View Online / Journal Homepage / Table of Contents for this issue
Dynamic Article Links

ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 2636–2638

www.rsc.org/chemcomm

COMMUNICATION

Efficient synthesis of isochromanones and isoquinolines *via* $Yb(OTf)_3$-catalyzed tandem oxirane/aziridine ring opening/Friedel–Crafts cyclization†

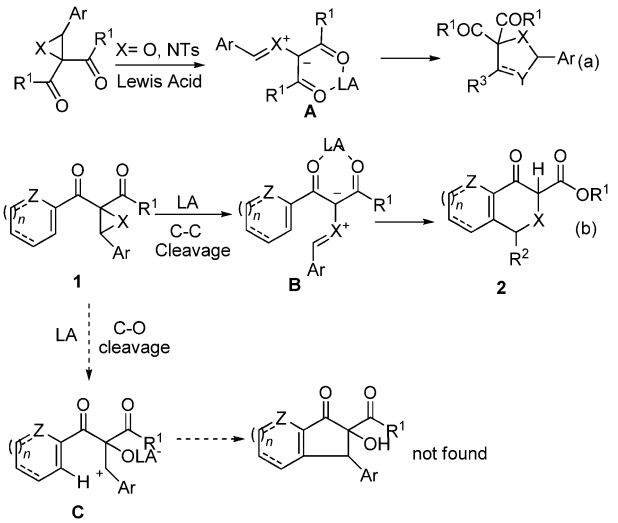
Lai Wei[a] **and Junliang Zhang***[ab]

Received 14th December 2011, Accepted 17th January 2012
DOI: 10.1039/c2cc17836b

The first example of $Yb(OTf)_3$-catalyzed tandem ring opening/Friedel–Crafts cyclization of oxiranyl and aziridinyl ketones *via* selective C–C bond cleavage under mild conditions was developed. Isochromanones and isoquinolines are formed in reasonable yields, which often serve as building blocks for complex chemical synthesis.

Isochromanones and isoquinolines are present in the core of many natural products and medicinally active molecules,[1,2] such as the ajudazols, (4*R*)-hydroxyochratoxin A, acetoxy-geranyloxy-mellein and so on. Furthermore, these ring-fused systems often serve as building blocks for complex chemical synthesis. Because of their growing popularity in the area of complex molecular construction, organic chemists have been steadily exploring efficient methods for their synthesis.[3] One such method that has been relatively underexplored is an acid-promoted ring opening/cyclization of aryl oxiranes and aziridines.

Very recently, our group developed a novel strategy to achieve carbon–carbon selective cleavage of oxiranes[4] and aziridines[5] under the catalysis of Lewis acids and the resultant intermediate reactive 1,3-dipole can easily undergo 1,3-dipolar cycloadditions with dipolarophiles such as aldehydes, olefins and alkynes, leading to highly substituted 1,3-dioxolanes, 1,3-oxazolidines, dihydrofurans, and pyrrolidines. With this concept in mind, we envisaged that compound **1** might be able to undergo tandem ring-opening/Friedel–Crafts cyclization under mild Lewis acidic conditions by introducing electron-rich aromatic systems or alkenes instead of the Ar group of **A**. If successful, it will provide a facile and general access to isochromanones and 1,2-dihydroisoquinolines **2**. However, one issue should be mentioned that this kind of substrates may also easily undergo the reported Friedel–Crafts cyclization reaction through intermediate **C** *via* the C–X bond cleavage,[6] leading to 2,3-dihydro-1*H*-inden-1-one under the catalysis of Brønsted acids or Lewis acids (Scheme 1).



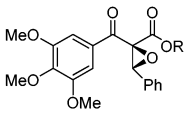
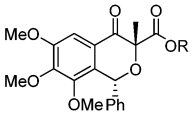
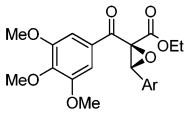
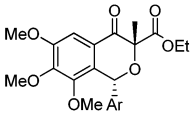
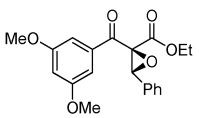
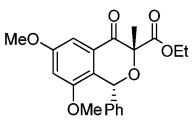
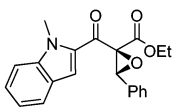
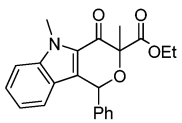
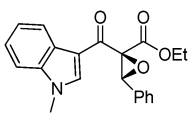
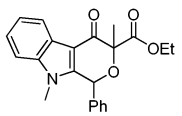
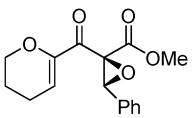
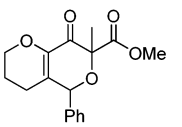
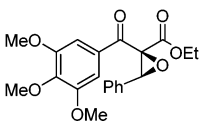
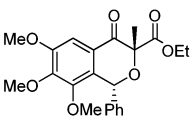
Scheme 1 Our previous work and the present work.

We chose (*Z*)-ethyl 3-phenyl-2-(3,4,5-trimethoxy benzoyl) oxirane-2-carboxylate **1a** as a model substrate to test our hypothesis (see Table S1 in ESI†). Initially, **1a** was subjected to the solution of 10 mol% of $Sc(OTf)_3$ in CH_2Cl_2 at room temperature. The reaction yielded the desired product **2a** in 73% NMR yield after running the reaction for 10 h (Table S1, entry 1, ESI†), and the product is not stable during the purification, which exists as a mixture of ketone and enolate forms (1 : 2). To improve the yield, a representative selection of Lewis acids, including $Cu(OTf)_2$, $In(OTf)_3$, $Yb(OTf)_3$, $Y(OTf)_3$, $Sn(OTf)_2$, $Fe(OTf)_3$, and $Mg(OTf)_2$, in various solvents were tested. Catalysts such as $Sn(OTf)_2$, $Cu(OTf)_2$, $Fe(OTf)_3$, $Mg(OTf)_2$ have either low efficiency or no catalytic activity. To our delight, the reaction worked very well in CH_2Cl_2 at room temperature under the catalysis of 10 mol% of $Yb(OTf)_3$ to give the cyclized target in 99% yield. Solvents other than DCE, toluene, THF, DMF failed to improve the yield or shorten the reaction time. Performing the reaction with a lower catalyst loading proved to be suboptimal. In the absence of 4 Å molecular sieves (MS), the reaction is sluggish, indicating that the anhydrous conditions are essential for this reaction.

[a] *Shanghai Key Laboratory of Green Chemistry and Chemical Processes, Department of Chemistry, East China Normal University, 3663 N, Zhongshan Road, Shanghai 200062, P. R. China. E-mail: jlzhang@chem.ecnu.edu.cn; Fax: +86 21-6223-3213*
[b] *State key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, P. R. China*

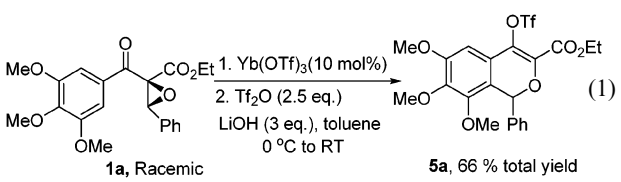
† Electronic supplementary information (ESI) available: Representative experimental procedure and characterization of reaction products. CCDC 842104 (**4a**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc17836b

Table 1 Cascade ring opening/cyclization of oxiranes[a]

Entry	Substrate **1**	Product, yield, dr
		
	R =	R =
1	Et (**1a**)	Et (**3a**), 86%, > 50 : 1
2	*t*-Bu (**1b**)	*t*-Bu (**3b**), 69%, > 50 : 1
		
	Ar =	Ar =
3[b]	4-NCC_6H_4 (**1c**)	4-NCC_6H_4 (**3c**), 75%, > 50 : 1
4	4-FC_6H_4 (**1d**)	4-FC_6H_4 (**3d**), 74%, > 50 : 1
5	4-ClC_6H_4 (**1e**)	4-ClC_6H_4 (**3e**), 78%, > 50 : 1
6	4-BrC_6H_4 (**1f**)	4-BrC_6H_4 (**3f**), 79%, > 50 : 1
7	4-MeC_6H_4 (**1g**)	4-MeC_6H_4 (**3g**), 68%, > 50 : 1
8	4-$MeOC_6H_4$ (**1h**)	4-$MeOC_6H_4$ (**3h**), 40%, > 50 : 1
9	1-Naphthyl (**1i**)	1-Naphthyl (**3i**), 66%, > 50 : 1
10	 **1j**	 **3j**, 85%, >50:1
11[c]	 **1k**	 **3k/3k'**, 88%, 3: 1
12	 **1l**	 **3l/3l'**, 63%, 3:1
13[d]	 **1m**	 **3m/3m'**, 66%, 6:1
14[e]	 **1a'**	 **3a**, 74%, >50:1

[a] The reaction was carried out at RT with **1** (racemic, 0.3 mmol), 4 Å MS (120 mg), 10 mol% $Yb(OTf)_3$ in CH_2Cl_2 at 25 °C and completed within 15 h, and after filtration to remove the catalyst and solvent, the crude product **2** was treated with 5 eq. CH_3I with *t*-BuOK (1.2 eq.) and *t*-BuOH (a drop) in THF at RT. [b] Reaction performed in 1,2-dichloroethane at 80 °C. [c] Flash chromatography with a short pad of silica gel. [d] Reaction performed with 15 mol% $Yb(OTf)_3$ within 21 h for the first step. [e] Refluxing DCM for the first step.

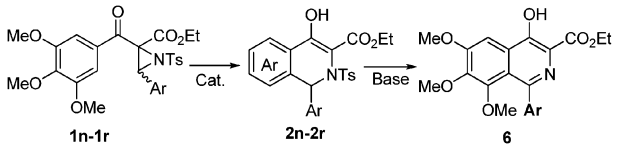
With the optimized conditions in hand, a variety of aryl oxiranes with different electronic and steric properties were examined to determine the reaction scope and limitation. The cascade ring opening/cyclization of **1a–1j** could give the corresponding isochromanones **2a–2j** in good to excellent yields with high diastereoselectivities, but all suffered somewhat enolization issue as mentioned in ESI.† In order to demonstrate the synthetic application and to avoid the enolization issue, further methylation reaction of **2a–2j** was carried out leading to **3a–3j** in moderate to good yields with excellent diastereoselectivities (Table 1, entries 1–10). Bulky *tert*-butyl ester is compatible under Lewis acidic conditions and **3b** can be isolated in 69% yield (Table 1, entry 2). Gratifyingly, substrates **1c–1h** bearing aryl groups of different nature proceeded smoothly to provide the corresponding cycloadducts **3c–3h** in 40–79% total yields after two steps, albeit **1c** with a strong electron-withdrawing CN group required higher temperature (DCE, 80 °C) to accomplish cyclization (Table 1, entries 3–8). Substrate **1g** with a poor electron-donating group ($-CH_3$) afforded **2g** in 99% yield, whereas it can only afford **3g** in 68% yield along with some decomposition during the methylation step (Table 1, entry 7). In contrast, a strong electron-donating methoxy group made the substrate **1h** too reactive to give **3h** in low yield (40%) (Table 1, entry 8). The 1-naphthyl group is also compatible with the present transformation (Table 1, entry 9). Similarly, substrate **1j** with a strong electron-rich aromatic system gave **3j** in 85% yield as a single isomer (Table 1, entry 10). What is more, it is interesting to find substrates **1k–1m** with electron-rich systems such as 2-substituted, 3-substituted indole and 3,4-dihydro-2*H*-pyranyl ring afforded **2k–2m** in good to excellent yields as ketone forms, albeit with moderate diastereoselectivities as mentioned in ESI.†[7] Further methylation reaction of **2k–2m** was carried out leading to **3k/3k′–3m/3m′** in moderate to good yields with moderate diastereoselectivities. It is noteworthy that only isolated examples of indoles and pyrans fused to pyrans were reported in the literature.[8] Compound **1a′** is less reactive than its diastereoisomer **1a** and requires higher temperature to make the reaction occur. After the further methylation reaction, the same product **3a** was isolated in 74% yield (Table 1, entry 14). The structure of the product was further confirmed by the single-crystal X-ray analysis[9] of the product **4a**, which was prepared from the ethylation of **2a**. Additionally, synthetically useful triflate **5a** can be easily prepared in 66% yield *via* the sequential tandem ring opening/cyclization and triflation reaction (eqn (1)).



(1)

Next, we attempted to extend the scope of this tandem ring opening/cyclization to the aziridines under the optimized reaction conditions (Table 2). Aziridines **1o–1r** with aryl groups (Ar) of different electronic properties could give the corresponding products **2o–2r**, which were then further converted to **6a–6e** under the basic conditions in high yields. Aziridine **1o** with

Table 2 Cascade ring opening/cyclization of aziridines[a,b]



1n-1r 2n-2r 6

Entry	**1**, Ar =, dr[c]	Product **2**[d]	Product **6**
1	**1n**, Ph (1.1 : 1)	**2n**, 80%	**6a**, 78%
2	**1n**, Ph (3.0 : 1)	**2n**, 83%	/
3	**1o**, 4-ClC_6H_4 (4.6 : 1)	**2o**, 85%	**6b**, 84%
4	**1p**, 4-BrC_6H_4 (2.4 : 1)	**2p**, 89%	**6c**, 89%
5	**1q**, 4-*i*-PrC_6H_4 (5.0 : 1)	**2q**, 71%	**6d**,70%
6	**1r**, 4-$NO_2C_6H_4$ (2.7 : 1)	**2r**, 55%[e]	**6e**, 42%

[a] Reactions of substrates **1n–1r** were run with 10 mol% $Yb(OTf)_3$ and 120 mg of activated 4 Å MS in DCM at RT within 15 h to afford products **2n–2r**. [b] Further elimination of crude products **2n–2r** was carried out with 1.05 eq. of K_2CO_3 in DCM, reflux. [c] The numbers in parentheses refer to the diastereoselectivity of the substrates **2n–2r**. [d] Isolated yields after column chromatography with 1% HOAc. [e] The reaction was performed at 40 °C.

different dr ratios (1.1 : 1 *vs.* 3.0 : 1) afforded 1,2-dihydroisoquinoline **2n** in almost the same yield (Table 2, entries 1 and 2), indicating that both diastereoisomers may proceed through the same reaction pathway. Aziridines **1p–1q** bearing weak electron-withdrawing groups at the *para* position of the phenyl ring yielded 1,2-hydroisoquinolines **2p** and **2q** in higher yields, while electron-donating *i*-Pr groups decreased the yield of **2r**, probably owing to the more unstable substrate (Table 2, entries 3–5). Furthermore, a strong electron-withdrawing group (–NO_2) made **1r** less reactive and the corresponding product **2r** was obtained in 55% yield at 40 °C, while a much higher temperature failed to improve the yield and resulted in faster decomposition (Table 2, entry 6).

In summary, a general protocol for the first example of catalytic ring opening/cyclization of aryl oxiranyl ketones and aryl aziridinyl ketones through selective C–C bond cleavage rather than the labile C–O/N bond cleavage under mild conditions has been explored. Synthetically useful aromatic ring-fused pyrans and isoquinolines can be easily prepared in excellent yields, which can undergo further transformations such as alkylation, triflation or elimination. Further studies including asymmetric catalysis, mechanism and enlargement of the scope are ongoing in our laboratory and will be reported in due course.

We are grateful to National Natural Science Foundation of China (21172074), the National Basic Research Program of China (973 Program: 2011CB808600) for financial support.

Notes and references

1 For some recent examples of naturally occurring or biologically active fused pyrans, see: (*a*) R. Jansen, B. Kunze, H. Reichenbach and G. Hofle, *Eur. J. Org. Chem.*, 2002, 917; (*b*) H. J. Reichenbach, *J. Ind. Microbiol. Biotechnol.*, 2001, **27**, 149; (*c*) B. Kunze, J. A. Rolf, G. Hofle and H. J. Reichenbach, *J. Antibiot.*, 2004, **57**, 151; (*d*) H. Zepnik, A. Pahler, U. Schauer and W. Dekant, *Toxicol. Sci.*, 2001, **59**, 59; (*e*) G. Appendino, H. C. Ozen and J. Jakupovic, *Phytochemistry*, 1994, **36**, 531; (*f*) T. Dethoup, L. Manoch, A. Kijjoa, M. Pinto, L. Gales, A. M. Damas, A. M. S. Silva, G. Eaton and W. J. Herz, *J. Nat. Prod.*, 2007, **70**, 1200; (*g*) H. Takahashi, M. Kosada, Y. Watanabe, K. Nakade and Y. Fukuyawa, *Bioorg. Med. Chem.*, 2003, **11**, 1781.

2 For some recent examples of naturally occurring or biologically active isoquolines, see: A. Cappelli, M. Anzini, S. Vomero, P. G. De Benedetti, M. C. Menziani, G. Giorgi and C. Manzoni, *J. Med. Chem.*, 1997, **40**, 2910.

3 For representative approaches to aromatic fused pyrans and pyridines, see: (*a*) S. P. Runyon, L. E. Brieaddy, S. W. Mascarella, J. B. Thomas, H. A. Navarro, J. L. Howard, G. T. Pollard and F. I. Carroll, *J. Med. Chem.*, 2010, **53**, 5290; (*b*) W. M. Abdou, A. F. M. Fahmy and A. A.-A. Kame, *Eur. J. Org. Chem.*, 2002, 1696; (*c*) J. I. Trujillo and M. J. Meyers, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4657; (*d*) R. Aggarwal, A. A. Brikbeck, C. B. de Koning, R. G. F. Giles, I. R. Green, S.-H. Li and F. J. Oosthuizan, *Tetrahedron Lett.*, 2003, **44**, 4535.

4 For metal mediated C–C bond cleavage of oxiranes, see: (*a*) T. Wang and J. Zhang, *Chem.–Eur. J.*, 2011, **17**, 86; (*b*) Z. Chen and L. Wei, *Org. Lett.*, 2011, **13**, 1170; (*c*) T. Wang, C.-H. Wang and J. Zhang, *Chem. Commun.*, 2011, **47**, 5578; (*d*) R. Liu, M. Zhang and J. Zhang, *Chem. Commun.*, 2011, **47**, 12870; (*e*) J. Zhang, Z. Chen, H.-H. Wu and J. Zhang, *Chem. Commun.*, 2012, **48**, 1817.

5 For Lewis acid mediated C–C bond cleavage of aziridines, see: (*a*) L. Li, X. Wu and J. Zhang, *Chem. Commun.*, 2011, **47**, 5049; (*b*) X. Wu, L. Li and J. Zhang, *Chem. Commun.*, 2011, **47**, 7824; (*c*) L. Li and J. Zhang, *Org. Lett.*, 2011, **13**, 5940; (*d*) P. D. Pohlhaus, R. K. Bowman and J. S. Johnson, *J. Am. Chem. Soc.*, 2004, **126**, 2294; (*e*) M. Vaultier and R. Carrie, *Tetrahedron Lett.*, 1978, **14**, 1195.

6 For selective examples, see: (*a*) G.-X. Li and J. Qu, *Chem. Commun.*, 2010, **46**, 2653; (*b*) S. Nagumo, T. Miura, M. Mizukami, I. Miyoshi, M. Imai, N. Kawahara and H. Akita, *Tetrahedron*, 2009, **65**, 9884; (*c*) B.-F. Sun, R. Hong, Y.-B. Kang and L. Deng, *J. Am. Chem. Soc.*, 2009, **131**, 10384; (*d*) R. Marcos, C. Rodríguez-Escrich, C. Herrerías and M. A. Pericàs, *J. Am. Chem. Soc.*, 2008, **130**, 16838; (*e*) Z.-J. Shi and C. He, *J. Am. Chem. Soc.*, 2004, **126**, 5964.

7 Compounds **2a–2j** were obtained with high diastereoselectivities but have enol form issue, but compounds **2k–2m** do not have enol form issue but have low diastereoselectivities, this difference may be caused by the different ring-fused system.

8 (*a*) K. Freter and V. Fuchs, *J. Heterocycl. Chem.*, 1982, **19**, 377; (*b*) C. A. Demerson, L. G. Humber, T. A. Dobson and R. Martel, *J. Med. Chem.*, 1975, **18**, 189; (*c*) D. J. Maloney and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2007, **46**, 7789.

9 CCDC 842104 (**4a**)†.

