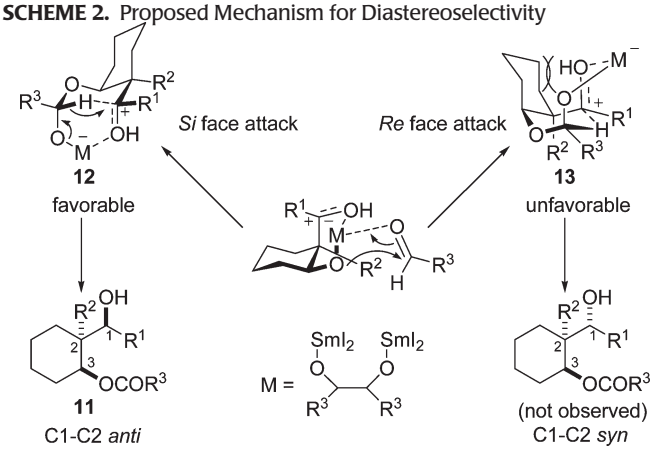
The mechanistic details of this tandem reaction were carefully studied and the actual catalytic species was determined to be a Sm-pinacol complex. The aldehyde served as simultaneously the hydride source and acylating agent. A plausible mechanism accounting for the perfect diastereoselectivity was proposed, whereby the *Re* face attack onto the aldehyde is hindered by the formation of an unfavorable transition state, due to steric hindrance between the cyclohexane ring and the 1,3-dioxo heterocycle. This forces the reaction to proceed through a more favorable *Si* face attack pathway, to give the observed diastereoselectivity (Scheme 2).

The Sm-catalyzed process was further extended to the secondary α-hydroxy epoxide **14**, resulting in ring-contracted 2-quaternary 1,3-diol monoesters **15** and/or **15′**, through a tandem sequence involving the semipinacol rearrangement with C1 to C3 carbon migration and a subsequent Tishchenko reaction (eq 4).[13] Excess triethylaluminum was also observed to promote the reductive semipinacol rearrangement of secondary α-hydroxy epoxide **16**, or its benzyl ether **17**, via a C1 to C3 migration (eq 5).[14]



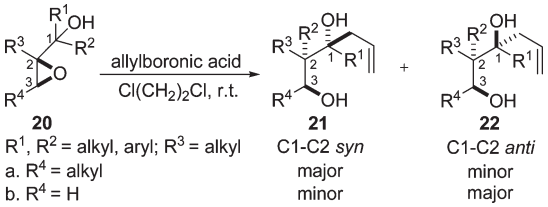


SCHEME 2. Proposed Mechanism for Diastereoselectivity



The realization of the tandem process mediated by Al(*i*-PrO)$_3$ or SmI_2 was based on the successful reduction of the latent C1 keto group formed by the seminacol rearrangement of the α-hydroxy epoxide. After succeeding in the establishment of the reductive rearrangements associated with hydride transfer, we questioned whether the latent carbonyl could be alkylated with an appropriate Lewis acidic alkylating agent. With this idea in mind and in light of the well-documented alkylating capability of alkylboronic compounds, we focused our attention on the exploration of

TABLE 3. Tandem Semipinacol Rearrangement/Allylation of α-Hydroxy Epoxides with Allylboronic Acid



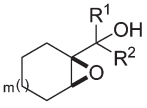
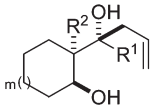
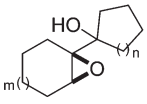
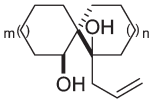
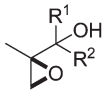
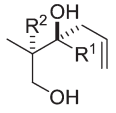
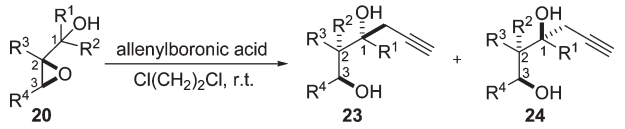
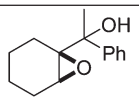
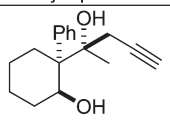
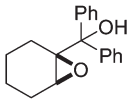
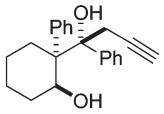
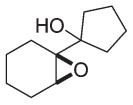
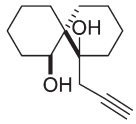
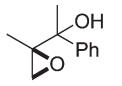
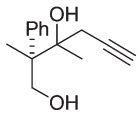
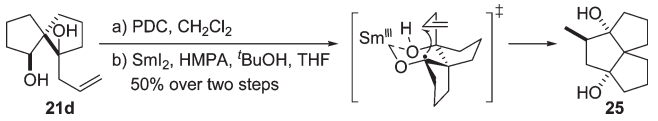
entry	substrate	*syn*:*anti*	major product	**21**:**22**	yield (%)
					
1	**20a**:m=1, R^1=Me, R^2=Ph	70:30	**21a**	>99:<1	75
2	**20b**:m=0, R^1, R^2=Ph		**21b**	>99:<1	81
3	**20c**:m=0, R^1=Me, R^2=2-thienyl	88:12	**21c**	>99:<1	69
					
4	**20d**:m=0,n=0		**21d**	71:29	>99
5	**20e**:m=1,n=0		**21e**	85:15	80
6	**20f**:m=1,n=1		**21f**	>99:<1	91
					
7	**20g**: R^1=Me, R^2=cyclopropyl	78:22	**22a**	31:69	71
8	**20h**: R^1=Me, R^2=Ph	69:31	**22b**	<1:>99	61

TABLE 4. Tandem Semipinacol Rearrangement/Propargylation of α-Hydroxy Epoxides with Allenylboronic Acid



entry	substrate	*syn*:*anti*	major product	**23:24**	yield (%)	t
1		70:30		>99:<1	55	70 h
2				>99:<1	40	78 h
3				>99:<1	74	65 h
4		69:31		1:1	48	4 d

SCHEME 3. Synthesis of Tricyclic Diol



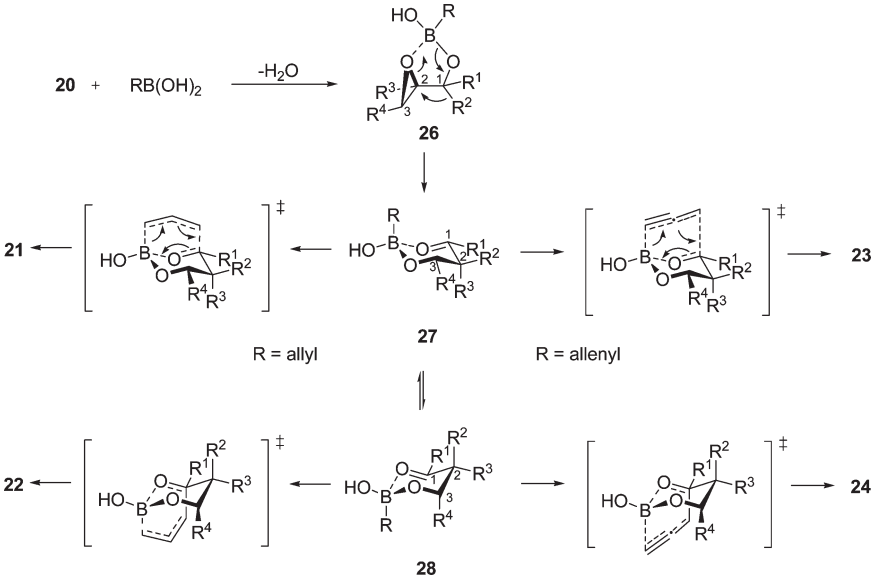
semipinacol rearrangement mediated by alkylboronic acids. We were delighted to find that, upon treatment with a stoichiometric amount of allylboronic or allenylboronic acid at ambient temperature, the α-hydroxy epoxide **20** underwent smoothly a tandem semipinacol rearrangement/alkylation to give the allylated or propargylated 1,3-diols with excellent diastereocontrol.[15] A variety of substrates derived from monocyclic, bicyclic, and acyclic allylic alcohols were amenable to this tandem process (Tables 3 and 4). One of the synthetically important features is the diastereoselective construction of three consecutive stereogenic centers, two of which are quaternary. Thus, the molecular complexity of the product is increased by incorporation of an allyl or propargyl group, compared to the Al(*i*-PrO)$_3$ or SmI$_2$ mediated processes, which could be elaborated for more advanced architecture, as exemplified by the construction of a tricyclic structure **25** from the spirocyclic 1,3-diol **21d** (Scheme 3).

It is noteworthy that the stereochemistry at C1 is substrate dependent and is sensitive to the nature of R^4 group in particular. When R^4 is incorporated in a carbocycle, diastereomers **21** and **23** are preferentially formed. For acyclic systems, the opposite diastereomers **22** or **24** are favorably produced. A possible mechanism to explain the stereoselectivity of this tandem reaction is proposed (Scheme 4). The relative steric interactions of R^4 and R^2 with allyl or propargyl account for the observed stereochemistry.

These successes prompted us to further explore other related synthetically valuable cascade transformations. The interception of the latent C1 keto group by means of reduction with hydride or alkylation with alkylboronic acid has proved crucial to ensure the overall tandem process. Beyond the above reactions with external intercepting species for C1 keto group, we questioned whether an intramolecular interception with an appropriate internal nucleophile would be possible. With this in mind, we reasoned that an azide group might be used to intercept the C1 keto group in light of an Aubé-type Schmidt reaction.[16] Thus, in conjunction with our long-term interest in the total synthesis of natural products, we devised a novel tandem semipinacol/Aubé-type Schmidt rearrangement of α-siloxy-epoxy-azide.[17] A wide range of carefully designed azido α-siloxy epoxides **29** underwent the overall rearrangement under the promotion of TiCl$_4$ in CH$_2$Cl$_2$, affording monocyclic amides, and bi- and tricyclic lactams bearing an aza-quaternary carbon stereocenter in good yield (Table 5). The excellent diastereocontrol was also observed in the relevant examples (entries 8–10).

To demonstrate the synthetic power of this cascade rearrangement, the first total synthesis of (±)-stemonamine,

SCHEME 4. Proposed Mechanism of the Tandem Semipinacol Rearrangement/Alkylation Reaction



a member of the Stemona alkaloids, which has a challenging molecular architecture involving two contiguous quaternary centers and a tetracyclic skeleton, was achieved in our laboratory with the tandem semipinacol/Aubé-type Schmidt reaction as the key, strategic step (Scheme 5).[18]

3. Diastereoselective Construction of Quaternary Carbon Stereocenters via the Semipinacol Rearrangement of 2,3-Aziridino Alcohols and Allylic Alcohols

In sharp contrast to the relatively extensive studies into the semipinacol rearrangement involving epoxides,[3] analogous research with aziridines was relatively unexplored prior to our investigation. The chemistry of aziridines is intriguing, due to their highly regio- and stereoselective ring-opening reactions and their great potential as building blocks for the synthesis of a wide range of biologically significant nitrogen-containing compounds.[19]

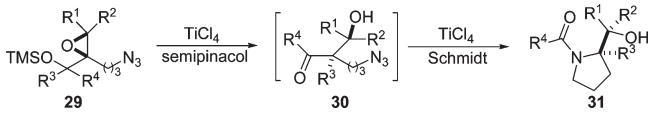
As a logical extension to our study of the semipinacol rearrangement of α-hydroxy epoxides, we investigated the related rearrangement of 2,3-aziridino alcohols **34**. Our efforts led to the discovery of a novel semipinacol rearrangement of 2,3-aziridino alcohols, mediated by a variety of Lewis acids, with $ZnBr_2$ being the most effective.[20] In this study, the preparation of the substrate **34** proved troublesome. We eventually obtained **34** in moderate yield from the corresponding allylic alcohols via an aziridination procedure developed by Sharpless and co-workers.[21] The rearrangement of 2,3-aziridino alcohols **34** under the promotion of $ZnBr_2$ in CH_2Cl_2 at room temperature proceeded smoothly, affording β-amino ketones or aldehydes **35** possessing an α-quaternary carbon center in diastereopure form and excellent yields. Investigations into substrate generality indicate that this rearrangement reaction is compatible with a variety of tertiary or secondary 2,3-aziridino alcohols, derived from acyclic, monocyclic, and bicyclic allylic alcohols with varying ring sizes and various R^1, R^2 substituents (Chart 1). A plausible mechanism accounting for the stereochemistry of this process is proposed (Scheme 6).

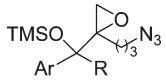
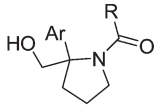
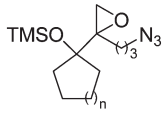
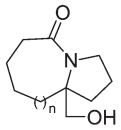
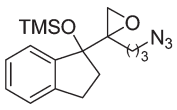
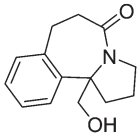
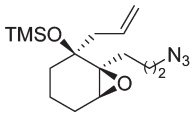
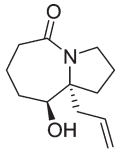
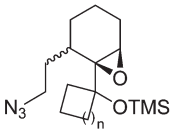
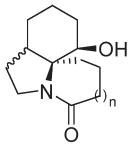
To highlight the synthetic value of this rearrangement, an efficient strategy for accessing *cis*-3*a*-aryloctahydroindole alkaloids was developed in our laboratory with this reaction as a key step, as exemplified by the total syntheses of (±)-crinane and (±)-memsembrine (Scheme 7). It was found in this study a catalytic amount of $ZnBr_2$ could efficiently promote this rearrangement.[22]

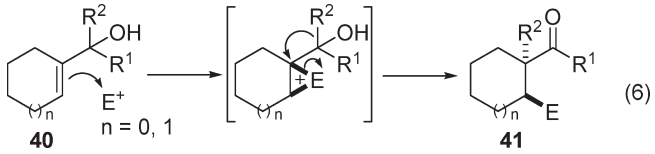
The α-hydroxy epoxides and aziridines in the semipinacol rearrangements discussed above were all derived from the corresponding allylic alcohols. In an attempt to both improve the overall efficiency and expand the substrate style, we initiated a study on the direct use of allylic alcohol as the substrate for semipinacol rearrangement. The electron-rich nature of the allylic alcohol **40** suggests that an appropriate electrophile, such as a cationic halogen reagent, could be used to induce the semipinacol rearrangement by means of an electrophilic addition triggered 1,2-carbon migration (eq 6). Indeed, there had been sporadic reports involving this notion. In a 1973 report, Johnson and Herr described a ring expansion reaction of isopropenylcycloalkanols by potentially explosive *t*-BuOCl.[23] Recently, a similar reaction was

reported by Maleczka and Ruggles with bleach/acetic acid system as the chlorinating reagent.[24] While both reactions afforded β-chloroketo compounds as the rearrangement product of allylic alcohols, however, very few in-depth investigations in terms of satisfactory scope, efficiency, and stereocontrol had appeared prior to our research into this subject.[25]

TABLE 5. Tandem Semipinacol Rearrangement/Schmidt Reaction of Azido α-Siloxy Epoxides

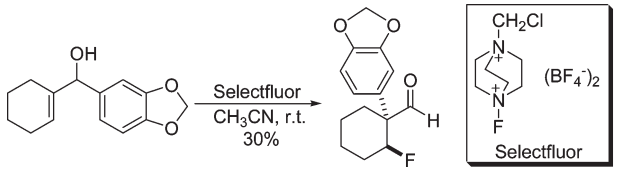


entry	substrate	product	yield (%)
			
1	**29a** R=Me	Ar = Ph **31a**	95
2	**29b** R=H	Ar = Ph **31b**	80
3	**29c** R=Me	Ar = *m*-MeOPh **31c**	77
			
4	**29d**	n=0 **31d**	77
5	**29e**	n=1 **31e**	67
6	**29f**	n=2 **31f**	66
7	 **29g**	 **31g**	61
8	 **29h**	 **31h**	92
			
9	**29i**	n=1 **31i**	78
10	**29j**	n=2 **31j**	92



(6)

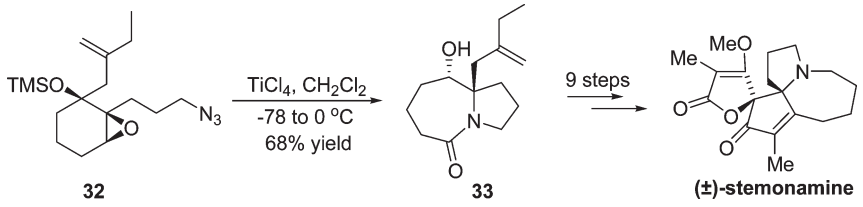
We initially focused on identifying an appropriate cationic halogen species that could serve the purpose. To our delight, we found that a combination of chloramine-T and $ZnBr_2$ was capable of effecting the semipinacol rearrangement of allylic alcohols **40**, with great efficiency and complete stereocontrol, to give α-quaternary β-bromoketo compounds **42** as products (Chart 2).[26] A wide variety of tertiary and secondary allylic alcohols were amenable to this procedure. It is noteworthy that this reaction was also effective with $ZnCl_2$ or ZnI_2, affording the corresponding chlorinated or iodinated products. A possible reaction mechanism is proposed, in which the in situ generated X−Cl through the oxidation of ZnX_2 by chloramine-T promoted the stereocontrolled semipinacol rearrangement via the formation of a halogenium ion (Scheme 8). Interestingly, the halogen source was further extended to fluoro species by using a cationic fluoro reagent, commercially available Selectfluor (eq 7).[27]



(7)

The α-quaternary β-haloketo compounds **42** produced by this protocol have the potential to serve as versatile building blocks for further elaboration, owing to the presence of the halo and carbonyl groups, together with the quaternary stereocenter. Using this methodology as a key step, the efficient total syntheses of an array of biologically important *Amaryllidaceae* alkaloids possessing intriguing molecular architecture were achieved in our laboratory. Initially, an efficient total synthesis of (±)-lycoramine, a

SCHEME 5. Total Synthesis of (±)-Stemonamine

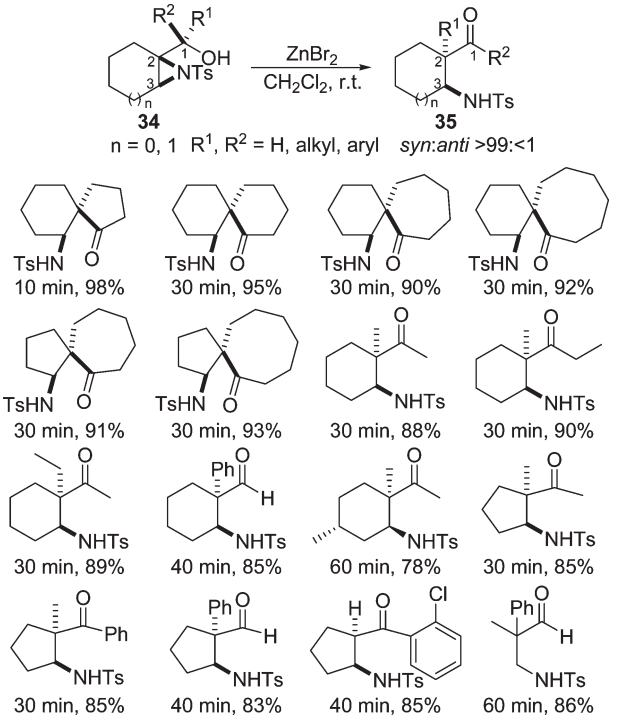


galanthamine-type alkaloid, was achieved in eight steps with 21% overall yield, wherein *N*-bromosuccinimide (NBS) was used as the rearrangement promoter for superior stereocontrol and efficiency (Scheme 9).[28] Subsequently, this strategy was applied to the concise total synthesis of (±)-galanthamine, a potent acetylcholinesterase inhibitor for the treatment of Alzheimer's disease, in 13 steps with a 12% overall yield (Scheme 10).[29] This strategy was further extended to the total syntheses of a group of structurally similar crinine-type alkaloids, (±)-hemeanthidine, (±)-pretazettine, (±)-tazettine, (±)-crinamine, and (±)-crinine (Scheme 11).[30]

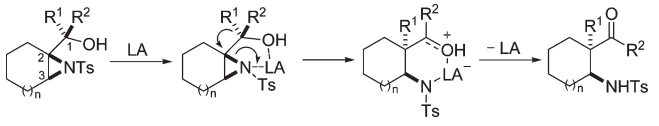
Noteworthy, this halogenium ion induced semipinacol rearrangement of allylic alcohol was further highlighted by Wood and co-workers in their elegant total synthesis of (±)-welwitindolinone A isonitrile (Scheme 12).[31]

The success in the development of the highly efficient halogenium ion induced semipinacol rearrangement of allylic alcohols with complete diastereocontrol, together with the great power of this strategy for total synthesis, stimulated us to make more efforts. In consideration of the low efficiency associated with preparing 2,3-aziridino alcohols **34** used in our previous studies,[20] we successfully developed a tandem aziridination/semipinacol rearrangement of allylic alcohols **53** by using a combination of *N*-aminophthalimide ($PhthNH_2$) and $PhI(OAc)_2$ with the assistance of silica gel.[32] This operationally trivial process obviated the need for the preparation of the 2,3-aziridino alcohols and offered an efficient alternative approach to α-quaternary β-amino carbonyl compounds **54** with a broad structural diversity (Chart 3).

CHART 1. Semipinacol Rearrangement of 2,3-Aziridino Alcohols



SCHEME 6. Proposed Mechanism for the Semipinacol Rearrangement of 2,3-Aziridino Alcohols



4. Enantioselective Construction of Quaternary Carbon Stereocenters via the Asymmetric Semipinacol Rearrangement of α-Hydroxy Epoxides and Allylic Alcohols

Asymmetric synthesis for producing chiral nonracemic organic compound has long been attracting considerable

SCHEME 7. Synthetic Applications of the Rearrangement of 2,3-Aziridino Alcohols

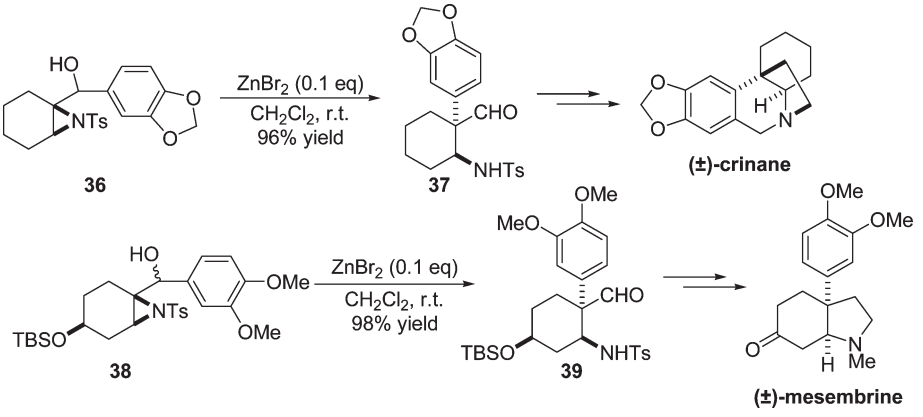
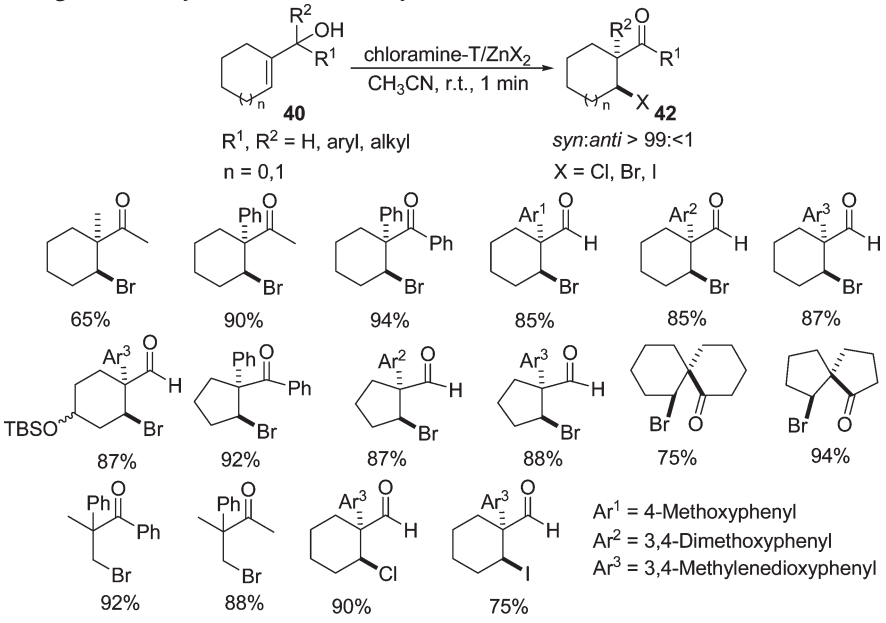
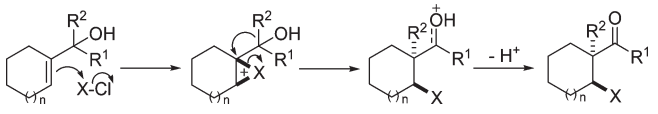


CHART 2. Semipinacol Rearrangement of Allylic Alcohols Induced by the Combination of Chloramine-T/ZnX_2

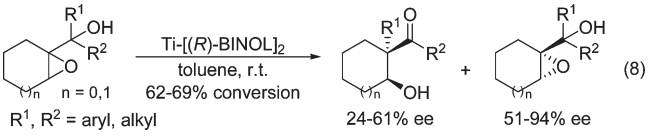


SCHEME 8. Proposed Mechanism for the Semipinacol Rearrangement of Allylic Alcohols



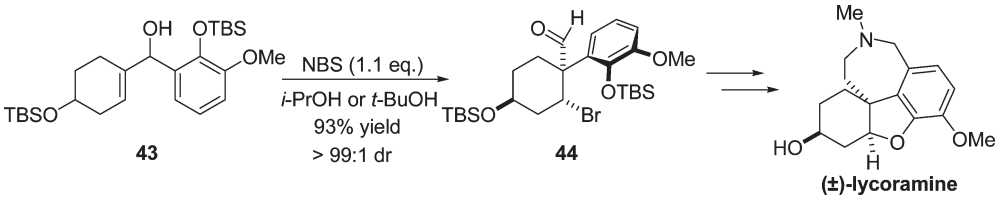
attention due to the significant importance of enantiomerically pure molecules in a variety of fields. In this context, the enantioselective construction of quaternary carbon stereocenters represents a challenging task.[1] The above-described studies demonstrate the unique capability of the semipinacol rearrangement in the diastereoselective assembly of quaternary carbon containing architectures, mainly in racemic form. This prompted us to develop an asymmetric version of this rearrangement protocol, by introducing an enantiocontrol element. To our delight, this notion has been brought to fruition in our laboratory with the identification of suitable chiral promoters. In the following part of this Account, we will focus on our achievements with the asymmetric semipinacol rearrangement for the enantioselective construction of quaternary carbon centers.

Initially, an asymmetric semipinacol rearrangement of the α-hydroxy epoxide was attempted. Our experiences with nonchiral Lewis acids led us to envisage that an appropriate chiral Lewis acid which could catalyze the rearrangement might be used to effect a kinetic resolution of the racemic α-hydroxy epoxide. With this in mind, a series of chiral Lewis acids based on the (*S*)-BINOL skeleton were evaluated. To our delight, Ti-[(*S*)-BINOL]$_2$ generated in situ from Ti(O^iPr)$_4$ and (*S*)-BINOL proved to be the catalyst of choice.[33] The enantiomeric catalyst based on (*R*)-BINOL was then applied to the kinetic resolution of a range of tertiary α-hydroxy epoxides via the asymmetric semipinacol rearrangement, affording enantioenriched α-quaternary β-hydroxy ketones in 24−61% ee and tertiary α-hydroxy epoxides in 51−94% ee (eq 8). It is noteworthy that one or two recrystallizations of the recovered tertiary α-hydroxy epoxides could raise the enantiomeric purity to ≥99% ee.

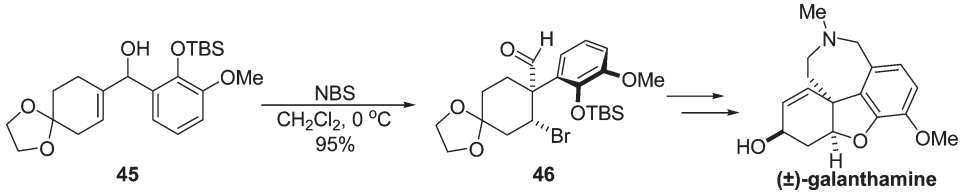


The halogenium ion induced semipinacol rearrangement of allylic alcohols and the synthetic utilities thereof stimulated our great interest in developing an asymmetric version of such reactions. In light of our preliminary result with the use of Selectfluor,[27] coupled with the literature precedent concerning asymmetric fluorination with the combination of cinchona alkaloid and Selectfluor,[34] we developed an unprecedented approach to the enantioselective synthesis of α-quaternary β-fluoro aldehydes through the asymmetric semipinacol rearrangement of allylic alcohols mediated by a quinine/Selectfluor

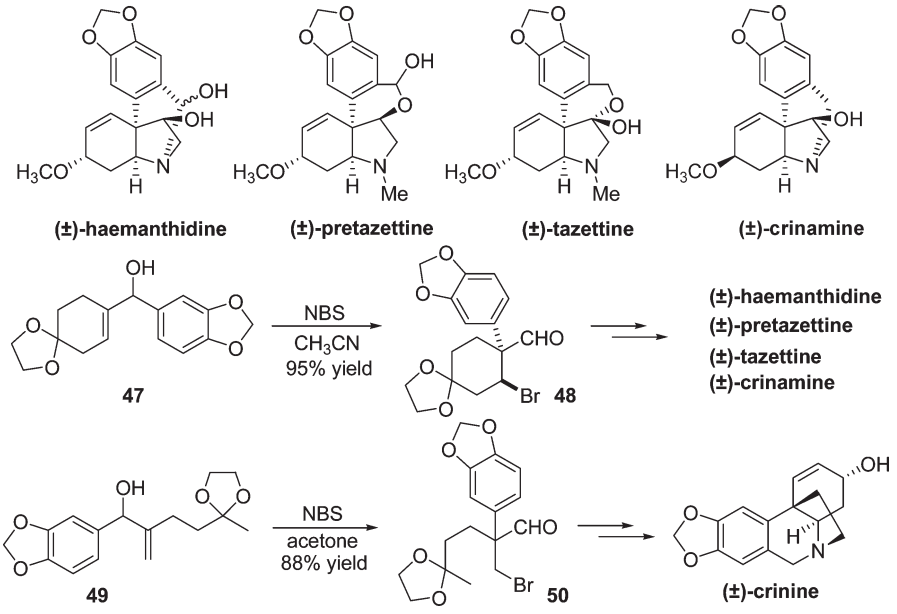
SCHEME 9. Total Synthesis of (±)-Lycoramine



SCHEME 10. Total Synthesis of (±)-Galanthamine



SCHEME 11. Total Synthesis of (±)-Haemanthidine, (±)-Pretazettine, (±)-Tazettine, (±)-Crinamine, and (±)-Crinine



combination.[35] Moderate yields (33−50%) and synthetically useful ee's (54−82%) were achieved on a range of secondary aryl allylic alcohols (Chart 4). Of note is that this reaction exhibited an excellent level of enantioconvergence, as no kinetic resolution of the racemic substrates was observed.

Very recently, the asymmetric semipinacol rearrangement of allylic alcohols was advanced further by incorporating organocatalysis. Inspired by the chiral iminium catalysis of enones,[36] we envisioned that a purposely designed enone substrate **57** possessing an allylic alcohol motif might undergo the semipinacol-type rearrangement under the promotion of a chiral amine catalyst to form enantioselectively the 1,4-diketone product **59** bearing a quaternary carbon (eq 9). To validate this hypothesis, the hydroxyl enone **60a** was studied as the model substrate. Gratifyingly, the combination of the cinchona-derived primary amine **62** and *N*-Boc-L-phenylglycine (NBLP) in CCl_4 could effectively catalyze the rearrangement, affording the spirocyclic diketone **61a** in 84% yield with

SCHEME 12. Total Synthesis of (±)-Welwitindolinone A Isonitrile

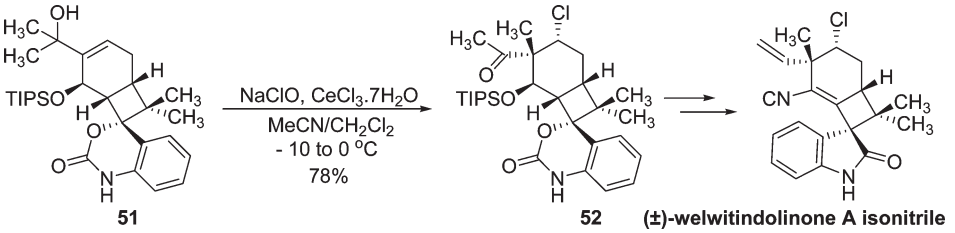


CHART 3. Tandem Aziridination/Semipinacol Rearrangement of Allylic Alcohols

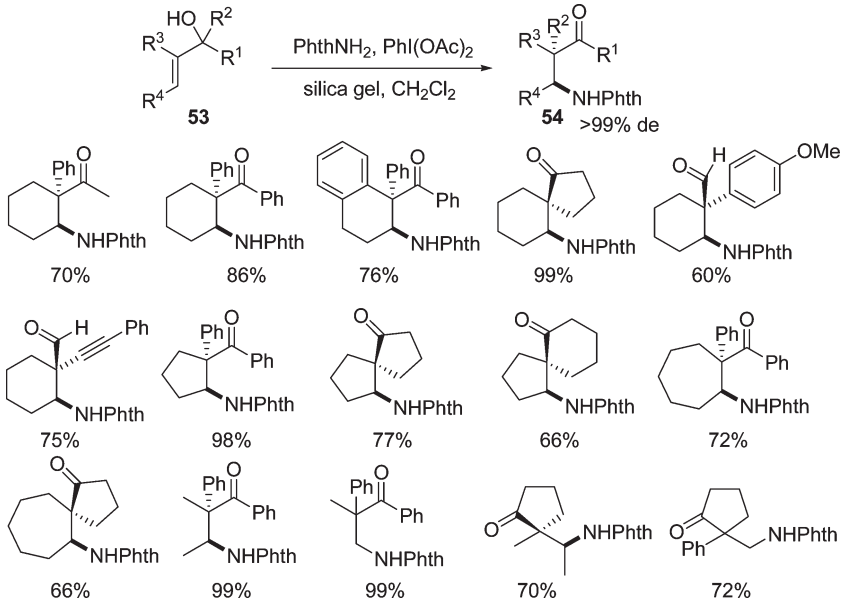


CHART 4. Asymmetric Semipinacol Rearrangement of Allylic Alcohols

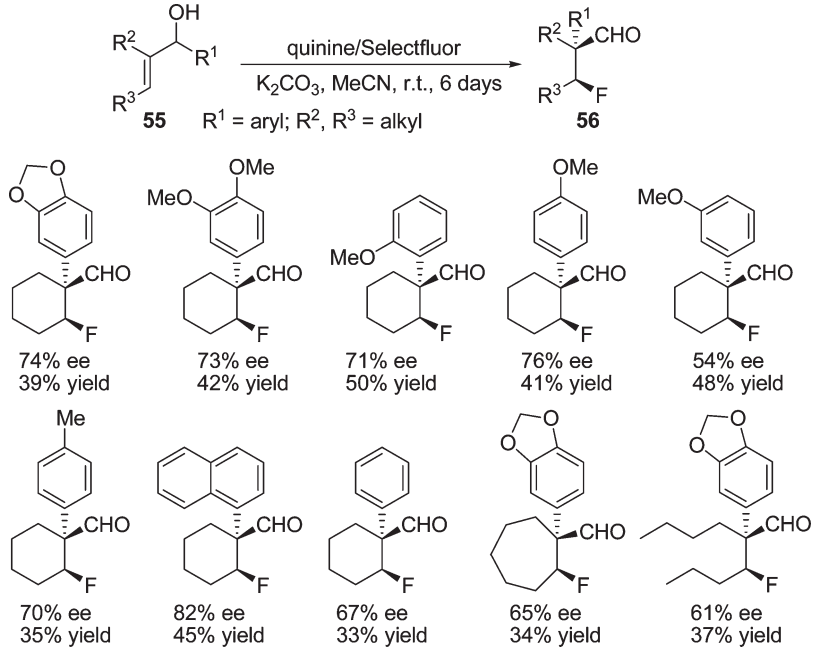
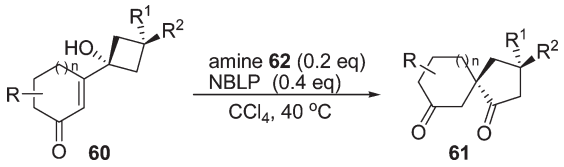


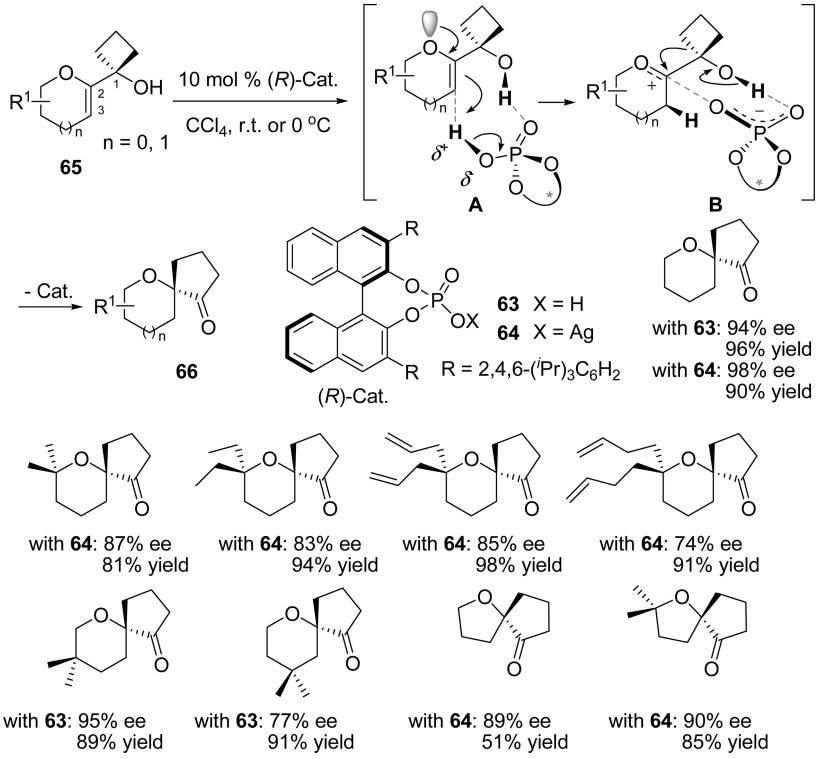
TABLE 6. Enantioselective Rearrangement of Hydroxy Enones Catalyzed by Chiral Amine



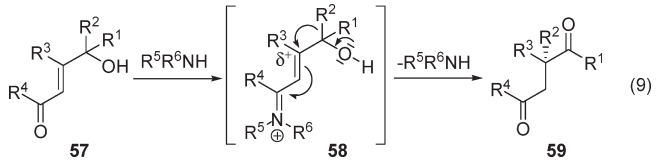
entry	substrate	product	yield (%)	ee (%)
1	**60a**	**61a**	84	77
2	**60b** (n=1)	**61b**	76	86
3	**60c** (n=2)	**61c**	66	92
4	**60d** (n=3)	**61d**	87	93
5	**60e**	**61e**	57	82
6	**60f**	**61f**	95	88
7	**60g**	**61g**	83	87
8	*cis*-**60h**/*trans*-**60h** (7:1)	**61h**	80 (17:1)	91
9	*cis*-**60h** (R^1 = Ph, R^2 = H)	**61h**	92 (29:1)	97
10	*trans*-**60h** (R^1 = H, R^2 = Ph)	**61h**	80 (2.3:1)	48
11	**60i** (6:1)	**61i**	87 (8:1)	94
12	**60j** (R^1 = Ph, 25:1)	**61j**	80 (17:1)	97
13	**60k** (R^1 = 4-BrC_6H_4, 7:1)	**61k**	80 (26:1)	96

77% ee (eq 10).[37] The substrate scope was then extended to a variety of cyclic hydroxyl enones **60**, bearing a cyclobutanol motif, to afford a wide range of spirocyclic 1,4-diketones **61** in moderate to high yields (57−95%)

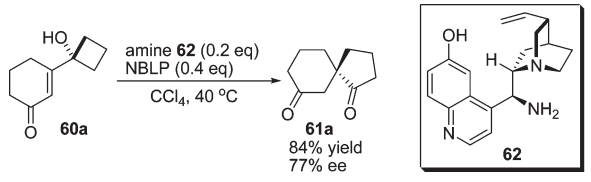
CHART 5. Asymmetric Semipinacol Rearrangement of Allylic Alcohols Catalyzed by Chiral Phosphoric Acid



and good to excellent enantioselectivities (77−97% ee) (Table 6).



(9)



(10)

In addition to cationic halogen species,[26,35] we proposed that the electron-rich nature of the carbon−carbon double bond in the allylic alcohols could be further harnessed by using other appropriate electrophilic species to enable a semipinacol-type rearrangement, especially in an asymmetric version. In the context of asymmetric protonation of the carbon−carbon double bond,[38] we conceived an idea of inducing the asymmetric semipinacol rearrangement of allylic alcohols with chiral Brønsted acid.[39] As proof of concept, we were delighted to find that, under the catalysis of the BINOL-derived phosphoric acid **63** or its silver salt **64** in CCl_4, the 2-oxo allylic alcohols **65** rearranged smoothly to the chiral spiroethers **66**, presumably through protonation of the enol ether and a subsequent 1,2-carbon migration involving hydrogen bonding.[40] A variety of 2-oxo allylic alcohols bearing dihydropyranyl or dihydrofuranyl moieties and a cyclobutanol motif were well suited to this rearrangement, affording spiroethers containing an oxo-quaternary carbon stereocenter in high yields (51−98%) and good to excellent enantioselectivities (74−98% ee) (Chart 5).

5. Conclusion

Encompassing the subject on the stereoselective construction of quaternary carbon stereocenters, we have developed a series of synthetic methodologies based on the semipinacol rearrangement strategy. A wide range of substrates, including α-hydroxy epoxides, 2,3-aziridino alcohols, and allylic alcohols, together with various promoters have been extensively studied. We have expanded upon the entire range of semipinacol rearrangements. These reactions provide efficient approaches to a variety of structurally diverse multifunctional architectures possessing quaternary carbon stereocenters with excellent stereocontrol. The great synthetic power of these methodologies is highlighted by their application as key steps in the total syntheses of a variety of naturally occurring alkaloids, which possess important

bioactivities and intriguing architectures. We anticipate that these new methodologies would continue to serve as important tools in synthetic organic chemistry.

BIOGRAPHICAL INFORMATION

Baomin Wang was born in 1973 in Shandong Province, China. He received his B.S. and M.S. from Lanzhou University in 1996 and 1999, respectively. In 2003, he obtained his Ph.D. in organic chemistry from Lanzhou University under the supervision of Prof. Yong Qiang Tu. In 2004, he joined the group of Dr. Laurent Micouin at Paris 5th University as a postdoctoral fellow. In 2005, he moved to Brandeis University in the United States where he performed his second postdoctoral study under the guidance of Prof. Li Deng. In 2007, he returned to China and became a professor at Dalian University of Technology.

Yong Qiang Tu was born in Guizhou Province, China, in 1958. He received his B.S. and M.S. from Lanzhou University in 1982 and 1985, respectively. In 1989, he obtained his Ph.D. in organic chemistry from Lanzhou University under the supervision of Prof. Yao-Zu Chen. From 1993 to 1995, he worked as a postdoctoral fellow with Prof. William Kitching at University of Queensland, Australia. In 2004–2005, he worked as a visiting professor at Bielefeld University, Germany. In 1995, he was appointed as a full professor at Lanzhou University and assumed the Director of State Key Laboratory of Applied Organic Chemistry from 2001 to 2010. In 2009, he was elected as an academician of Chinese Academy of Sciences.

We are indebted to our co-workers whose names are cited in the references. Financial support from National Natural Science Foundation of China (Nos. 20732002, 20921120404, 20972059, 20972022, and 21072085), the "973" program (2010CB833200), the "111" program, and the Chang Jiang Scholars Program of the Ministry of Education of China is gratefully acknowledged.

FOOTNOTES

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REFERENCES

1 For reviews on stereoselective construction of quaternary carbon centers, see: (a) Fuji, K. Asymmetric Creation of Quaternary Carbon Centers. *Chem. Rev.* **1993**, *93*, 2037–2066. (b) Corey, E. J.; Guzman-Perez, A. The Catalytic Enantioselective Construction of Molecules with Quaternary Carbon Stereocenters. *Angew. Chem., Int. Ed.* **1998**, *37*, 388–401. (c) Christoffers, J.; Mann, A. Enantioselective Construction of Quaternary Stereocenters. *Angew. Chem., Int. Ed.* **2001**, *40*, 4591–4597. (d) Denissova, I.; Barriault, L. Stereoselective formation of quaternary carbon centers and related functions. *Tetrahedron* **2003**, *59*, 10105–10146. (e) Cozzi, P. G.; Hilgraf, R.; Zimmermann, N. Enantioselective Catalytic Formation of Quaternary Stereogenic Centers. *Eur. J. Org. Chem.* **2007**, 5969–5994. (f) Bella, M.; Gasperi, T. Organocatalytic Formation of Quaternary Stereocenters. *Synthesis* **2009**, 1583–1614.

2 Coveney, D. J. The Semipinacol and Other Rearrangements. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Chapter 3.4, pp 777–801.

3 Snape, T. J. Recent advances in the semi-pinacol rearrangement of α-hydroxy epoxides and related compounds. *Chem. Soc. Rev.* **2007**, *36*, 1823–1842.

4 Shimazaki, M.; Hara, H.; Suzuki, K.; Tsuchihashi, G. On the Use of Epoxy Alcohol-Aldol Rearrangement for Stereoselective Construction of Quarternary Carbon Centers. *Tetrahedron Lett.* **1987**, *28*, 5891–5894.

5 Marson, C. M.; Walker, A. J.; Pickering, J.; Hobson, A. D.; Wrigglesworth, R.; Edge, S. J. Stereoselective Construction of Quaternary Centers at Ambient Temperature by the Highly Stereocontrolled Migration of Groups Containing sp-, sp^2-, and sp^3-Hybridized Carbon Atoms. *J. Org. Chem.* **1993**, *58*, 5944–5951.

6 (a) Jeon, S. J.; Walsh, P. J. Asymmetric Addition of Alkylzinc Reagents to Cyclic α,β-Unsaturated Ketones and a Tandem Enantioselective Addition/Diastereoselective Epoxidation with Dioxygen. *J. Am. Chem. Soc.* **2003**, *125*, 9544–9545. (b) Snape, T. J. Application of the semi-pinacol rearrangement towards the generation of alkenyl-substituted quaternary carbon centres. *Org. Biomol. Chem.* **2006**, *4*, 4144–4148.

7 Jia, Y. X.; Wu, B.; Li, X.; Ren, S. K.; Tu, Y. Q.; Chan, A. S. C.; Kitching, W. Synthetic Studies of HIV-Protease Inhibitive Didemnaketals: Stereocontrolled Synthetic Approach to the Key Mother Spiroketals. *Org. Lett.* **2001**, *3*, 847–849.

8 (a) Chan, A. S. C.; Hu, W.; Pai, C.-C.; Lau, C.-P.; Jiang, Y.; Mi, A.; Yan, M.; Sun, J.; Lou, R.; Deng, J. Novel Spiro Phosphinite Ligands and Their Application in Homogeneous Catalytic Hydrogenation Reactions. *J. Am. Chem. Soc.* **1997**, *119*, 9570–9571. (b) Tu, Y. Q.; Yang, L. M.; Chen, Y. Z. A Facial One-step Approach to Stereospecific Spirocyclic Diols from a-Hydroxyepoxides. *Chem. Lett.* **1998**, *27*, 285–286.

9 Tu, Y. Q.; Sun, L. D.; Wang, P. Z. Stereoselective Reductive Rearrangement of α-Hydroxy Epoxides: A New Method for Synthesis of 1,3-Diols. *J. Org. Chem.* **1999**, *64*, 629–633.

10 Maruoka, K.; Hasegawa, M.; Yamamoto, H. Epoxy Silyl Ether Rearrangements: A New, Stereoselective Approach to the Synthesis of β-Hydroxy Carbonyl Compounds. *J. Am. Chem. Soc.* **1986**, *108*, 3827–3829.

11 Tu, Y. Q.; Fan, C. A.; Ren, S. K.; Chan, A. S. C. Zinc bromide as catalyst for the stereoselective construction of quaternary carbon: improved synthesis of diastereomerically enriched spirocyclic diols. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3791–3794.

12 Fan, C. A.; Wang, B. M.; Tu, Y. Q.; Song, Z. L. Samarium-Catalyzed Tandem Semipinacol Rearrangement/Tishchenko Reaction of α-Hydroxy Epoxides: A Novel Approach to Highly Stereoselective Construction of 2-Quaternary 1,3-Diol Units. *Angew. Chem., Int. Ed.* **2001**, *40*, 3877–3880.

13 Fan, C. A.; Hu, X. D.; Tu, Y. Q.; Wang, B. M.; Song, Z. L. Progressive Studies on the Novel Samarium-Catalyzed Diastereoselective Tandem Semipinacol Rearrangement/Tishchenko Reduction of Secondary α-Hydroxy Epoxides. *Chem.—Eur. J.* **2003**, *9*, 4301–4310.

14 (a) Li, X.; Wu, B.; Zhao, X. Z.; Jia, Y. X.; Tu, Y. Q.; Li, D. R. An Interesting $AlEt_3$-Promoted Stereoselective Tandem Rearrangement/Reduction of α-Hydroxy (or Amino) Heterocyclopropane. *Synlett* **2003**, 623–626. (b) Li, D. R.; Xia, W. J.; Tu, Y. Q.; Zhang, F. M.; Shi, L. A novel $AlEt_3$-promoted tandem reductive rearrangement of 1-benzyloxy-2,3-epoxides: new route to 2-quaternary 1,3-diol units. *Chem. Commun.* **2003**, 798–799.

15 Hu, X. D.; Fan, C. A.; Zhang, F. M.; Tu, Y. Q. A Novel Tandem Semipinacol Rearrangement/Alkylation of α-Epoxy Alcohols: An efficient and Stereoselective Approach to Multifunctional 1,3-Diols. *Angew. Chem., Int. Ed.* **2004**, *43*, 1702–1705.

16 For a review on Aubé-type Schmidt reaction, see: Nyfeler, E.; Renaud, P. Intramolecular Schmidt Reaction: Applications in Natural Product Synthesis. *Chimia* **2006**, *60*, 276–284.

17 Gu, P.; Zhao, Y. M.; Tu, Y. Q.; Ma, Y.; Zhang, F. Tandem Semipinacol/Schmidt Reaction Leading to a Versatile and Efficient Approach to Azaquaternary Alkaloid Skeletons. *Org. Lett.* **2006**, *8*, 5271–5273.

18 Zhao, Y. M.; Gu, P.; Tu, Y. Q.; Fan, C. A.; Zhang, Q. An Efficient Total Synthesis of (±)-Stemonamine. *Org. Lett.* **2008**, *10*, 1763–1766.

19 For recent reviews on aziridine chemistry, see: (a) Hu, X. E. Nucleophilic ring opening of aziridines. *Tetrahedron* **2004**, *60*, 2701–2743. (b) Watson, I. D. G.; Yu, L.; Yudin, A. K. Advances in Nitrogen Transfer Reactions Involving Aziridines. *Acc. Chem. Res.* **2006**, *39*, 194–206.

20 Wang, B. M.; Song, Z. L.; Fan, C. A.; Tu, Y. Q.; Shi, Y. Lewis Acid Promoted Highly Stereoselective Rearrangement of 2,3-Aziridino Alcohols: A New Efficient Approach to β-Amino Carbonyl Compounds. *Org. Lett.* **2002**, *4*, 363–366.

21 Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. Bromine-Catalyzed Aziridination of Olefins. A Rare Example of Atom-Transfer Redox Catalysis by a Main Group Element. *J. Am. Chem. Soc.* **1998**, *120*, 6844–6845.

22 Song, Z. L.; Wang, B. M.; Tu, Y. Q.; Fan, C. A.; Zhang, S. Y. A General Efficient Strategy for *cis*-3a-Aryloctahydroindole Alkaloids via Stereocontrolled $ZnBr_2$-Catalyzed Rearrangement of 2,3-Aziridino Alcohols. *Org. Lett.* **2003**, *5*, 2319–2321.

23 Johnson, C. R.; Herr, R. W. Substituent Effects in the Ring Expansion Reactions of Isopropenylcycloalkanols by *tert*-Butyl Hypochlorite. *J. Org. Chem.* **1973**, *38*, 3153–3159.

24 Ruggles, E. L.; Maleczka, R. E., Jr. Bleach/Acetic Acid-Promoted Chlorinative Ring Expansion of [2.2.1]- and [2.2.2]-Bicycles. *Org. Lett.* **2002**, *4*, 3899–3902.

25 For related reactions, see: (a) Trost, B. M.; Mao, M. K. T.; Balkovec, J. M.; Buhlmayer, P. A Total Synthesis of Plumericin, Allamcin, and Allamandin. 1. Basic Strategy. *J. Am. Chem. Soc.* **1986**, *108*, 4965–4973. (b) Albert, S.; Robin, S.; Rousseau, G. Preparation of oxetanes by 4-*endo trig* electrophilic cyclisations of cinnamic alcohols. *Tetrahedron Lett.* **2001**, *42*, 2477–2479. (c) Paquette, L. A.; Owen, D. R.; Bibart, R. T.; Seekamp, C. K.; Kahane, A. L.; Lanter, J. C.; Corral, M. A. 1-Oxaspiro[4.4]nonan-6-ones. Synthetic Access

via Oxonium Ion Technology, Optical Resolution, and Conversion into Enantiopure Spirocyclic α,β-Butenolides. *J. Org. Chem.* **2001**, *66*, 2828–2834. (d) Hurley, P. B.; Dake, G. R. N-Bromosuccinimide Promoted Ring Expansion Reactions: Diastereoselective Formation of Functionalized Azaspirocyclic Cyclopentanones. *Synlett* **2003**, 2131–2134.

26 Wang, B. M.; Song, Z. L.; Fan, C. A.; Tu, Y. Q.; Chen, W. M. Halogen Cation Induced Stereoselective Semipinacol-type Rearrangement of Allylic Alcohols: A Highly Efficient Approach to α-Quaternary β-Haloketo Compounds. *Synlett* **2003**, 1497–1499.

27 Wang, B. M. In Studies on the Rearrangement Reactions of 2,3-Heterocyclopropyl Alcohols and Allylic Alcohols. Doctoral Dissertation, Lanzhou University, P. R. China, 2003, p. 99.

28 Fan, C. A.; Tu, Y. Q.; Song, Z. L.; Zhang, E.; Shi, L.; Wang, M.; Wang, B.; Zhang, S. Y. An Efficient Total Synthesis of (±)-Lycoramine. *Org. Lett.* **2004**, *6*, 4691–4694.

29 Hu, X. D.; Tu, Y. Q.; Zhang, E.; Gao, S.; Wang, S.; Wang, A.; Fan, C. A.; Wang, M. Total Synthesis of (±)-Galanthamine. *Org. Lett.* **2006**, *8*, 1823–1825.

30 (a) Zhang, F. M.; Tu, Y. Q.; Liu, J. D.; Fan, X. H.; Shi, L.; Hu, X. D.; Wang, S. H.; Zhang, Y. Q. A general approach to crinine-type *Amaryllidaceae* alkaloids: total syntheses of (±)-haemanthidine, (±)-pretazettine, (±)-tazettine, and (±)-crinamine. *Tetrahedron* **2006**, *62*, 9446–9455. (b) Liu, J. D.; Wang, S. H.; Zhang, F. M.; Tu, Y. Q.; Zhang, Y. Q. Concise Total Synthesis of (±)-Crinine. *Synlett* **2009**, 3040–3042.

31 (a) Reisman, S. E.; Ready, J. M.; Hasuoka, A.; Smith, C. J.; Wood, J. L. Total Synthesis of (±)-Welwitindolinone A Isonitrile. *J. Am. Chem. Soc.* **2006**, *128*, 1448–1449. (b) Reisman, S. E.; Ready, J. M.; Weiss, M. M.; Hasuoka, A.; Hirata, M.; Tamaki, K.; Ovaska, T. V.; Smith, C. J.; Wood, J. L. Evolution of a Synthetic Strategy: Total Synthesis of (±)-Welwitindolinone A Isonitrile. *J. Am. Chem. Soc.* **2008**, *130*, 2087–2100.

32 Zhang, E.; Tu, Y. Q.; Fan, C. A.; Zhao, X.; Jiang, Y. J.; Zhang, S. Y. Tandem Aziridination/Rearrangement Reaction of Allylic Alcohols: An Efficient Approach to 2-Quaternary Mannich Bases. *Org. Lett.* **2008**, *10*, 4943–4946.

33 Wang, F.; Tu, Y. Q.; Fan, C. A.; Wang, S. H.; Zhang, F. M. Kinetic resolution via semipinacol rearrangement of α-hydroxy epoxides: a new method for asymmertric synthesis of α-hydroxy epoxides and β-hydroxy ketones containing an α-quaternary carbon. *Tetrahedron: Asymmetry* **2002**, *13*, 395–398.

34 Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. Enantioselective Fluorination Mediated by Cinchona Alkaloid Derivatives/Selectfluor Combinations: Reaction Scope and Structural Information for N-Fluorocinchona Alkaloids. *J. Am. Chem. Soc.* **2001**, *123*, 7001–7009.

35 Wang, M.; Wang, B. M.; Shi, L.; Tu, Y. Q.; Fan, C. A.; Wang, S. H.; Hu, X. D.; Zhang, S. Y. Quinine/selectfluor combination induced asymmetric semipinacol rearrangement of allylic alcohols: an effective and enantioselective approach to α-quaternary β-fluoro aldehydes. *Chem. Commun.* **2005**, 5580–5582.

36 For recent reviews on chiral iminium catalysis, see: (a) Lelais, G.; MacMillan, D. W. C. Modern strategies in organic catalysis: the advent and development of iminium activation. *Aldrichimica Acta* **2006**, *39*, 79–87. (b) Erkkilä, A.; Majander, I.; Pihko, P. M. Iminium Catalysis. *Chem. Rev.* **2007**, *107*, 5416–5470.

37 Zhang, E.; Fan, C. A.; Tu, Y. Q.; Zhang, F. M.; Song, Y. L. Organocatalytic Asymmetric Vinylogous α-Ketol Rearrangement: Enantioselective Construction of Chiral All-Carbon Quaternary Stereocenters in Spirocyclic Diketones via Semipinacol-Type 1,2-Carbon Migration. *J. Am. Chem. Soc.* **2009**, *131*, 14626–14627.

38 For recent reviews on enantioselective protonation, see: (a) Duhamel, L.; Duhamel, P.; Plaquevent, J.-C. Enantioselective Protonations: Fundamental Insights and New Concepts. *Tetrahedron: Asymmetry* **2004**, *15*, 3653–3691. (b) Mohr, J. T.; Hong, A. Y.; Stoltz, B. M. Enantioselective protonation. *Nat. Chem.* **2009**, *1*, 359–369.

39 For reviews on asymmetric catalysis with chiral Brønsted acid, see: (a) Akiyama, T. Stronger Brønsted Acids. *Chem. Rev.* **2007**, *107*, 5744–5758. (b) Terada, M. Chiral Phosphoric Acids as Versatile Catalysts for Enantioselective Transformations. *Synthesis* **2010**, 1929–1982.

40 Zhang, Q. W.; Fan, C. A.; Zhang, H. J.; Tu, Y. Q.; Zhao, Y. M.; Gu, P. Brønsted Acid Catalyzed Enantioselective Semipinacol Rearrangement for the Synthesis of Chiral Spiroethers. *Angew. Chem., Int. Ed.* **2009**, *48*, 8572–8574.