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Catalytic Allylic Cation-induced Intermolecular Allylation-Semipinacol Rearrangement

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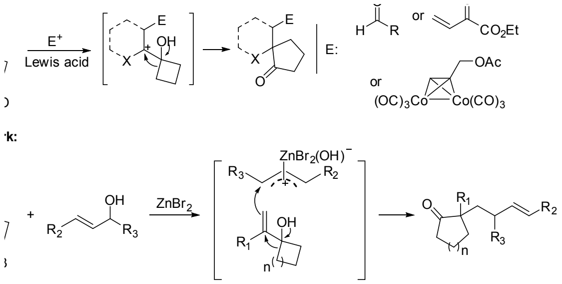
A catalytic intermolecular semipinacol rearrangement induced by allylic-carbocations has been realized. This tandem reaction is highly efficient under the catalysis of $ZnBr_2$, generating a wide range of α-homoallyl substituted ketones which contain an all-carbon quaternary centre in good to excellent yields (up to 98%) with moderate to high diastereoselectivities (up to > 20:1). Synthetic applications of this novel methodology on the construction of core structures of nature products are also reported.

All-carbon quaternary centres are widely found in a number of bioactive natural products and represent a challenging structural unit in organic synthesis due to its congested nature.[1] Over the past decades, various synthetic methods,[2] especially the asymmetric ones,[3] have been established for the construction of such moieties. Although these novel approaches have enriched the arsenal of synthetic chemists in assembling these crowded carbon centres, more general and efficient methodologies capable of introducing useful functionalities for further elaboration are still rather limited.[4] Among the numerous strategies documented, cation-induced rearrangement is considered to be a versatile reaction,[5] as a wide range of electrophiles, such as proton, halonium ion, iminium, oxonium, or even carbocations, could be introduced to the β position of the quaternary carbon atom after its formation.[6] Compared with the heteroatom electrophiles, the carbon electrophile induced tandem reactions would generate molecular complexity more expeditiously in that two C-C bonds could be forged in a single transformation with the introduction of other functionalities initially attached to the electrophile. However, despite the potential synthetic utility, development of such rearrangements has met with difficulties because of the low electrophilicity of carbocations.

In the past decade, our group has engaged in the development of novel intermolecular semipinacol rearrangement reactions induced by carbocations.[7] A number of activated carbon electrophiles, such as dimethyl acetal,[7b] propargyl,[7d] and β,γ-unsaturated α-ketoester[7e] (Scheme 1a) have been found to be suitable in promoting the rearrangement, and the products obtained could be transformed into more complex core structures of nature products,[7b,8] further demonstrating the versatile utility of these methodologies. In connection with our continued interest in this research topic, we hypothesized that the allylic cations generated from suitable allylic alcohols[9] would be viable electrophiles to induce the rearrangement reactions (Scheme 1b). Such an allyl functionality would be a synthetically useful scaffold for late-stage derivation.[10] Herein, preliminary results of our investigation on this tandem reaction are reported.



Scheme 1. Design of the allylic cation-induced intermolecular semipinacol Rearrangement

Initially, allylic alcohols **1a** and **2a** were selected as model substrates to investigate the allylic cation-induced semipinacol rearrangement under the catalysis of $ZnBr_2$. To our delight, the desired α-homoallyl substituted ketone **3a** could be obtained, albeit with only marginal yield. The low conversion of this reaction was presumably attributed to the coordination of the diethyl ether with $ZnBr_2$, which reduced the Lewis acidity of the catalyst. Therefore, various other solvents were next screened (Table 1, entries 1-10). Consistent with our speculation, solvents that had a strong coordination with the

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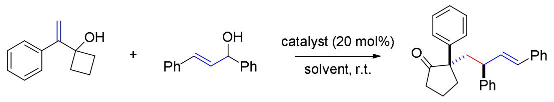
catalyst (entries 2-7) would completely prohibit the reaction, and no conversion of **1a** was observed in these cases. The reaction generally performed better in solvents like DCM, $CHCl_3$, and DCE (entries 7-10), with the best result obtained in DCM (98% yield, d.r. 5.5 : 1). Next, the influence of Lewis acids on the reaction outcome was investigated in order to further improve the diastereoselectivity. Although the rate of the reaction could be enhanced under the catalysis of some strong Lewis acids such as $Sc(OTf)_3$, $AlCl_3$ and $AlBr_3$, the yield or diastereoselectivity was lower in each case (entries 11-13). Additionally, for other Lewis acids with similar acidity with $ZnBr_2$ (entries 14-16), decreased product yields were obtained.

Table 1. Optimization of the allylic cation-induced semipinacol rearrangement reaction[a]



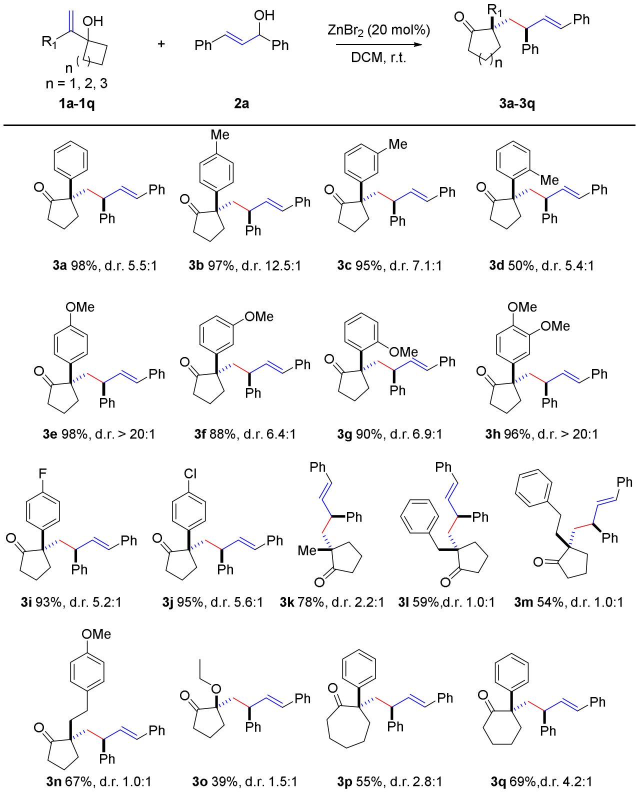
1a **2a** **3a**

Entry	Catalyst	Solvent	Yield[b](%)	d.r.[c]
1	$ZnBr_2$	Et_2O	2%	—
2	$ZnBr_2$	THF	NR	—
3	$ZnBr_2$	MeOH	NR	—
4	$ZnBr_2$	EA	NR	—
5	$ZnBr_2$	MeCN	trace	—
6	$ZnBr_2$	toluene	29	3.7:1
7	$ZnBr_2$	DCM	98	5.5:1
8	$ZnBr_2$	$CHCl_3$	57	3.9:1
9	$ZnBr_2$	CCl_4	9	2.7:1
10	$ZnBr_2$	DCE	96	5.1:1
11	$AlCl_3$	DCM	67	5.3:1
12	$AlBr_3$	DCM	80	2.0:1
13	$Sc(OTf)_3$	DCM	95	5.0:1
14	$Cu(OTf)_2$	DCM	76	5.0:1
15	$Zn(OTf)_2$	DCM	71	5.0:1
16	$ZnCl_2$	DCM	87	5.5:1

[a]Unless otherwise noted, the reaction was conducted at room temperature with allylic alcohols **1a** (0.15 mmol, 1.0 equiv.), **2a** (1.0 equiv.), and catalyst (20 mol%) in solvent (1.0 mL); [b]Yield of isolated product. The diastereomers of the product were inseparable. [c]d.r. determined by ^1H NMR. THF = tetrahydrofuran, EA = ethyl acetate, DCM = dichloromethane, DCE = 1,2-dichloroethane.

With the optimal conditions in hand, we began to probe the substrate scope of this tandem reaction. As summarized in Table 2, a wide range of tertiary allylic alcohols **1a**-**1q** were shown to be suitable rearrangement substrates. Generally, their reactions with **2a** could afford the α-homoallyl substituted ketones in moderate to good yields with moderate diastereoselectivities. For β-aryl substituted allylic alcohols, different substitutions on arene had a strong influence on the diastereoselectivities of the reactions, although the product yield of each reaction varied slightly (**3a**-**3j**). Specifically, alcohols **1** with an electron-rich aryl group would give better diastereoselectivities than those with an electron-deficient aryl group (**3b**, **3e**, **3h**-**3j**). The position of the electron-donating group also played an important role in the diastereoselection, and a decrease of selectivity was observed when the substituent was placed from *para*- to *ortho*-site (**3b**-**3g**). Next, the reactivity of several β-alkyl substituted allylic alcohols was investigated (**3k**-**3q**). Despite the generation of the desired ketones in moderate yields, the rearrangement reactions only proceeded with diminished diastereoselectivities probably due to a less steric interaction of the alkyl group with the allylic cation of **2a**. The same low diastereoselectivity was also observed in the reaction of allylic alcohol **1o** with a vinyl ether motif (**3o**). In this case, only low yield of **3o** was obtained. Finally, the 1,2-migration could be extended to involve the unstrained cyclopentanol and cyclohexanol, whose expansions were unprecedented in previously reported semipinacol rearrangement induced by carbon electrophiles (**3p**-**3q**).

Table 2. Scope of tertiary allylic alcohols as rearrangement substrates[a]



3a 98%, d.r. 5.5:1
3b 97%, d.r. 12.5:1
3c 95%, d.r. 7.1:1
3d 50%, d.r. 5.4:1
3e 98%, d.r. > 20:1
3f 88%, d.r. 6.4:1
3g 90%, d.r. 6.9:1
3h 96%, d.r. > 20:1
3i 93%, d.r. 5.2:1
3j 95%, d.r. 5.6:1
3k 78%, d.r. 2.2:1
3l 59%,d.r. 1.0:1
3m 54%, d.r. 1.0:1
3n 67%, d.r. 1.0:1
3o 39%, d.r. 1.5:1
3p 55%, d.r. 2.8:1
3q 69%,d.r. 4.2:1

[a]**1** (0.15 moml, 1.0 equiv.), allylic alcohols **2a** (1.0 equiv.), and $ZnBr_2$ (20 mol%) in DCM (1.0 mL) were stirred at room temperature. The diastereomers of the products were inseparable. d.r. determined by ^1H NMR.

Subsequently, various carbon electrophiles **2** were examined under the standard reaction conditions. 1,3-diaryl substituted allylic alcohols **2b** and **2c** with *para*-electron-withdrawing groups on the phenyl rings would furnish the rearrangement products in relatively higher yields and diastereoselectivities compared with the reaction of alcohol **2d** with *para*-methyl phenyl groups (**3r**-**3t**). The 1-methyl substituted alcohols **2e**-**2g** were also amenable to the rearrangement reaction, affording **3u**-**3w** in low to moderate yields with good diastereoselectivities. Although these allylic electrophiles would probably generate two allylic carbocations in the reaction sequence, a regioselective electrophilic addition of the non-benzyl cation to the alkene was generally

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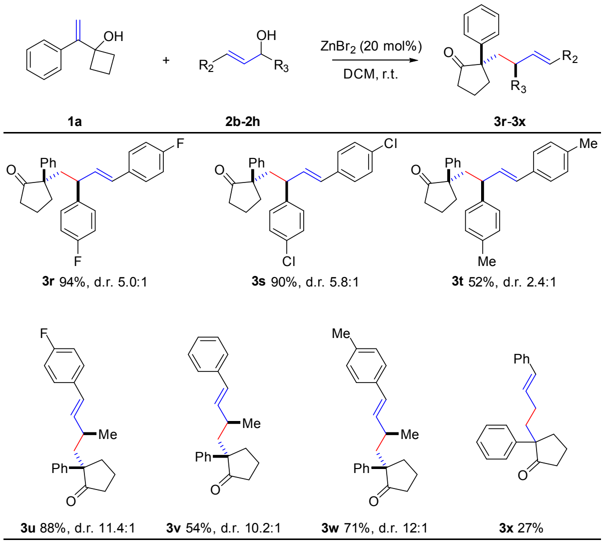
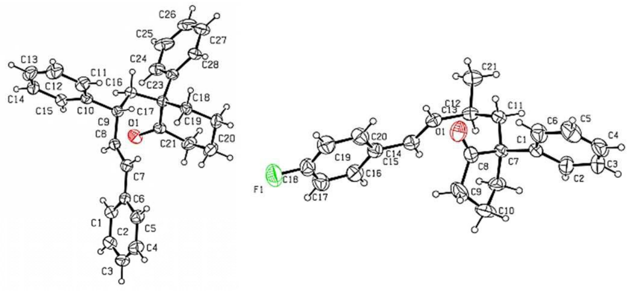
favoured and produced only one isomer (**3u**, **3v**, or **3w**) with complete regioselection. Despite a low yield of **3v** obtained due to a low conversion of **2f**, the formation of the other regioisomer was not observed in this reaction. These results suggested that a steric repulsion between the substituent of the allylic cation and the β-phenyl group of **1a** should exist during the electrophilic addition step, and the minimal interaction between the methyl substituent and the phenyl group could only exist when the non-benzyl cation was added to the alkene. In similar ways, allylic alcohol **2h** would generate **3x** as the sole product. The relative configurations of the major diastereoisomers of **3q** and **3u** have unambiguously been confirmed by X-ray diffraction (Scheme 2). From these results, it is deduced that the major diastereoisomers of other α-disubstituted ketones would have the same relative configuration as **3q** and **3u**.[11]

Table 3. Scope of allylic alcohols as carbon electrophiles[a]

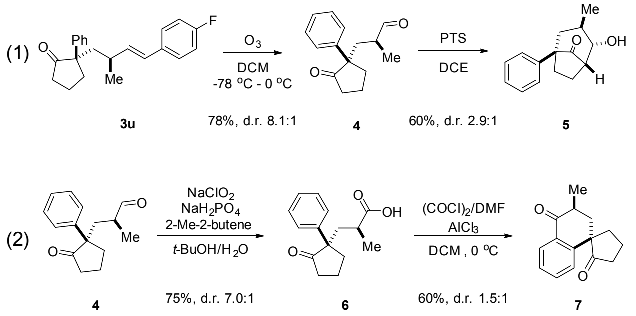


[a] **1a** (0.15 mmol, 1.0 equiv.), allylic alcohols **2** (1.0 equiv.), and $ZnBr_2$ (20 mol%) in DCM (1.0 mL) were stirred at room temperature. The diastereomers of the products were inseparable. d.r. determined by ^{1}H NMR.


3q **3u**

Scheme 2. X-ray diffraction of the major diastereoisomers of **3q** and **3u**.

Having successfully realized the allylic cation-induced semipinacol rearrangement, its synthetic applications were next investigated. Ozonolysis of cyclopentanone **3u** would produce aldehyde **4**, which, under the catalysis of PTS, would take part in an intramolecular aldol reaction to deliver [3.2.1]-cyclic ketone[12] **5** in 60% total yield (Scheme 1, entry 1). This bridged cyclic ketone motif is widely found in a number of bioactive natural products as represented by ialibinone A, ialibinone B and enaimeone A.[13] From intermediate **4**, a Pinnick oxidation of the aldehyde followed by intermolecular Friedel-Crafts acylation would give tricyclic diketone **7**, a core structure of naturally occurring merochlorins A and B.[14]



Scheme 3. Transformations of cyclopentanone **3u**.

Conclusions

In conclusion, we have developed a $ZnBr_2$-catalyzed allylic cation-induced intermolecular allylation-semipinacol rearrangement. This tandem reaction has a broad substrate scope in terms of both the tertiary allylic alcohols and the carbon electrophiles. Generally, high product yields and diastereoselectivities are obtained for these reactions, and the allyl group introduced to the ketone products could be further functionalized and used in the synthesis of the core structures of nature products. Further applications of this reaction on the total synthesis of natural products are currently underway in our lab.

Conflicts of interest

There are no conflicts to declare.

Acknowledgement

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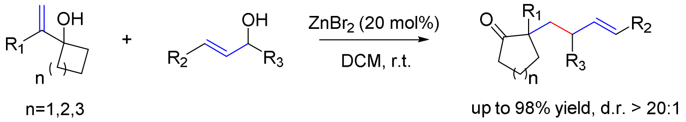
Catalytic Allylic Cation-induced Intermolecular Allylation-Semipinacol Rearrangement



A catalytic intermolecular semipinacol rearrangement induced by allylic carbocations have been realized and used in the synthesis of α-homoallyl ketones.