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Divergent synthesis of CF_3-substituted polycyclic skeletons based on control of activation site of acid catalysts†

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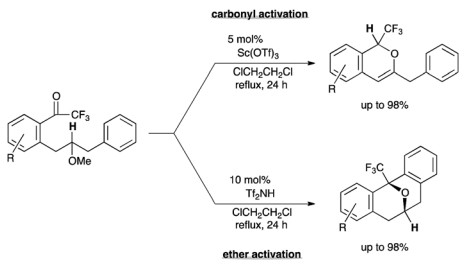
We report a divergent synthesis of CF_3-substituted fused skeletons based on precise control of the activation site through the selection of acid catalysts. When trifluoromethyl ketones with an *ortho*-phenethyl ether group were treated with a catalytic amount of $Sc(OTf)_3$, a hydride shift triggered C(sp^3)–H bond functionalization proceeded to give CF_3-substituted isochromene derivatives by selective activation of the carbonyl group. In sharp contrast, CF_3-substituted bicyclo[3.3.1]-nonanes were obtained exclusively *via* the activation of ether oxygen initiated sequential reactions (nucleophilic attack of carbonyl oxygen, and intramolecular Friedel–Crafts reaction) under strong Brønsted acid catalysis (Tf_2NH).

The efficient synthesis of a large number of structurally different small molecules (diversity-oriented synthesis)[1] has aroused much interest due to its high potential for generating numerous libraries of molecules with diverse skeletons from readily accessible and/or common intermediates. Because of its utility, this strategy is popular among synthetic organic chemists and various effective synthetic methods have been developed in recent years.[2,3]

The discrimination of several functional groups having similar reactivity, namely, ''chemoselective reaction'', is an important tool to satisfy these demands (structure diversity from a common intermediate).[4] In particular, the selective reaction of carbonyl and ketal (or acetal) moieties has stirred up excitement because these functional groups can undergo a wide variety of acid-catalyzed reactions, such as the aldol-type reaction, the Friedel–Crafts reaction, cyanation, and so on. The key to achieving high chemoselectivity between carbonyl and ketal (or acetal) moieties is strongly dependent on the discrimination of the activation site (carbonyl oxygen *vs.* ether oxygen) by an acid catalyst. However, accomplishing selective activation is not an easy task. For example, in a typical Mukaiyama aldol reaction,[5] both carbonyl and ketal moieties are good substrates and well-chosen Lewis acids are required to realize a carbonyl-selective reaction.[6] A ketal (acetal)-selective reaction is sometimes achievable with a relatively simple Lewis acid, such as $RTiCl_3$ (R = alkyl)[7] and TMSOTf;[8] however, examples are limited. Thus, the selective activation of two oxygen moieties, that is, carbonyl oxygen and ether oxygen, is not a trivial issue even in modern synthetic organic chemistry, and the development of a highly selective reaction involving divergent synthesis is strongly desired.

Herein we report a promising reaction to resolve this issue, that is, the divergent synthesis of a CF_3-substituted polycyclic skeleton based on control of the activation site (Scheme 1). The key to realizing this reaction is the careful selection of acid catalysts. When trifluoromethyl ketones with an *ortho*-phenethyl ether group were treated with a catalytic amount of $Sc(OTf)_3$, the hydride shift triggered C(sp^3)–H bond functionalization (internal redox reaction) proceeded to give CF_3-substituted isochromene derivatives by selective activation of the carbonyl group. In sharp contrast, a catalytic amount of Tf_2NH enabled the exclusive formation of CF_3-substituted tetracyclic skeletons *via* an intramolecular tandem process triggered by the activation of ether oxygen (intramolecular nucleophilic attack of carbonyl oxygen followed by Friedel–Crafts reaction).

This protocol was accidentally discovered in a survey of new synthetic transformations by hydride shift triggered C(sp^3)–H bond functionalization (internal redox reaction).[9–11] Because of



Scheme 1 Structure divergent synthesis by precise control of activation site.

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its high potential for biological applications, our group has been interested in the development of a synthetic method for CF_3-substituted polycyclic structures, such as CF_3-substituted isoquinolines.[9h] Along these lines, we also tried to accomplish the synthesis of CF_3-substituted isochromenes starting from CF_3-ketone **1a** bearing a phenethyl ether moiety at the *ortho* position. Surprisingly, effective methods leading to this skeleton are limited in spite of the potent biological activity derived from the hybrid structure of an isochromane or isochromene core and a CF_3 group.[12] At first, **1a** was treated with 5 mol% of $Sc(OTf)_3$, which exhibited excellent catalytic performance in most of the internal redox reactions we reported.[9] Gratifyingly, the reaction proceeded smoothly to afford desired CF_3-substituted isochromene **2a** in excellent chemical yield (94%, entry 1). To find a more effective catalyst, we conducted extensive catalyst screening as shown in Table 1, which offered us quite interesting results. Although other metal triflates, such as $Gd(OTf)_3$, $Yb(OTf)_3$, $Sn(OTf)_2$, and some Lewis acids ($BF_3{\cdot}OEt_2$ and $TiCl_4$) resulted in almost complete recovery of the starting material (entries 2–6), $SnCl_4$ led to the complete consumption of **1a** (entry 7). Interestingly, not only isochromene **2a**, but also unexpected bicyclo[3.3.1]nonane derivative **3a**, whose structure was determined by X-ray analysis, was obtained (**2a**: 39%, **3a**: 44%).[13] Further screening for the catalysts revealed that this unexpected adduct **3a** was obtained selectively with Brønsted acid catalysts (entries 8–11). $TsOH{\cdot}H_2O$ resulted in preferential formation of **3a** over **2a** (**2a**: 5%, **3a**: 49%, entry 8). This low material balance was significantly improved by TfOH and **3a** was obtained in an acceptable chemical yield (72%), accompanied by a small amount of **1a** (12%, entry 9). Exclusive formation of **3a** was achieved with Tf_2NH (entries 10 and 11). Although 5 mol% of Tf_2NH was not sufficient (**3a**: 6%, **1a**: 92%, entry 10), increasing the catalyst loading to 10 mol% dramatically improved the chemical yield to 98% and no trace amount of **1a** was observed (entry 11).

The plausible reaction mechanisms for the formation of **2a** and **3a** are depicted in Fig. 1. Isochromene derivative **2a** is produced by the expected [1,5]-H shift, which is induced by the activation of the carbonyl group by an acid catalyst, followed by cyclization and elimination of MeOH. On the other hand, the intramolecular nucleophilic substitution of methoxy group by the oxygen of CF_3-carbonyl group is the initial event under Brønsted acid catalysis. Subsequent intramolecular Friedel–Crafts reaction/aromatization sequence resulted in the formation of bicyclo[3.3.1]nonane derivative **3a**.

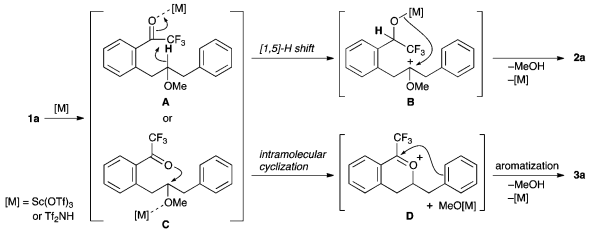
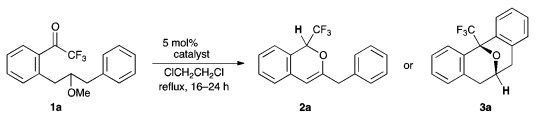


Fig. 1 Reaction mechanisms for the formation of **2a** and **3a**.

The key factor for the change of the reaction course is considered to be the difference of the activation site of the acid catalyst (carbonyl oxygen *vs.* ether oxygen), as illustrated in Fig. 2. The high site selectivity by Brønsted acid catalysts is well explained by considering the difference of the pK_a values of their conjugate acids. In the case of strong Brønsted acid catalysts, the oxygen atom is almost completely protonated. The Brønsted acidity of the conjugate acid of the carbonyl moiety is extremely high compared to that of the ether moiety (*e.g.*, the pK_a value of the conjugate acid of methyl phenyl ketone is −6.2 in H_2O and that of dimethyl ether is −3.8 in H_2O).[14] This difference would induce the preferential activation of ether oxygen, leading to the selective formation of bicyclo[3.3.1]nonane derivative **3a**. The ether-selective activation was also supported by ^{13}C NMR experiments involving mixing of Tf_2NH and substrate **1a** in $CDCl_3$ (Tf_2NH : **1a** = 1 : 1). In contrast to the low-field shift of the peak derived from the carbon adjacent to the methoxy group (83.2 ppm to 83.7 ppm), the peak of carbonyl carbon remained unchanged by mixing with Tf_2NH (183.6 ppm to 183.6 ppm).

The selective activation of the carbonyl moiety with $Sc(OTf)_3$ is ascribed to the high affinity of $Sc(OTf)_3$ for fluorine atom. Mori and coworkers reported a unique chelating effect of $Sc(OTf)_3$ to fluorine atom in the hydrolysis of the acetate moiety adjacent to a difluoromethylene or trifluoromethyl group.[15] This unique high fluorine affinity of $Sc(OTf)_3$ would effectively assist carbonyl activation by double coordination, as depicted in Fig. 2 (*vs.* mono coordination on ether oxygen), and as a result, internal redox reaction would proceed selectively.[16]

Table 1 Screening for catalysts and reaction conditions[a]



		Yield[b] (%)		
Entry	Catalyst	**2a**	**3a**	**1a**
1	$Sc(OTf)_3$	94	—	—
2	$Gd(OTf)_3$	—	—	98
3	$Yb(OTf)_3$	—	—	98
4	$Sn(OTf)_2$	—	—	98
5	$BF_3{\cdot}OEt_2$	—	—	98
6	$TiCl_4$	—	—	98
7	$SnCl_4$	39	44	—
8	$TsOH{\cdot}H_2O$	5	49	9
9	TfOH	12	72	—
10	Tf_2NH	—	6	92
11[c]	Tf_2NH	—	98	—

[a] Unless otherwise noted, all reactions were performed with 0.10 mmol of CF_3-ketone **1a** and 5 mol% catalyst in $ClCH_2CH_2Cl$ (1.0 mL) at refluxing temperature. [b] Isolated yield. [c] 10 mol% catalyst loading.

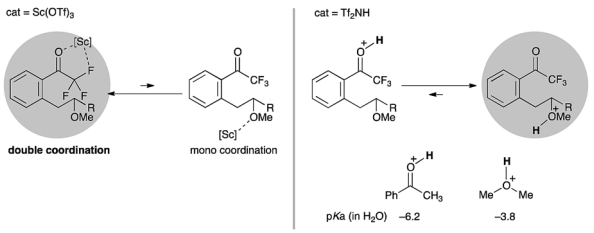


Fig. 2 Rationale for selective activation by changing acid catalysts.

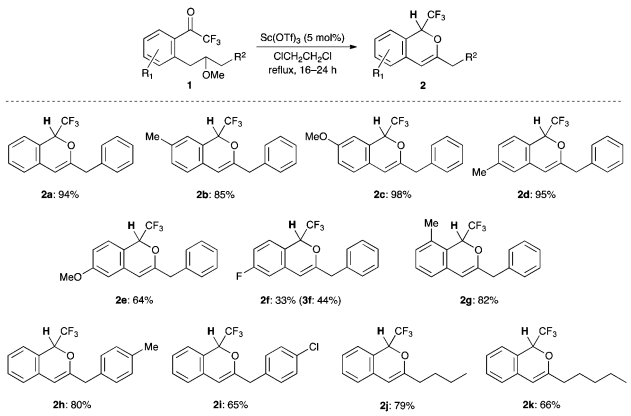


Fig. 3 Substrate scope for isochromene formation.

The substrate scope of the isochromene formation reaction ($Sc(OTf)_3$-catalyzed reaction) is shown in Fig. 3. This reaction was applicable to a wide variety of substrates and the exclusive formation of isochromenes **2a–e** and **2g–i** was observed in many cases. In contrast to the excellent results in the substrate **2b–e** with electron-donating groups on aromatic ring, such as Me and OMe, the electron-withdrawing group (F) substituted substrate **1f** gave disappointing results. The selectivity between isochromene **2f** and bicyclo[3.3.1]nonane derivative **3f** significantly dropped to a moderate level (**2f**:**3f** = 1:1.3) while maintaining chemical yield (77% combined yield). This result is acceptable considering the reduced Lewis basicity of carbonyl oxygen, which is the key factor for the formation of isochromene derivatives, by the strong electron-negative property of fluorine atom. This reaction system was not limited to aryl-type substrates (R_2 = Ar), and aliphatic products **2j** and **2k** (R_2 = propyl and butyl) were also obtained in moderate to good chemical yields (**2j**: 79%, **2k**: 66%).

Fig. 4 illustrates the substrate scope of the Tf_2NH-catalyzed formation of bicyclo[3.3.1]nonane derivatives.[17] Bicyclo[3.3.1]nonane derivatives **3a–f** were obtained in excellent chemical yields under Tf_2NH catalysis (73–98%) and no isochromenes **2a–f** were formed. Unfortunately, a large portion of the starting material was recovered (73%) in the case of 6-Me analog **1g**. This is ascribed to the difficulty of taking the desired conformation for the intramolecular cyclization (see Fig. 1) due to the severe steric repulsion between the CF_3 group and the 6-Me group. The nucleophilicity of terminal aromatic ring was important in this reaction; while 10 mol of Tf_2NH sufficed in the case of **1a** and **1h** with *p*-tolyl group (**3a**: 98%, **3b**: 86%), increased amount of Tf_2NH (20 mol%) was required to achieve satisfactory chemical yield (**3i**: 72%) when the substrate **1i** with *p*-chlorophenyl group was employed.

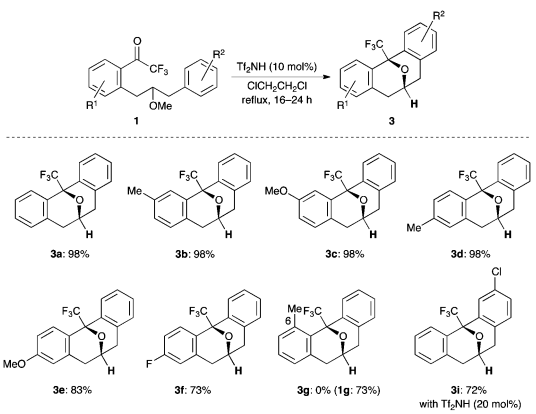


Fig. 4 Substrate scope for bicyclo[3.3.1]nonane formation.

In summary, we have developed a divergent synthesis of CF_3-substituted polycyclic skeletons. The key to achieving structural diversity was the precise control of the activation site (carbonyl oxygen *vs.* ether oxygen) by the selection of acid catalysts. In the case of $Sc(OTf)_3$, selective activation of carbonyl oxygen occurred to give CF_3-substituted isochromene derivatives. In sharp contrast, CF_3-substituted bicyclo[3.3.1]nonane derivatives were obtained exclusively under Tf_2NH catalysis *via* the activation of ether oxygen initiated sequential reactions. This high selectivity was observed in a wide variety of substrates and various CF_3-substituted isochromenes and bicyclo[3.3.1]nonanes were selectively synthesized by changing the acid catalyst. Further investigations of other divergent syntheses based on the control of the activation site are under way in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

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17 Catalyzed asymmetric variant of bicyclo[3.3.1]nonane formation reaction by chiral Brønsted acid failed. The reaction did not proceed completely even when a solution of **1a** in $ClCH_2CH_2Cl$ was treated with 30 mol% of chiral phosphoric acid with *p*-nitrophenyl groups at 3,3′-positions at refluxing temperature for 24 h.

