Domino Reactions

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Selectivity Control in Lewis Acid Catalyzed Regiodivergent Tandem Cationic Cyclization/Ring Expansion Terminated by Pinacol Rearrangement**

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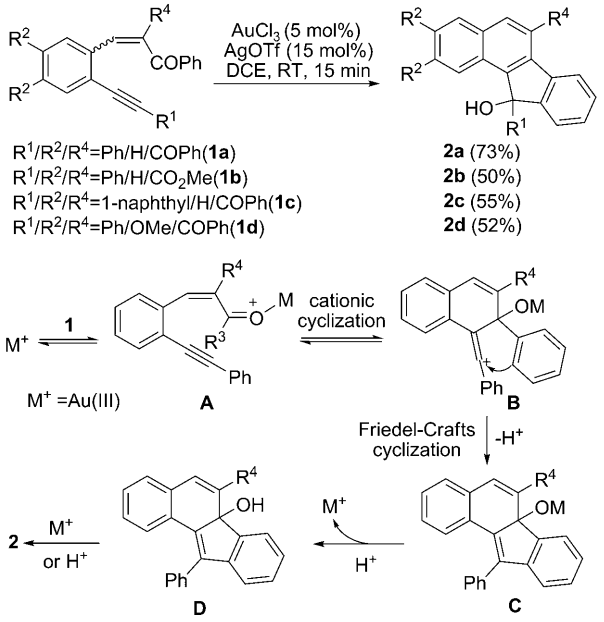
Cationic domino reactions are highly attractive and significant in the synthesis of polycyclic compounds owing to their unrivalled power of forming many bonds in only one step.[1] Within this context, tandem cationic cyclization reactions that are terminated by pinacol rearrangement are truly fascinating.[2,3] Overman and co-workers have developed a Prins cyclization terminated by pinacol rearrangement and applied this reaction in the total synthesis of several natural products such as sclerophytin A, (−)-citreoviral, and (+)-shahamin K.[4] Cationic cyclization or rearrangement reactions of substrates tethered by alkynes have been investigated by many groups,[5] however, most of these reactions were realized by metal activation of the alkyne moiety where the alkyne act as an electrophile. Herein, we report a Lewis acid catalyzed intramolecular regiodivergent[6,7] tandem cationic reaction featuring cyclization/ring expansion terminated by pinacol rearrangement. In this sequence the alkyne moiety may act as a nucleophile[8] to react with the carbonyl group which is activated by a Lewis acid.[9]

Our recent work on silver(I)-catalyzed cyclization of *ortho*-alkynyaryl aldehyde oxime derivatives led to different products and was dependent upon the substituent on the oxime unit.[10] These results promoted us to study the cyclization of the substrates **1** in which the nucleophilic aldehyde oximes were replaced by the electrophilic α,β-unsaturated ketones (Scheme 1).[11,12] Pleasingly, the reaction of **1** proceeded smoothly in DCE at room temperature under $AuCl_3$ (5 mol%)/AgOTf (15 mol%) catalysis to afford the benzo[*a*]-fluorenol **2** in moderate to high yields.



Scheme 1. Gold(III)-catalyzed cationic domino cyclization and the plausible mechanism. DCE = 1,2-dichloroethane, M = gold, Tf = trifluoromethanesulfonyl

In the proposed mechanism,[13] intermediate alkenyl cation **B**, which is generated from intermediate **A** through the intramolecular cyclization, prompted us toward further design to control the outcome of the reaction (Scheme 1). As we know, the cyclopropyl alkenyl cation would immediately undergo ring expansion to afford an allylic cation, which could be trapped by a nucleophile to afford two regioisomeric products.[14] However, the question of how to regioselectively trap allylic carbocations is still yet to be answered by chemists.[15] Herein, we envisaged that the phenyl group of **B** can be replaced by a cyclopropyl group, as in intermediate **E**, which could further convert into two interconvertible allylic carbocations **F** and **G** (Scheme 2). The intermediate **G** might be terminated by a pinacol rearrangement to afford naphthalen-2(1*H*)-one **3**, whereas intermediate **F** could be terminated by a tandem rearrangement to provide another product **4**.

Initially, we tested the tandem reactions of cyclopropyl substituted **1e** under the same conditions as in Scheme 1, $AuCl_3$ (5 mol%)/AgOTf (15 mol%). The cyclization of **1e** indeed produced two products, that is, naphthalen-2(1*H*)-one **3e** (63% yield) and naphthalene **4e** (31% yield).[16] Compound **3e** is the exact product formed from intermediate **G** by

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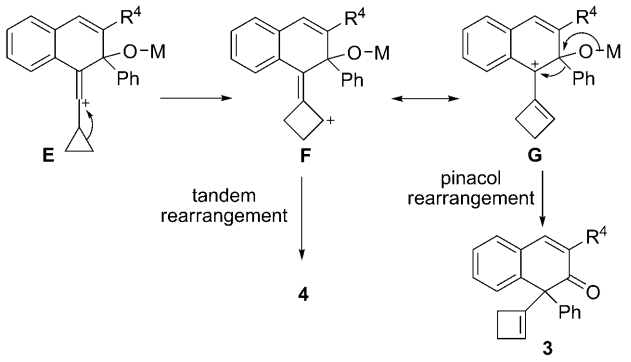
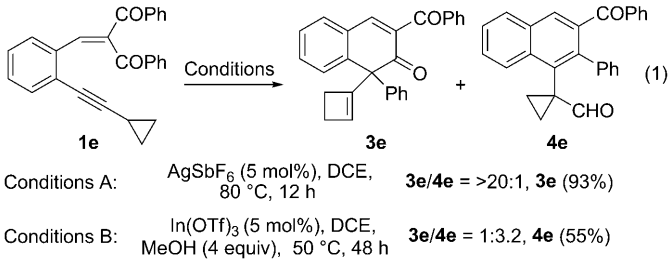


Scheme 2. Projected divergent termination of tandem cationic cyclization/ring expansion reactions of a cyclopropyl substituted substrate.

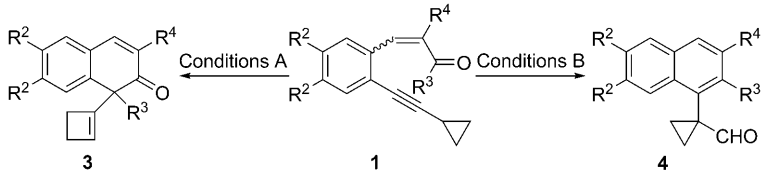


pinacol rearrangement, while **4e** must be the product formed from intermediate **F** by a tandem rearrangement. After numerous attempts, we were pleased to find that the tandem cationic cyclization/ring expansion/pinacol rearrangement sequence for **1e** proceeded smoothly in DCE at 80 °C under $AgSbF_6$ (5 mol %) catalysis and afforded **3e** in 93 % yield [Eq. (1); Conditions A]. We found that the nucleophilicity of the counterion affected the ratio of the two products (see Table 1 in the Supporting Information). Thus, the addition of more nucleophile to the reaction might be beneficial in producing **4e**. Among the nucleophiles we tested, MeOH was the most effective. Finally, we are pleased to find that **4e** could be obtained in the highest yield (55 %) under Conditions B ($In(OTf)_3$ (5 mol %), MeOH (4 equiv), 50 °C). Furthermore, Brønsted acids such as TfOH (2 mol %) and $HNTf_2$ (5 mol %) can also catalyze this transformation at room temperature to afford **3e** as the major product and in high yield.[17] Notably, the reaction of **1e** could be scaled up to 2 grams under Conditions A and gave the same excellent yield.

To study the scope of this transformation, various substituted substrates **1** were examined and the results are summarized in Table 1. Several points are noteworthy: 1) The R^4 group can be either an ester or a ketone group. The reactions of both *E* and *Z* isomers of **1f–j** and **1m** proceeded smoothly and afforded the corresponding products in the same yields (Table 1, entries 1–10 and 15–16). This result indicated that in this transformation both *E* and *Z* isomers probably proceed through the same intermediate; 2) The migration ability of the R^3 group had a significant impact on selectivity, that is, the ease of migration was beneficial to the formation of product **3**. Interestingly, the ethyl group is a much better migrating group than the methyl group under these conditions (compare **1k** and **1o**; Table 1, entries 11, 12, 19, and 20); 3) The substituents on the phenyl group (R^2) probably have little effect on the selectivity.

Furthermore substrates **5–8**, which have substituents on the cyclopropane group, were prepared and tested. These results showed that substituents on the cyclopropane ring have a significant effect on the transformations. The reactions of **5** and **6**, which have substituent at the α position of the cyclopropane ring, produced naphthalen-2(1*H*)-ones (**5a** and **6a**) in excellent yields and as single isomers under Conditions A and Conditions B [Eq. (2)]. The cyclization reaction of **7**, which had substituents -$(CH_2)_4$- at both β positions of the

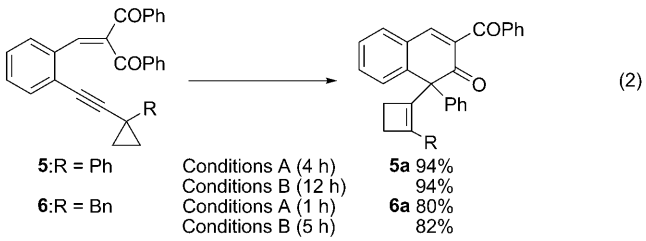
Table 1: Scope of regiodivergent tandem reactions.



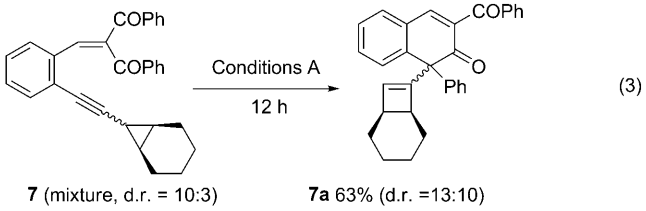
Entry	Substrate **1**	$R^2/R^3/R^4$	Cond.[a]	*t* [h]	Ratio of **3**/**4**[b]	Product	Yield [%][c]
1	**1f** (*E*/*Z* = 10:1)	H/Ph/CO_2Me	A	12	>20:1	**3f**	80
2	**1f**		B	48	1:2.7	**4f**	44
3[d]	**1g** (*E*/*Z* = 10:1)	H/Ph/CO_2Et	A	12	>20:1	**3g**	84
4	**1g**		B	36	1:2.5	**4g**	40
5	**1h** (*E*)	H/4-MeOC_6H_4/CO_2Me	A	5	>20:1	**3h**	86
6	**1h**		B	60	>20:1	**3h**	77
7	**1i** (*E*/*Z* = 20:1)	H/4-MeC_6H_4/CO_2Me	A	12	>20:1	**3i**	82
8	**1i**		B	72	1:0.6	**4i**	31[e]
9	**1j** (*E*)	H/4-ClC_6H_4/CO_2Me	A	12	5.6:1	**3j**	56[f]
10	**1j**		B	72	1:12.5	**4j**	68
11	**1k**	H/Me/COMe	A	10	1:1	**3k**	40[g]
12	**1k**		B	25	<1:20	**4k**	70
13	**1l**	MeO/Ph/COPh	A	5	>20:1	**3l**	90
14	**1l**		B	36	1:6.7	**4l**	63
15	**1m** (*E*)	MeO/Ph/CO_2Et	A	3	>20:1	**3m**	70
16	**1m**		B	48	1:4.3	**4m**	40
17	**1n**	5-F (4-H)/Ph/COPh	A	6	12.5:1	**3n**	90
18	**1n**		B	32	1:4.4	**4n**	61
19	**1o**	H/Et/COEt	A	12	>20:1	**3o**	88
20	**1o**		B	12	1.5:1	**4o**	30[h]

[a] Conditions A: substrate (0.1 M) in DCE, $AgSbF_6$ (5 mol %), 60 °C (except entries 11 and 13, 80 °C); Conditions B: substrate (0.1 M) in DCE, $In(OTf)_3$ (5 mol %), MeOH (4 equiv), 50 °C. [b] Determined by ^{1}H NMR spectroscopy of the crude product. [c] Yield of isolated product. [d] The reactions of *E*-**1g** and *Z*-**1g** gave the same yields under Conditions A. [e] **3i** was isolated in 42 % yield. [f] **4j** was isolated in 12 % yield. [g] **4k** was isolated in 41 % yield. [h] **3o** was isolated in 43 % yield.

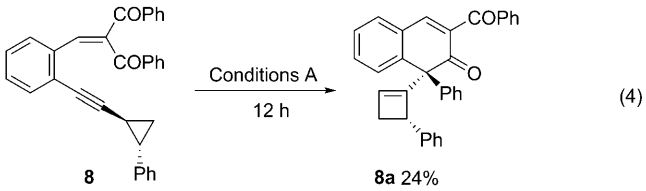
cyclopropane ring, afforded the naphthalen-2(1*H*)-one **7a** in 63% yield under Conditions A [Eq. (3)].[18] However, the reaction of **8**, which had a phenyl group at the β position of cyclopropane ring, gave the naphthalen-2(1*H*)-one **8a**[16] in only 24% yield, along with some unidentified products [Eq. (4)].



(2)



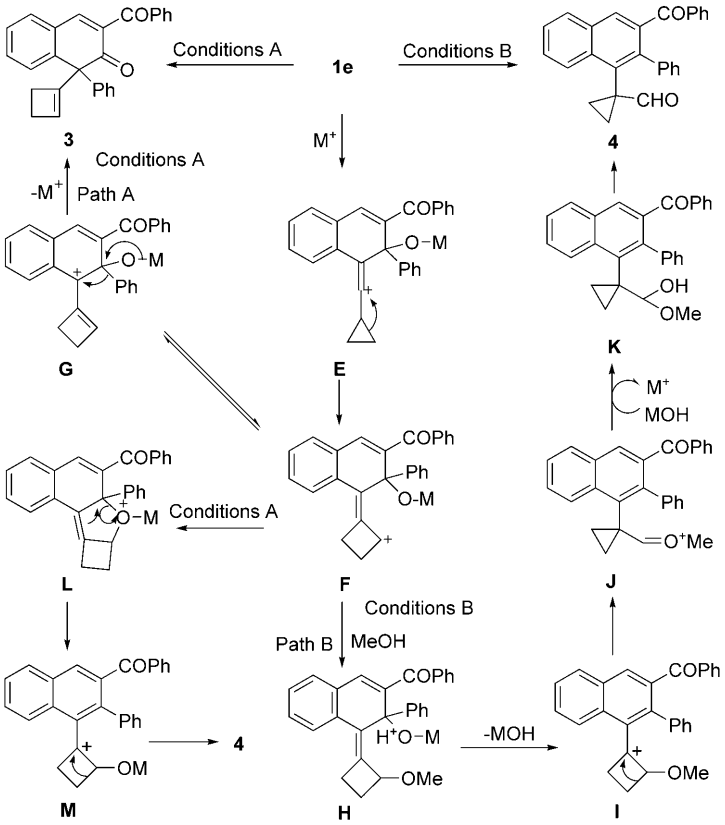
(3)



(4)

Based on the above results, a plausible mechanism of this Lewis acid catalyzed regiodivergent tandem reaction is depicted in Scheme 3. The carbonyl group of **1e** is activated by a Lewis acid, and the alkyne group attacks the carbonyl unit to produce cyclopropyl alkenyl cation **E**. Then the cyclopropyl alkenyl cation **E** undergoes ring expansion to form two interconvertible allylic cations **F** and **G**. Under Conditions A, cation **G** would undergo a pinacol rearrangement to afford product **3** and regenerate the catalyst. Under Conditions B, cation **F** is trapped by MeOH to produce the intermediate **H**, which would undergo aromatization through the elimination of MOH to give **I**, before a pinacol rearrangement to form the oxonium ion intermediate **J**. The addition of MOH to intermediate **J** regenerates the catalyst and affords the hemiacetal **K**, which could immediately produce **4**. In the absence of MeOH, intermediate **F** could undergo cyclization to produce **L**, before isomerization and pinacol rearrangement to give **4**.

In conclusion, we have developed a Lewis acid catalyzed regiodivergent tandem cationic cyclization/ring expansion terminated by pinacol rearrangement to selectively afford naphthalen-2(1*H*)-ones or naphthalenes. In this work, both the Lewis acid and the nucleophile play significant roles in controlling the reaction pathway. Furthermore, a mild method



Scheme 3. Plausible mechanism of Lewis acid catalyzed regiodivergent tandem cyclization.

for the synthesis of benzo[*a*]-fluorenol by a gold-catalyzed cascade reaction was also demonstrated. The scope, mechanism, synthetic applications of this transformation, and design of other related cascade reactions from intermediate **B** are ongoing in our laboratory.

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[16] CCDC 724757 (**2a**), 724758 (**3e**), 714759 (**4e**) and 724760 (**8a**) 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.

[17] More reaction conditions were screened and can be found in Table 1 of the Supporting Information.

[18] Under Conditions B, the reaction of **7** gave no aldehyde product but gave the normal naphthalen-2(1*H*)-one **7a** in only 5% yield and some other unidentified products, which were detected by ^{1}H NMR spectroscopy of the crude products.

