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Efficient Oxa-Diels−Alder/Semipinacol Rearrangement/Aldol Cascade Reaction: Short Approach to Polycyclic Architectures

Jin-Bao Peng, Yue Qi, Ze-Ran Jing, Shao-Hua Wang, Yong-Qiang Tu,* Dao-Yong Zhu, and Fu-Min Zhang*

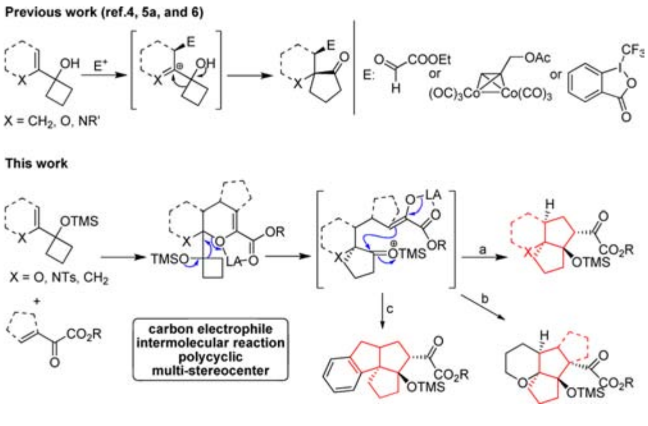
A State Key Laboratory of Applied Organic Chemistry & College of Chemistry and Chemical Engineering, Lanzhou University, Lanzhou 730000, P. R. China

Ⓢ *Supporting Information*

ABSTRACT: A novel carbon electrophile induced intermolecular oxa-Diels−Alder/semipinacol rearrangement/aldol cascade reaction of allylic silyl ether with β,γ-unsaturated α-ketoester has been developed under the promotion of SnCl$_4$. This highly efficient transformation enables the quick construction of polycyclic architectures with up to five contiguous stereogenic centers in a single operation with moderate to good yields as well as high diastereoselectivity and would provide versatile short approaches to frameworks and/or analogues of numerous biologically important polycyclic natural products.

Development of a general method for quickly generating structurally complex organic molecules in step- and atom-economical manners has always been an ideal goal for synthetic chemistry. Among the "quick synthesis" methods achieved,[1] the cascade reaction[2] has been proven to be one of the most powerful methods and plays growing roles in organic synthesis. Toward this topic,[3] we have explored the intermolecular electrophilic addition/semipinacol rearrangements of ethyl glyoxalate,[4] Togni's reagent,[5a] and Nicholas reagent[6] with allylic silyl ethers by using the corresponding Lewis acid promoters (Scheme 1). These methods not only expanded the scope of carbon electrophiles but also achieved the construction of complex as well as diverse carbon frameworks compared with the intramolecular semipinacol rearrangements.[7] Encouraged by these results, our effort turned to developing more efficient semipinacol rearrangement-based cascade reactions to construct structurally more complex polycyclic architectures, such as the frameworks and/or analogues of bioactive alliacol A, hirsutene, conidiogenone, and subergorgic acid (Figure 1).[8] Although several synthetic strategies have been available for these units,[9] most of them involve multistep transformations and/or harsh reaction conditions. Therefore, we think it is still highly desirable to pursue other efficient approaches for these skeletons, especially, considering the high feasibility of a cascade reaction involving an oxa-Diels−Alder reaction,[10] semipinacol rearrangement,[11] and aldol cyclization (Scheme 1). Herein, we present our research results about this sequence with three versions of substrate compositions.

Scheme 1. Design of the Cascade Reaction Approaching to Polycycles



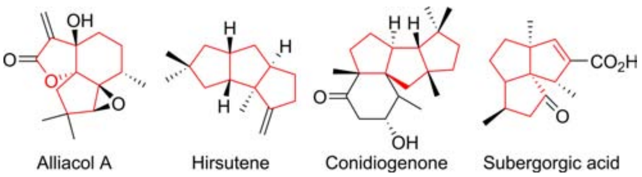


Figure 1. Natural products containing polycyclic structures.

With this guideline, we initially attempted the cascade reaction toward constructing the tricyclic analogues of alliacol A with dihydropyrane (DHP)-/dihydrofuran (DHF)-type allylic silyl ether and β,γ-unsaturated α-ketoesters. Thus, DHP-type cyclobutyl silyl ether **1a** and ethyl 2-oxobut-3-enoate **2a**[12] were

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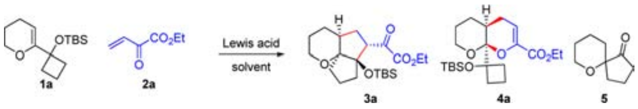
selected as model substrates and subjected to our previous reported reaction conditions using $Cu(OTf)_2$ (0.2 equiv) as catalyst in toluene.[4] Unfortunately, only an oxa-Diels–Alder reaction occurred to give ketal intermediate **4a** along with the self-semipinacol rearrangement product **5**[13] (Table 1, entry 1).

Table 1. Optimization of the Cascade Reaction Conditions[a]



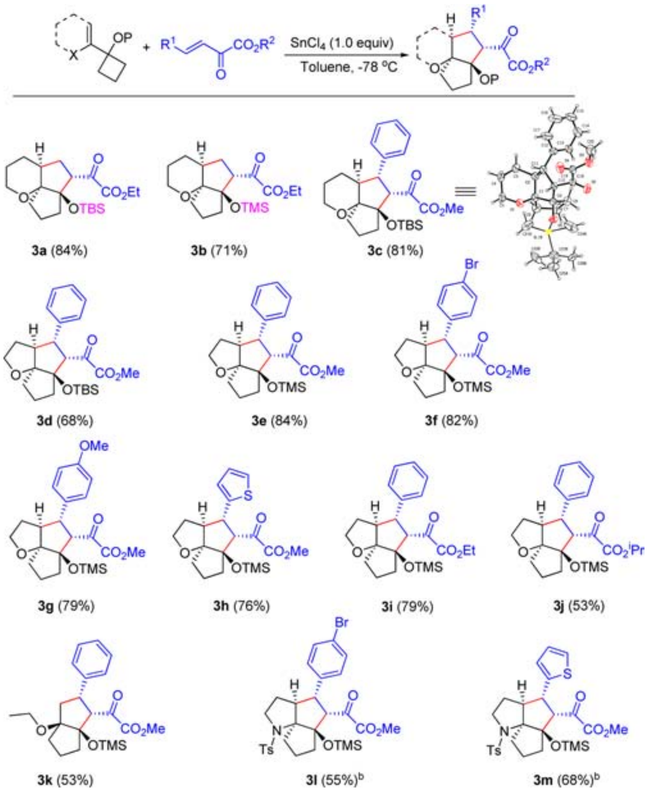
entry	acid (equiv)	solvent	temp (°C)	time (min)	**3a**[b] (%)	**4a**[b] (%)	**5**[b] (%)
1	$Cu(OTf)_2$ (0.2)	toluene	25	30	0	75	15
2	$Sc(OTf)_3$ (0.2)	toluene	25	30	0	71	ND[c]
3	$In(OTf)_3$ (0.2)	toluene	25	30	0	68	ND[c]
4	$TiCl_4$ (0.2)	toluene	−78	10	10	53	trace
5	$TiCl_4$ (1.0)	toluene	−78	10	73	trace	trace
6	$SnCl_4$ (1.0)	toluene	−78	10	84	trace	trace
7	$SnCl_4$ (1.0)	CH_2Cl_2	−78	10	79	trace	trace

[a] Conditions: **1a** (0.20 mmol), **2a** (0.30 mmol), Lewis acid, solvent (5.0 mL). [b] Isolated yield. [c] ND: not detected.

Further investigations revealed that Lewis acid was crucial to promote the subsequent rearrangement. Similarly, stronger Lewis acids such as $Sc(OTf)_3$ and $In(OTf)_3$ still could not promote the rearrangement and only provided **4a** (entries 2 and 3). Fortunately, when much stronger $TiCl_4$ (0.2 equiv) was used, we obtained the expected cascade reaction product **3a**, albeit in a low yield of 10%, along with 53% yield of oxa-Diels–Alder product **4a** (entry 4). As such low yield of **3a** might be caused by the chelation between $TiCl_4$ and biscarbonyl group of **3a**, one equiv of $TiCl_4$ was tested for the reaction, which could be completed perfectly and provided **3a** in 73% yield (entry 5). Finally, $SnCl_4$ (1.0 equiv) was found to give the best result with 84% yield of **3a** (entry 6). Additionally, some other solvents such CH_2Cl_2, Et_2O, THF, or DMF were also tested, but they resulted in either reduced yield of **3a** (entry 7) or only the self-rearrangement product **5** or no reaction at all.

With the optimized conditions in hand (Table 1 entry 6, also see experimental details in the Supporting Information), we studied the scope of the reaction with different allylic silyl ethers **1** and unsaturated α-ketoesters **2**. As shown in Scheme 2, the DHP-type cyclobutyl silyl ether **1** could react well with both non- and phenyl-substituted unsaturated α-ketoesters, affording the corresponding tricyclic products **3a**–**c** in good yields (71–84%) as well as high diastereoselectivity. In addition, the DHF-type cyclobutyl silyl ether was investigated, which also reacted well with both electron-rich and electron-deficient R^1-substituted unsaturated α-ketoesters to afford corresponding tricyclic products **3d**–**j**. The influence of silicon protecting groups (TBS and TMS) on this reaction was also observed. On the one hand, since the TMS protecting group was more labile to Lewis acid than TBS, a self-rearrangement might take place with corresponding TMS-protected substrates. Therefore, when 1 equiv of the TBS- and TMS-protected substrates were subjected respectively to the reaction with excess unsaturated α-ketoester **2a**,[14] the TBS protected substrate gave a higher yield (84%) of tricyclic product **3a** than the TMS-protected one (71% of **3b**), while on the other hand, the steric effect of the protecting group was quite clear. The TBS-protected substrate gave the lower yield of tricyclic product **3d** (68%) than **3e** (84%) when 1 equiv of unsaturated α-ketoester **2b** reacted with excess allylic silyl ether,[14] due to the greater steric hindrance of OTBS located at quaternary carbon position. It was also interesting that the ester group R^2 of unsaturated α-ketoester showed a significant impact on the reaction. For example, methyl ester obtained an excellent yield 84% of **3e**, while ethyl and isopropyl ester afforded the lower yields 79% and 53% of **3i** and **3j**, respectively. Furthermore, when an ethoxyvinyl cyclobutyl silyl ether was subjected to this reaction, we obtained multisubstituted bicycle compound **3k** in 53% yield, which was existed widely in natural products. In addition, the dihydropyrrole-type cyclobutyl silyl ether was also tolerated well and reacted with γ-substituted unsaturated α-ketoesters and afforded the corresponding products **3l**,**m**, with moderate yields. The relative configuration of all these products above was assigned based on X-ray diffraction of **3c** as a representative example.[14,15]

Scheme 2. Substrate Scope of the Cascade Reaction[a]

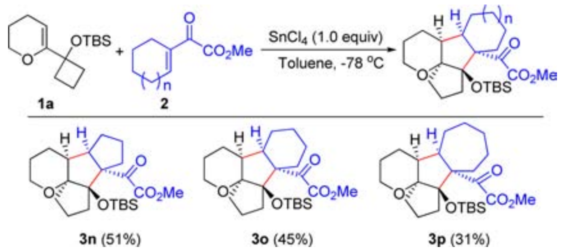


[a] Isolated yield. [b] CH_2Cl_2 as a solvent.

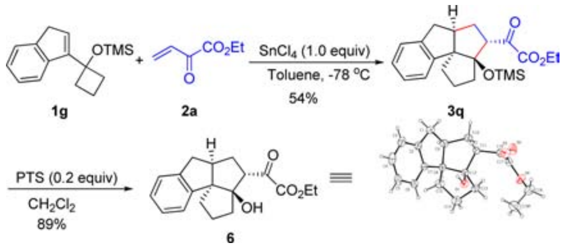
In order to construct the complex linear triquinane structures and its analogues (Figure 1), cyclic unsaturated ketoesters were subjected to the reaction conditions above. To our delight, they also reacted well with **1a**, providing the corresponding tetracyclic compounds **3n**, **3o**, and **3p** in moderate to acceptable yields (Scheme 3).[15] These compounds were synthetically versatile as the formed polycyclic structures were frequently encountered in numerous bioactive natural products and pharmaceuticals such as hirsutene and conidiogenone (Figure 1). In other words, this method provided a much simple way to generate diversity of triquinane structures and its analogues with five contiguous stereogenic centers.

We also tested indene-type allylic silyl ether to construct angular triquinanes. After some trial and error, we succeeded in

Scheme 3. Substrates of Cyclic Unsaturated Ketoesters

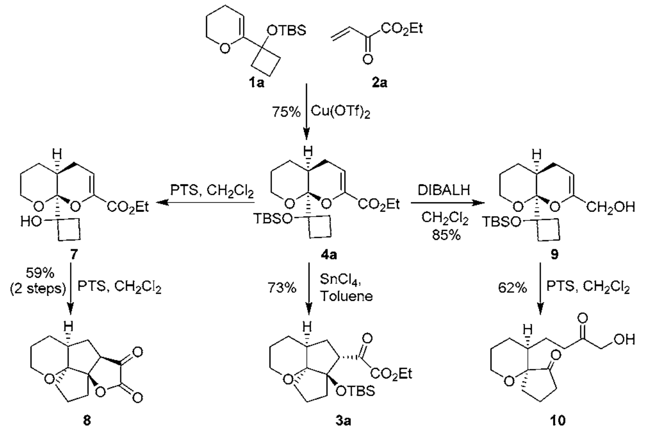


Scheme 4. Indenyl Cyclobutanol for the Construction of Tetracyclic Compound

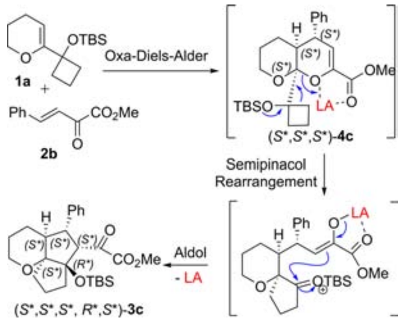


the cascade reaction of indenyl cyclobutyl silyl ether **1g** with unsaturated α-ketoesters **2a** and obtained tetracyclic product **3q** in moderate yield (Scheme 4). The relative configuration of **3q** was confirmed by X-ray crystallography of **6**,[15] which was produced by deprotection of TMS group. It should be noticed particularly that all of the above reactions proceeded diastereoselectively; therefore, this efficient methodology enables the construction of polycyclic structures with up to five contiguous stereogenic centers with high level of diastereoselectivity.

Scheme 5. Further Derivatization of Compound 4a



Scheme 6. Speculated Reaction Mechanism



To better understand the properties of the oxa-Diels–Alder adduct intermediate **4a** and speculate on the mechanism of this cascade reaction, we further carried out an additional set of experiments (Scheme 5). First, when the isolated **4a** was treated with 1.0 equiv of $SnCl_4$, the desired product **3a** was obtained in 73% yield. When compared with the 84% yield of **3a** achieved in a one-step cascade transformation, the two separate transformations gave the much lower 55% total yield, indicating this cascade reaction involving three transformations proceeded synergistically and efficiently. In addition, we tested the protonic acid PTS promoted rearrangement of **4a**, and found that TBS group was removed smoothly to give an alcohol **7**, which underwent a further rearrangement/aldol/lactonization to afford the tetracyclic lactone **8** in 59% total yield. Moreover, the presence of the ester group of **4a** was found to be crucial to the aldol cyclization. For example, a **4a**-derived compound **9** bearing an oxymethyl, instead of an ethyl ester, took only rearrangement under PTS promotion to give the bicyclic dione **10**. After all, this additional information not only indicated that alternation of reaction conditions of **4a** would bring some more possibilities but also supported the reaction mechanism we proposed in Scheme 6 (using product **3c** as an example.). Initially, a stereoselective exo oxa-Diels–Alder cyclization between silyl ether **1a** and α-ketoesters **2b** would afford the intermediate **4c** with three stereocenters. Subsequently, **4c** further underwent a $SnCl_4$-induced semipinacol rearrangement followed by an aldol cyclization to provide the tricyclic product **3c** with two newly created stereocenters.

In summary, we have developed a novel intermolecular oxa-Diels–Alder/semipinacol/aldol cascade reaction of allylic silyl ether and unsaturated α-ketoester. This efficient methodology involved the formation/reorganization of several C–C bonds, and enabled the quick construction of polycyclic structures with up to five contiguous stereogenic centers with moderate to good yields and high diastereoselectivity. Further studies on this reaction and its synthetic application are currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and corresponding data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: tuyq@lzu.edu.cn.
*E-mail: zhangfm@lzu.edu.cn.

Notes

The authors declare no competing financial interest.

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(14) For details, see the Supporting Information.

(15) The relative configuration was confirmed by X-ray crystallography. CCDC 979257 (**3c**), CCDC 979259 (**3o**), and CCDC 979261 (**6**) 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.