Fe-catalyzed highly selective ring expansion of alkynylcyclopropyl alkanols to cyclobutanols†

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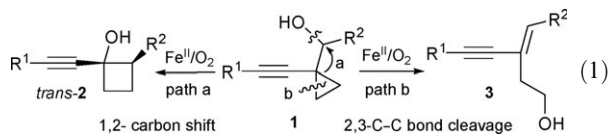
A Fe-catalytic highly selective ring expansion reaction of alkynylcyclopropyl alkanols to alkynylcyclobutanols *via* a 1,2-carbon shift under mild conditions was developed. A new class of homogeneous $FeCl_2/O_2$ catalytic system was employed in these novel transformations.

Transition metal-promoted ring expansion reactions of three-membered carbocycles[1] activated by additional functional groups, such as cyclopropenes,[2,3] methylenecyclopropanes (MCP)[4,5] and vinylcyclopropanes (VCP),[6,7] have been widely used in organic synthesis. Unlike the well-known chemistry of the above three-membered carbocycles, the ring expansion of relatively inactive alkynylcyclopropanes has not been well-developed and therefore has attracted much attention.[8] Pioneering work has been achieved by the groups of Iwasawa,[9a] Toste,[9b] Ardura[9c] and Trost[9d] in the ring expansion of alkynylcyclopropanols catalyzed by Co, Au or Ru catalysts. Moreover, the groups of Schmalz[10a] and Zhang[10b] have reported the Au-catalyzed ring expansion of alkynylcyclopropyl ketones. However, examples of the ring expansion of alkynylcyclopropyl alkanols have not been recorded in the relevant literature so far.



(1)

On the pathway of sustainable chemistry, Fe catalysts[11,12] have been extensively investigated of late because of their low price and environmentally-benign features. However, unlike noble metal catalysts such as Au, Pd, Rh, Ru and Pt,[1–10] to the best of our knowledge, Fe catalysts have not been explored in the ring expansion of carbocycles.[13] Herein, we describe the first highly selective ring expansion reactions of alkynylcyclopropyl alkanols catalyzed by $FeCl_2$ leading to alkynylcyclobutanols (**2**) under mild conditions (path a, eqn (1)). In contrast to the above ring expansion, C–O bond cleavage is involved in this mild and highly selective ring expansion.

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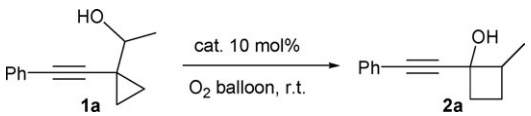
† Electronic Supplementary Information (ESI) available: Further experimental details, characterisation data and spectra. See DOI: 10.1039/b916623h

Table 1 Transition metal-catalyzed ring expansion of **1a**[a]

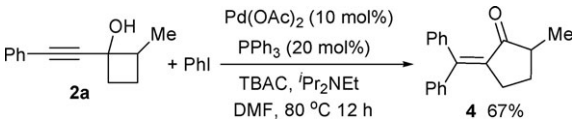


Entry	Catalyst	Solvent[b]	*t*/h	Yield of **2** (%) (*trans*/*cis*)[c]
1	$Yb(OTf)_3$	CH_3NO_2	48	6 (4 : 1)
2	$FeCl_3$	CH_3NO_2	48	33 (9 : 1)
3[d]	$FeCl_3$	CH_3NO_2	72	20 (7 : 1)
4	HCl	CH_3NO_2	48	0
5	$FeCl_3$	Acetone	72	43 (5 : 1)
6	$FeCl_3$	1 : 1	48	47 (5 : 1)
7	**$FeCl_2$**	**1 : 1**	**48**	**78 (9 : 1)**[e]
8[f]	$FeCl_2$	1 : 1	72	Trace
9[g]	$FeCl_2$	1 : 1	48	63 (8 : 1)
10	$FeBr_2$	1 : 1	48	55 (6 : 1)
11	$Fe(acac)_2$	1 : 1	72	0
12	$Fe(OTf)_3$	1 : 1	48	20 (5 : 1)
13	TfOH	1 : 1	48	12 (2 : 1)

[a] **1a** (0.25 mmol), catalyst, solvent (2 mL), r.t. under O_2. [b] 1 : 1 is the volume ratio of CH_3NO_2 to acetone. [c] Isolated yield, the ratio was determined by ^1H NMR calculation; **3a** was not observed. [d] The reaction was carried out at 40 °C. [e] 12% of **1a** was recovered. [f] The reaction was carried out under N_2. [g] The reaction was carried out in air.

We initially chose alkynylcyclopropyl methanol **1a** as the substrate (Table 1). However, no product was obviously observed when catalysts such as AuCl, AgOTf, $PtCl_4$, CuI, $PdCl_2$, $RhCl_3$ or $Sc(OTf)_3$ were applied to catalyze the expected ring expansion reaction. It is noteworthy that alkynylcyclobutanol **2a** (*trans*/*cis* = 4 : 1) was formed using $Yb(OTf)_3$ as the catalyst, despite the very low 6% yield (entry 1, Table 1). The *trans*- and *cis*-isomers could be separated by column chromatography over silica gel. Gratifyingly, Fe catalysts presented a slightly higher catalytic efficiency, giving **2a** in 33% yield (*trans*/*cis* = 9 : 1; entry 2, Table 1), whereas non-cyclic product **3a** was not observed. An increase in reaction temperature inhibited this transformation. After a great deal of screening of different parameters (see the ESI†), we were pleased to find that the ring expansion catalyzed by $FeCl_2$ using a mixture of CH_3NO_2 and acetone (1 : 1) as the solvent at room temperature under O_2 (1 atm) gave the highest efficiency (78% yield; entry 7, Table 1). The yield decreased slightly when the reaction was carried out in air (entries 7 and 9, Table 1). In contrast, only a trace of **2a** was transformed under a nitrogen atmosphere (entries 7 and 8, Table 1). A further investigation indicated that this transformation was not efficiently catalyzed by well-known

Brønsted acid catalysts such as HCl or TfOH (entries 4 and 13, Table 1).

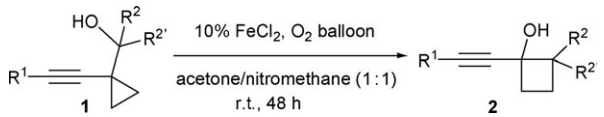


(2)

To confirm the structure of the product, **2a** was employed in the reported transformation with iodobenzene catalyzed by Pd.[14] The expected cyclopentanone, **4**, was formed in 67% yield (eqn (2)),[15] which suggests that the hypothesized structure of **2a** was correct. As cyclobutanols are a common structural unit of natural products, they are of great importance in the area of pharmaceuticals and are also versatile building blocks for further transformations.[16] Our discovered ring expansions may provide an efficient method for the construction of alkynylcyclobutanols.

With the optimized reaction conditions in hand, the scope of the $FeCl_2$-catalyzed ring expansion was subsequently investigated (Table 2). A range of secondary alkanols were tolerated in this ring expansion (entries 1–8, Table 2). When ^{t}Bu was used as a substitutent, *trans*-**2f** was formed with a high diastereoselectively (*trans*-**2f**/*cis*-**2f** >99 : 1), regardless of the low yield due to steric hindrance of the ^{t}Bu group (entry 6, Table 2). Furthermore, when tertiary alkanol **1i** was employed, spirocyclic **2i** was produced (entry 9, Table 2). In contrast, primary alcohol **1j** failed to furnish the desired product (entry 10, Table 2). Notably, both aryl- and alkyl-substituted alkynes perfectly fitted this ring expansion (entries 11–17, Table 2). All *para*-, *meta*- and *ortho*-substituted phenyl alkynyl

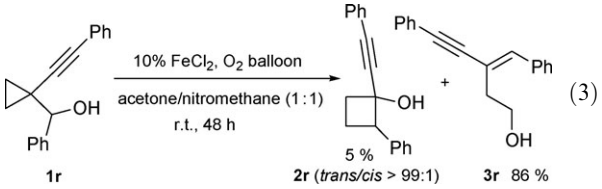
Table 2 The $FeCl_2$-catalyzed ring expansion of **1** *via* a 1,2-carbon shift[a]



Entry	R^1	R^2	$R^{2\prime}$	**1**	Yield of **2** (%) (*trans*/*cis*)[b]
1	Ph	Me	H	**1a**	78 (9 : 1) (**2a**)[c]
2	Ph	Et	H	**1b**	88 (6 : 1) (**2b**)[d]
3	Ph	*n*-Pr	H	**1c**	57 (4 : 1) (**2c**)
4	Ph	*i*-Pr	H	**1d**	49 (6 : 1) (**2d**)
5	Ph	Cyclohexyl	H	**1e**	38 (4 : 1) (**2e**)
6	Ph	*t*-Bu	H	**1f**	14 (>99 : 1) (**2f**)
7	Ph	$PhCH_2CH_2$	H	**1g**	54 (2 : 1) (**2g**)
8	Ph	Bn	H	**1h**	50 (4 : 1) (**2h**)
9	Ph	$-(CH_2)_5-$		**1i**	20 (**2i**)[e]
10	Ph	H	H	**1j**	0
11	2-Me-C_6H_4	Me	H	**1k**	62 (3 : 1) (**2k**)
12	3-Me-C_6H_4	Me	H	**1l**	53 (3 : 1) (**2l**)
13	4-Me-C_6H_4	Me	H	**1m**	60 (3 : 1) (**2m**)
14	4-OMe-C_6H_4	Me	H	**1n**	63 (5 : 1) (**2n**)
15	4-Ph-C_6H_4	Me	H	**1o**	64 (4 : 1) (**2o**)
16	$Ph(CH_2)_3$	*n*-Pr	H	**1p**	75 (4 : 1) (**2p**)[f]
17	*n*-Hexly-	Me	H	**1q**	54 (4 : 1) (**2q**)

[a] **1a** (0.25 mmol), catalyst, solvent (2 mL), r.t. under O_2. [b] Isolated yield; noncyclic **3** were not observed, except for **3i**. [c] 12% of **1a** was recovered. [d] 32% of **1b** was recovered. [e] **3i** was obtained in 31% yield. [f] 25% of **1p** was recovered.

substrates could be smoothly transformed into the desired products, indicating that the steric effect did not significantly affect the reactivity. It is noteworthy that alkyl-substituted alkynyl cyclobutanol **1q** underwent a smooth reaction, producing **2q** in 54% yield (*trans*/*cis* = 4 : 1) (entry 17, Table 2).

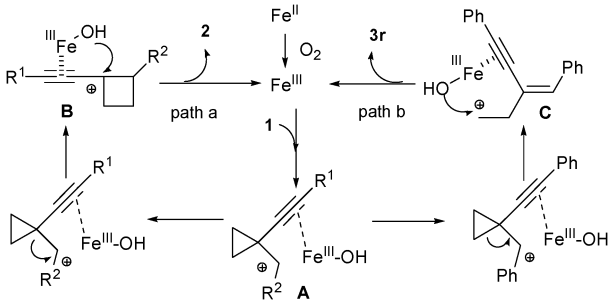


(3)

It is interesting to note that when benzylic alcohol **1r** was used as a substrate, this transformation did not efficiently afford cyclobutanol **2r** (5%, *trans*/*cis* >99 : 1) but instead gave non-cyclic product **3r** in 86% yield (eqn (3)). We envision that the phenyl group could stabilize the cationic intermediate that assists the 2,3-C–C bond cleavage of intermediate **A** to afford non-cyclic cationic intermediate **C** (path b, Scheme 1).

Based on these preliminary results, a plausible mechanism for this transformation is hypothesized, as shown in Scheme 1. Fe^{II} is initially oxidized to Fe^{III},[17] which then reacts with **1** to afford cyclopropylmethyl cation[5a] **A** (path a, Scheme 1). A subsequent 1,2-carbon shift[18] forms intermediate **B** (path a, Scheme 1). Alternatively, 2,3-C–C bond cleavage of cationic intermediate **A** occurs to form intermediate **C** (path b, Scheme 1). Hydroxylation of **B** or **C** then affords product **2** or **3r**, respectively. Diastereoselectivity is possible due to the effect of steric hindrance. After the formation of cationic intermediate **B**, the hydroxyl group favors attack on the face *anti* to that of the methyl group, resulting in the formation of *trans*-**2a** (Fig. 1).

In conclusion, we have developed a new class of homogeneous $FeCl_2/O_2$ catalytic system for ring expansion reactions. A highly selective 1,2-carbon shift of alkynylcyclopropyl alkanols was successfully realized to afford alkynylcyclobutanols under mild conditions. This observation not only expands the application of inexpensive and environmentally benign Fe catalysts, but also provides a new synthetic



Scheme 1 Proposed mechanism for the Fe-catalyzed ring expansion of **1** to alkynylcyclobutanols.

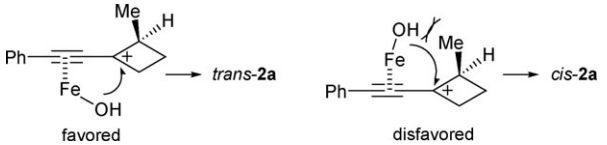


Fig. 1 The steric hindrance effect.

tool for constructing synthetically and medicinally important alkynylcyclobutanols. Further studies on system's the scope and synthetic applications are ongoing in our laboratory.

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