Reactions of cyclopropyl aryl ketones with α-ketoacetic acids catalyzed by $C_8F_{17}SO_3H$ in fluorous phase†

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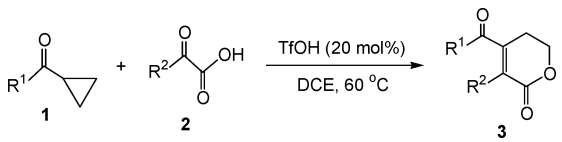
In this paper, we successively apply the "fluorous biphase system" (FBS) technique to the reactions of cyclopropyl aryl ketones with α-ketoacetic acids catalyzed by $C_8F_{17}SO_3H$ (30 mol%) using perfluorodecalin ($C_{10}F_{18}$, *cis*- and *trans*-mixture) and DCE as a co-solvent to give the corresponding products 5,6-dihydropyran-2-ones in good yields. Moreover, the reaction system can be performed for several times without reloading the catalyst and the fluorous solvent.

Recently, we developed a cascade process involving the ring-opening of monoactivated cyclopropanes **1** by H_2O, followed by transesterification reaction and an aldol type reaction mediated by Lewis acid to provide an efficient synthetic protocol for the preparation of 5,6-dihydropyran-2-ones in 1,2-dichloroethane (DCE),[1] which are an important class of compounds because they are skeletal motifs in many natural products possessing important biological activity.[2] During this investigation, we found that when an α-ketoacetic acid **2** was subjected to the reaction instead of an α-ketoester, the corresponding 5,6-dihydropyran-2-one (**3**) can be obtained in good yield in the presence of 20 mol% of TfOH (Scheme 1).[1]

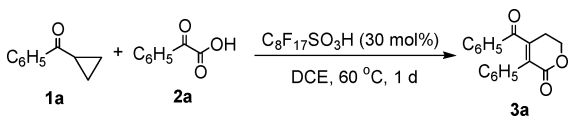


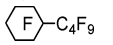
Scheme 1 TfOH-catalyzed reaction of monoactivated cyclopropanes **1** with α-ketoacetic acid **2**.

Perfluorocarbon fluids, especially perfluoroalkanes, esters and amines have some unique properties that make them attractive alternatives for conventional organic solvents.[3] They have limited miscibility with conventional organic solvents. Compounds functionalized with perfluorinated groups often dissolve preferentially in fluorous solvents. This character can be used to extract fluorous components from reaction mixtures.[4] The "fluorous biphase system" (FBS) technique was first reported by Horvath and Rabai.[4a] It allows the catalysis to be performed in a two-phase reaction mixture consisting of a perfluorinated solvent and an organic solvent. Therefore, by introducing a perfluorinated catalyst in a catalytic reaction system, the catalyst is solubilized and simultaneously immobilized in the "fluorous phase". By elevating the temperature the biphasic system forms a homogenous solution and the catalytic process can take place. Cooling down the reaction mixture leads to the reformation of two separate phases. Therefore, the recovery of the perfluoro-tagged catalyst can be achieved by simple phase separation along with the product isolation.[5] The isolation and recovery of perfluorinated components can be accomplished not only by a phase separation of immiscible liquid layers but also by solid–liquid extraction using a perfluorinated non-polar stationary phase.[4a]

Based on this concept, we attempted the application of fluorous phase separation technique to the syntheses of 5,6-dihydropyran-2-ones from cyclopropyl aryl ketones and α-ketoacetic acids using a perfluorinated acid as a catalyst. After several trials and errors, we ultimately found that the commercially available heptadecafluorooctanesulfonic acid ($C_8F_{17}SO_3H$, 30 mol%) is fairly effective for the reaction. Next, we screened several combinations of DCE with different fluorous solvents, such as perfluorohexane (C_6F_{14}), perfluoro(*n*-butylcyclohexane) ($C_{10}F_{20}$), perfluorotributylamine ($N(C_4F_9)_3$) and perfluorodecalin ($C_{10}F_{18}$, *cis*- and *trans*-mixture) in this FBS catalytic system with the reaction of **1a** with **2a**. The results are summarized in Table 1. During the reaction process, we observed at 60 °C (upon heating), that the organic phase is miscible with fluorous phase to give a homogeneous phase and the corresponding 5,6-dihydropyran-2-one (**3a**) can be smoothly formed, although at 20 °C (room temperature), it became a biphasic system (Fig. 1). However,

Table 1 Reactions of **1a** with **2a** in different fluorous solvents



Entry	Solvent	Yield (%)[a] 3a
1	C_6F_{14}	10
2		68
3	$N(C_4F_9)_3$	73
4		92

[a] Isolated yields.

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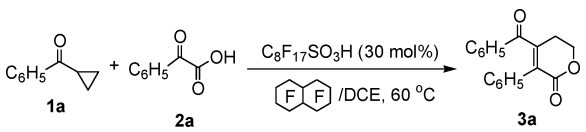
Fig. 1

the loss of fluorous solvent was very serious at 60 °C and **3a** was obtained in lower yield when using volatile perfluorohexane (C_6F_{14}) (bp 58 °C) (Table 1, entry 1). The combination of DCE and perfluoro(*n*-butylcyclohexane) ($C_{10}F_{20}$) gave moderate yield of **3a** under the same reaction conditions (Table 1, entry 2). The co-solvent system of DCE and perfluorotributylamine (bp 178 °C) produced the corresponding product **3a** in 73% yield under identical conditions (Table 1, entry 3). However, the basicity of $N(C_4F_9)_3$ could bring about the lose of the perfluorinated acid and subsequently make the catalytic system become ineffective in the recycle of the fluorous solvent. Perfluorodecalin ($C_{10}F_{18}$, *cis*- and *trans*-mixture) was the best fluorous solvent for this reaction to give the corresponding **3a** in the highest yield of 92% (Table 1, entry 4). This fluorous phase is not volatile (bp 142 °C).

The perfluorodecalin fluorous phase containing $C_8F_{17}SO_3H$ catalyst can be easily isolated by simple separation of the fluorous phase. This catalytic phase can be reused for five times to give similar results without reloading fluorous solvent and the catalyst (Table 2, entries 1–5). However, in order to attain a good yield of **3a** in the fifth cycle of the reaction of cyclopropyl phenyl ketone **1a** with **2a**, the reaction time must be prolonged to 3 d in the bisphasic method, presumably due to the partial leaching of $C_8F_{17}SO_3H$ during the reaction because the DCE phase can dissolve $C_8F_{17}SO_3H$ and it is deeply colored during the recycle (Table 2, entry 5 and Fig. 1). After removal of the solvent under

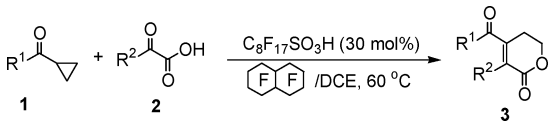
Table 2 Recycling of catalyst in the reaction of **1a** with **2a** using FBS



Run	Reaction time/d	Yield (%)[a] 3a	TON
1	1	92	3.1
2	1	90	3.0
3	1	85	2.8
4	1	78	2.6
5	3	84	2.8

[a] Isolated yields.

Table 3 Reaction of cyclopropyl aryl ketones **1a–f** with various α-ketoacetic acids using FBS



Entry	R^1	R^2; reaction time/d	Yield (%)[a] 3
1	**1a**, C_6H_5	**2a**, C_6H_5; 1	**3a**, 92
2	**1a**, C_6H_5	**2b**, *p*-MeC_6H_4; 3	**3b**, 80
3	**1a**, C_6H_5	**2c**, *p*-$MeOC_6H_4$; 3	**3c**, 71
4	**1a**, C_6H_5	**2d**, *p*-ClC_6H_4; 1	**3d**, 92
5	**1a**, C_6H_5	**2e**, Me; 1	**3e**, 94
6	**1b**, *p*-FC_6H_4	**2e**, Me; 2	**3f**, 71
7	**1c**, *p*-MeC_6H_4	**2e**, Me; 2	**3g**, 93
8	**1d**, *o*,o-$Me_2C_6H_3$	2e, Me; 2	**3h** 86
9	**1e**, *p*-$MeOC_6H_4$	**2e**, Me; 5	**3i**, 89
10	**1f**, thiophen-2-yl	**2e**, Me; 5	**3j**, 56

[a] Isolated yields.

reduced pressure, part of $C_8F_{17}SO_3H$ was isolated by column chromatography (SiO_2).

Using $C_8F_{17}SO_3H$ as a catalyst and the combination of perfluorodecalin ($C_{10}F_{18}$, *cis*- and *trans*-mixture) and DCE as a co-solvent, the reactions of a series of cyclopropyl aryl ketones **1** and various α-ketoacetic acids **2** were examined as well. As shown in Table 3, starting from cyclopropyl phenyl ketone (**1a**) and various α-ketoacetic acids **2**, the corresponding 5,6-dihydropyran-2-ones **3a–e** were obtained in moderate to excellent yields (Table 3, entries 1–5). In addition, from the reactions of **1a** with various aryl α-ketoacetic acids, electronic effects were clearly observed. In general, aryl α-ketoacetic acids having no substituents or an electron-withdrawing group on the aromatic ring were more reactive to afford the corresponding products **3** in higher yields (Table 3, entries 1 and 4). For aryl α-ketoacetic acids **2b** and **2c**, bearing an electron-donating substituent (methyl or methoxyl group) on the aromatic ring, the corresponding products **3** were obtained in lower yields even after a prolonged reaction time (Table 3, entries 2 and 3). The electronic trend in the reaction is consistent with the α-ketoacetic acid's role, as an aldol acceptor, in the reaction process. As for aliphatic α-ketoacetic acid **2e**, the reaction of ethyl pyruvate (**2e**) with **1a** proceeded smoothly to afford **3e** in 94% yield (Table 3, entry 5). Furthermore, we also examined the reactions of a variety of cyclopropyl aryl ketones with ethyl pyruvate **2e** under these optimized conditions (Table 3, entries 5–10). A series of 4-substituted-3-methyl-5,6-dihydropyran-2-ones were obtained in good to excellent yields. Similar electronic effects were also observed as illustrated in Table 3. For cyclopropyl aryl ketones bearing electron-rich aryl group, such as cyclopropyl 4-methoxyphenyl ketone (**1e**) and thiophene-derived substrate **1f**, a prolonged reaction time (5 d) was required and the corresponding products **3i** and **3j** were obtained in 89 and 56% yields, respectively (Table 3, entries 9 and 10). The structures of all products were determined by ^1H NMR spectroscopic data, which are consistent with those reported in our previous paper.[1] NMR data can be found in the ESI.†

In summary, we reported in this paper a new process to carry out the reaction of cyclopropyl aryl ketones and α-ketoacetic acids in fluorous phase. Using perfluorodecalin ($C_{10}F_{18}$, *cis*- and *trans*-mixture) and DCE as a co-solvent, $C_8F_{17}SO_3H$ as a catalyst, the reactions of cyclopropyl aryl ketones and α-ketoacetic acids can be repeated several times without reloading fluorous solvent and the catalyst with the similar yields of 5,6-dihydropyran-2-ones. By this technology, the catalytic phase can be easily recovered and can be reused for the next reaction without any treatment. Since 30 mol% of perfluorinated acid was used a catalyst, which is certainly beyond the usual definition of catalytic system, this system might be described as a unique recyclable reagent. Further investigations to develop other types of reactions in fluorous phase with perfluorinated acids are now in progress.

Experimental

General remarks

^{1}H NMR spectra were recorded on a Varian Mercury 300 spectrometer for solution in $CDCl_3$ with tetramethylsilane (TMS) as internal standard; *J*-values are in Hz. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF254 silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel.

Typical reaction procedure for reaction of cyclopropyl aryl ketone with α-ketoacetic acid catalyzed by $C_8F_{17}SO_3H$ in fluorous phase

To a solution of $C_8F_{17}SO_3H$ (45 mg, 0.09 mmol, 30 mol%) in perfluorodecalin ($C_{10}F_{18}$, *cis*- and *trans*-mixture) (solvent, 1.0 mL) was added cyclopropyl aryl ketone (**1**, 0.3 mmol), α-ketoacetic acid (**2**, 0.3 mmol) and DCE (solvent, 1.0 mL). Then, the mixture was stirred at 60 °C for the necessary time. The fluorous layer was separated for the next reaction. The reaction mixture (organic layer) was washed by water (5 mL) and extracted with dichloromethane (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (EtOAc–hexane = 1 : 4) to give the corresponding product **3**.

4-Benzoyl-3-phenyl-5,6-dihydropyran-2-one (3a). This compound was obtained as a white solid, yield: 77 mg, 92%. This is a known compound.[1] ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 2.87 (t, J = 6.3 Hz, 2H, CH_2), 4.63 (t, J = 6.3 Hz, 2H, OCH_2), 7.10–7.13 (m, 3H, Ar), 7.20–7.23 (m, 2H, Ar), 7.26–7.31 (m, 2H, Ar), 7.40–7.45 (m, 1H, Ar), 7.66–7.69 (m, 2H, Ar).

4-Benzoyl-3-*p*-tolyl-5,6-dihydropyran-2-one (3b). This compound was obtained as a red oil, yield: 70 mg, 80%. This is a known compound.[1] ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 2.17 (s, 3H, CH_3), 2.87 (t, J = 6.3 Hz, 2H, CH_2), 4.64 (t, J = 6.3 Hz, 2H, OCH_2), 6.93 (d, J = 8.1 Hz, 2H, Ar), 7.11 (d, J = 8.1 Hz, 2H, Ar), 7.31 (t, J = 7.5 Hz, 2H, Ar), 7.46 (t, J = 7.5 Hz, 1H, Ar), 7.70 (d, J = 7.8 Hz, 2H, Ar).

4-Benzoyl-3-(4-methoxyphenyl)-5,6-dihydropyran-2-one (3c). This compound was obtained as a pale red oil, yield: 66 mg, 71%. This is a known compound.[1] ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 2.88 (t, J = 6.0 Hz, 2H, CH_2), 3.66 (s, 3H, OCH_3), 4.64 (t, J = 6.0 Hz, 2H, OCH_2), 6.65 (d, J = 8.1 Hz, 2H, Ar), 7.17 (d, J = 8.1 Hz, 2H, Ar), 7.30 (t, J = 7.5 Hz, 2H, Ar), 7.42 (t, J = 6.9 Hz, 1H, Ar), 7.69 (d, J = 7.4 Hz, 2H, Ar).

4-Benzoyl-3-(4-chlorophenyl)-5,6-dihydropyran-2-one (3d). This compound was obtained as a white solid, yield: 86 mg, 92%. This is a known compound.[1] ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 2.88 (t, J = 6.0 Hz, 2H, CH_2), 4.65 (t, J = 6.0 Hz, 2H, OCH_2), 7.10 (dd, J = 9.0 Hz, J = 2.1 Hz, 2H, Ar), 7.17 (dd, J = 9.0 Hz, J = 2.1 Hz, 2H, Ar), 7.33 (t, J = 7.2 Hz, 2H, Ar), 7.48 (t, J = 7.2 Hz, 1H, Ar), 7.67–7.70 (m, 2H, Ar).

4-Benzoyl-3-methyl-5,6-dihydropyran-2-one (3e). This compound was obtained as a yellow oil, yield: 61 mg, 94%. This is a known compound.[1] ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 1.81 (s, 3H, CH_3), 2.70 (t, J = 6.6 Hz, 2H, CH_2), 4.54 (t, J = 6.6 Hz, 2H, OCH_2), 7.53–7.58 (m, 2H, Ar), 7.67–7.70 (m, 1H, Ar), 7.89–7.93 (m, 2H, Ar).

4-(4-Fluorobenzoyl)-3-methyl-5,6-dihydropyran-2-one (3f). This compound was obtained as a white solid, yield: 50 mg, 71%. This is a known compound.[1] ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 1.81 (t, J = 1.5 Hz, 3H, CH_3), 2.70 (dt, J = 1.5 Hz, J = 6.0 Hz, 2H, CH_2), 4.55 (t, J = 6.0 Hz, 2H, OCH_2), 7.21–7.26 (m, 2H, Ar), 7.93–7.98 (m, 2H, Ar).

3-Methyl-4-(4-methylbenzoyl)-5,6-dihydropyran-2-one (3g). This compound was obtained as a white solid, yield: 64 mg, 93%. This is a known compound.[1] ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 1.80 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.69 (dt, J = 1.2 Hz, J = 6.0 Hz, 2H, CH_2), 4.53 (t, J = 6.0 Hz, 2H, OCH_2), 7.34 (d, J = 7.8 Hz, 2H, Ar), 7.80 (t, J = 7.8 Hz, 2H, Ar).

4-(3,5-Dimethylbenzoyl)-3-methyl-5,6-dihydropyran-2-one (3h). This compound was obtained as a white solid, yield: 63 mg, 86%. This is a known compound.[1] ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 1.80 (s, 3H, CH_3), 2.40 (s, 6H, CH_3), 2.69 (dt, J = 1.8 Hz, J = 6.0 Hz, 2H, CH_2), 4.54 (t, J = 6.0 Hz, 2H, OCH_2), 7.30 (s, 1H, Ar), 7.49 (s, 2H, Ar).

4-(4-Methoxybenzoyl)-3-methyl-5,6-dihydropyran-2-one (3i). This compound was obtained as a pale oil, yield: 66 mg, 89%. This is a known compound.[1] ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 1.80 (t, J = 1.8 Hz, 3H, CH_3), 2.69 (dt, J = 1.8 Hz, J = 6.3 Hz, 2H, CH_2), 3.92 (s, 3H, OCH_3), 4.53 (t, J = 6.3 Hz, 2H, OCH_2), 7.01 (dd, J = 7.2 Hz, J = 2.1 Hz, 2H, Ar), 7.88 (dd, J = 7.2 Hz, J = 2.1 Hz, 2H, Ar).

3-Methyl-4-(thiophene-2-carbonyl)-5,6-dihydropyran-2-one (3j)[1]. This compound was obtained as a white solid, yield: 37 mg, 56%. This is a known compound.[1] ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ 1.89 (d, J = 1.8 Hz, 3H, CH_3), 2.73 (dt, J = 1.8 Hz, J = 6.0 Hz, 2H, CH_2), 4.53 (t, J = 6.0 Hz, 2H, OCH_2), 7.22 (dd, J = 5.1 Hz, J = 3.9 Hz, 1H, Ar), 7.67 (dd, J = 3.9 Hz, J = 1.2 Hz, 1H, Ar), 7.67 (dd, J = 5.1 Hz, J = 1.2 Hz, 1H, Ar).

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