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Mannich-type reactions of aromatic aldehydes, anilines, and methyl ketones in fluorous biphase systems created by rare earth (III) perfluorooctane sulfonates catalysts in fluorous media

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Abstract

Rare earth (III) perfluorooctane sulfonates ($RE(OPf)_3$) catalyze the three-component Mannich-type reactions of different ketones with various aromatic aldehydes and aromatic amines in fluorous media to give various β-arylamino ketones in good yields. By simple separation of the fluorous phase containing only catalyst, reaction can be repeated several times.

Keywords: Mannich reaction; Fluorous biphasic catalysis; Rare earth (III) perfluorooctanesulfonates; Perfluorocarbon

1. Introduction

Mannich and related reactions provide one of the most basic and useful methods for synthesis of β-amino carbonyl compounds, which constitute various pharmaceuticals, natural products, and versatile synthetic intermediates [1]. However, due to the drastic reaction conditions, severe side-reactions and substrate limitations, the classical intermolecular Mannich reaction is plagued by a number of serious disadvantages [1]. The Lewis acid-catalyzed condensation of silyl enol ethers or silyl ketene acetals to pre-formed imines is an excellent variant of the classical Mannich reaction [2]. However, this Lewis acid-catalyzed three-component reaction of aldehydes, amines, and silyl enolates in the same vessel has to be carried out under strict anhydrous conditions because many of the imines are unstable in water. In addition, most Lewis acids cannot be used in this one-pot reaction because of the presence of free amines and water produced in the imine formation. From atom economical and environmental points of view, therefore, it is desirable to develop a new efficient system for Mannich-type reactions in which the parent carbonyl compounds are directly used and environment-friendly solvent is used as a solvent [3].

Kobayashi reported that dodecylbenzenesulfonic acid [4] or supported sulfonic acid [5] can catalyze the Mannich reaction of ketones with aldehydes and amines in good to excellent yield in water. However, the recovery of the catalyst from aqueous solution in such protocol is not an economic process. Quite recently, it was found that ytterbium triflate ($Yb(OTf)_3$) was a highly efficient catalyst for the same type of reaction [6]. However, reusing of this catalyst required tedious work up procedures such as filtration, purification and drying.

Recently, a new kind of Lewis acids of rare earth (III) perfluorooctanesulfonates ($RE(OSO_2C_8F_{17})_3$, $RE(OPf)_3$, RE = Sc, Y, La–Lu) has been of special interest in that they have characteristic features such as low hygroscopicity, ease of handling, robustness for the recycling using and high solubility in fluorous solvent [7]. On the other hand, perfluorocarbon solvents, one of most important environment-friendly solvents, especially perfluoro-alkanes have some unique properties which make them attractive alternatives for conventional organic solvents [8]. The compounds functionalized with perfluorinated groups often dissolve preferentially in fluorous solvents and this property can be used to extract fluorous components from reaction mixtures [9]. Shi et al. used $RE(OPf)_3$ as catalysts in the reaction of arylaldehydes with aromatic amines and (1-methoxy-2-methylpropenyloxy)-trimethylsilane in fluorous media [2i]. As a part of our studies to explore the utility of lanthanide perfluorooctanesulfonates catalyzed reactions in fluorous solvents [10], we decided to

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investigate $RE(OPf)_3$-catalyzed the three-component one-pot Mannich-type reactions of aldehydes, amines, and ketones.

2. Results and discussion

The reaction of benzaldehyde, aniline, and acetophenone in the presence $RE(OPf)_3$ in fluorous media was selected as a model reaction. Based on the general concept of fluorous phase chemistry [9], we also used toluene as a co-solvent for the reaction. It was found that, upon heating at 60 °C, the organic phase is miscible with fluorous phase and the reaction system became homogenous. Among these catalysts (Table 1, entries 1–16), $Sc(OPf)_3$ and $Yb(OPf)_3$ are the most efficient catalysts for the reaction. This would be ascribed to the higher Lewis acidity of $Sc(OPf)_3$ and $Yb(OPf)_3$ than those of other $RE(OPf)_3$ [11]. The control experiment elucidates that no product of Mannich reaction could be obtained in the absence of catalyst and fluorous solvent. In addition, we found that a catalyst loading of only 0.4 mol% was required when using fluorous phase technology, which is more effective than the 5 mol% of $Yb(OTf)_3$ required to catalyzed the reaction. Next, the effect of fluorous solvents such as, perfluorohexane (C_6F_{14}), perfluoromethylcyclohexane (C_7F_{14}), perfluorotoluene (C_7F_8), perfluorooctane (C_8F_{18}), perfluorooctyl bromide ($C_8F_{17}Br$), and perfluorodecalin ($C_{10}F_{18}$, *cis* and *trans*-mixture) was examined for the Mannich reaction (Table 1, entries 16–21). The results showed that yields of the desired products in perfluorooctane (C_8F_{18}) and perfluorooctyl bromide ($C_8F_{17}Br$) are lower than other solvents. The fluorous solvents perfluorohexane (C_6F_{14}) and perfluorotoluene (C_7F_8)

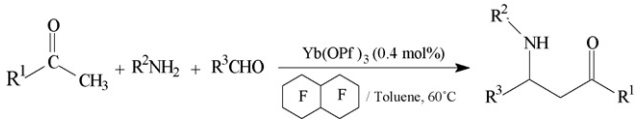
Table 1
Reaction of benzaldehyde, aniline, and acetophenone

Entry	Catalyst	Fluorous solvent	Yield (%)[a]
1	$Sc(OPf)_3$	$C_{10}F_{18}$[b]	96
2	$Y(OPf)_3$	$C_{10}F_{18}$	82
3	$La(OPf)_3$	$C_{10}F_{18}$	73
4	$Ce(OPf)_3$	$C_{10}F_{18}$	82
5	$Pr(OPf)_3$	$C_{10}F_{18}$	71
6	$Nd(OPf)_3$	$C_{10}F_{18}$	85
7	$Sm(OPf)_3$	$C_{10}F_{18}$	73
8	$Eu(OPf)_3$	$C_{10}F_{18}$	85
9	$Gd(OPf)_3$	$C_{10}F_{18}$	79
10	$Tb(OPf)_3$	$C_{10}F_{18}$	70
11	$Dy(OPf)_3$	$C_{10}F_{18}$	79
12	$Ho(OPf)_3$	$C_{10}F_{18}$	88
13	$Er(OPf)_3$	$C_{10}F_{18}$	91
14	$Tm(OPf)_3$	$C_{10}F_{18}$	79
15	$Lu(OPf)_3$	$C_{10}F_{18}$	78
16	$Yb(OPf)_3$	$C_{10}F_{18}$	96
17	$Yb(OPf)_3$	$CF_3(CF_2)_4CF_3$	90
18	$Yb(OPf)_3$	$C_6F_5CF_3$	98
19	$Yb(OPf)_3$	$C_6F_{13}CF_3$	95
20	$Yb(OPf)_3$	$CF_3(CF_2)_6CF_3$	84
21	$Yb(OPf)_3$	$CF_3(CF_2)_6CF_2Br$	82

Reaction conditions: benzaldehyde (0.01 mol), aniline (0.01 mol), acetophenone (0.01 mol), $RE(OPf)_3$ (0.4 mol%), fluorous solvent (2 ml), toluene (4 ml), 60 °C.

[a] Isolated yields.

[b] .



Scheme 1.

are in fact miscible with aromatic compounds at room temperature. Thus, it is impossible to recover fluorous phase by phase-separation. At the same time, we found that during repeated Mannich reactions the loss of fluorous solvent is very serious when using perfluoromethylcyclohexane (C_7F_{14}) as a fluorous solvent because it is very volatile (bp 76 °C). Therefore, perfluorodecalin ($C_{10}F_{18}$, *cis* and *trans*-mixture) is the best fluorous solvent for the reaction.

In order to seek out a practical, useful 'one-pot' Manncih reaction process, we decided to use the relatively cheap and similarly active catalyst $Yb(OPf)_3$ and perfluorodecalin ($C_{10}F_{18}$, *cis* and *trans*-mixture) as a fluorous solvent for reaction of a variety of acetophenones, aromatic aldehydes, and aromatic amines (Scheme 1). The reaction proceeds typically through the imine formation of the aldehyde and the amine, protonation of the imine, and the attack of the enol derived from the ketone to the protonated imine. The following features are noteworthy in these reactions. (1) The reaction was not affected by the electronic effect of substituent groups of aniline. When *o*-substituted anilines were performed as substrate, the reaction gave no desired product due to the hindrance of *ortho* substituents. (2) In the investigation of various benzaldehydes, it was found that *p*-methylbenzaldehyde is most active for the reaction. This is because substituents on benzaldehyde have remarkable influence on the intermediate '$RC_6H_4C^+HNHC_6H_5$' derived from the aldehyde and the amine: rich electron-donating substituents such as '–OCH_3' result in low stability of the intermediate, furthermore, difficulty to formation of the intermediate; rich electron-withdrawing ones such as '–NO_2' degrades the activity of the intermediate which does not favor the following reaction. Similarly, the reaction suffer remarkably from the hindrance of *ortho* substituents. (3) The reactivity order of the aromatic amines is *p*-nitroacetophenone > *p*-chloroacetophenone > acetophenone > *p*-methyl-acetophenone, indicating the importance of the electronic nature of the aromatic ketone.

In order to ascertain the scope and limitation of this catalyzed Mannich reaction, the use of the catalytic systems was extend to the reaction of aliphatic ketones, various aldehydes and amines (Scheme 1; Table 2). In the case of cyclopentanone and cyclohexanone, the reactions were finished within 12–24 h and good yields (76–94%) of β-amino ketones were obtained, regardless of the kind of substituent group on benzaldehydes and anilines. The purity of the products thus obtained was consistently high, probably because the perflates-catalyzed reactions took place under neutral conditions, as opposed to the acid system, which may result in decomposition of Mannich base at 60 °C or higher reaction temperature [6]. Notably, not only benzaldehyde but also hetero-aromatic

Table 2
Mannich-type reactions of different ketones with various aromatic aldehydes and aromatic amines

Entry	Ketone (R^1)	Amine (R^2)	Aldehyde (R^3)	Time (h)	Yield (%)[a]
1	Ph	4-$O_2NC_6H_4$–	Ph	8	96
2	Ph	4-$CH_3C_6H_4$–	Ph	16	87
3	Ph	4-ClC_6H_4–	Ph	12	92
4	Ph	4-$CH_3OC_6H_4$–	Ph	14	89
5	Ph	4-$HOOCC_6H_4$–	Ph	10	90
6	Ph	4-$CH_3CH_2OOCC_6H_4$–	Ph	10	91
7	Ph	3-$O_2NC_6H_4$–	Ph	10	94
8	Ph	2-$O_2NC_6H_4$–	Ph	24	–
9	Ph	2-ClC_6H_4–	Ph	24	–
10	Ph	Ph	4-$CH_3C_6H_4$–	12	99
11	Ph	Ph	4-$CH_3OC_6H_4$–	12	89
12	Ph	Ph	4-$O_2NC_6H_4$–	12	81
13	Ph	Ph	4-ClC_6H_4–	12	92
14	Ph	Ph	2-HOC_6H_4–	12	–
15	4-$CH_3C_6H_4$–	Ph	Ph	12	86
16	4-$O_2NC_6H_4$–	Ph	Ph	12	99
17	4-ClC_6H_4–	Ph	Ph	12	97
18	Cyclohexanone	Ph	Ph	16	88
19	Cyclohexanone	4-$CH_3C_6H_4$–	Ph	18	91
20	Cyclohexanone	4-ClC_6H_4–	Ph	18	93
21	Cyclohexanone	4-ClC_6H_4–	4-$CH_3OC_6H_4$–	18	84
22	Cyclohexanone	Ph	2-Furfural	24	86
23	Cyclohexanone	Ph	2-Pyridinecarbaldehyde	24	81
24	Cyclopentanone	Ph	Ph	18	82
25	Cyclopentanone	4-ClC_6H_4–	Ph	12	83
26	Cyclopentanone	3-$O_2NC_6H_4$–	Ph	16	78
27	Cyclopentanone	4-ClC_6H_4–	4-$CH_3OC_6H_4$–	18	76
28	Propiophenone	4-ClC_6H_4–	Ph	32	72
29	CH_3CH_2–	4-$CH_3C_6H_4$–	Ph	32	81
30	$CH_3CH_2CH_2$–	Ph	Ph	24	79
31	CH_3–	4-$CH_3C_6H_4$–	$(CH_3)_2CHCH_2$–	48	–
32	Ph	$CH_3(CH_2)_2CH_2$–	Ph	36	–
33	Ph	$PhCH_2$–	Ph	36	–

Reaction conditions: aldehyde (0.01 mol), amine (0.01 mol), ketone (0.01 mol), $Yb(OPf)_3$ (0.4 mol%), perfluorodecalin (2 ml), toluene (4 ml), 60 °C, 12 h.
[a] Isolated yields.

aldehydes such as 2-furfural and 2-pyridine-carbaldehyde worked well for the Mannich reaction with cyclohexanone and aniline. The reaction of propiophenone with *p*-chloroaniline and benzaldehyde gave corresponding β-amino ketones in 72% yield. In the reactions of unsymmetrical aliphatic ketones such as 2-butanone and 2-pentanone, the adduct aminoalkylated at C_1 was formed preferentially. The catalyst $Yb(OPf)_3$ system appeared to show no catalytic activity for the reaction in which the aliphatic amines such as butylamine and benzylamine, and aliphatic aldehydes such as isovaleraldehyde were performed as substrates.

When the reaction was finished, the reaction mixture was cooled to room temperature. The fluorous phase with $RE(OPf)_3$ catalyst separates from the organic layer and returns to the bottom layer [8]. Based on the ^{19}F NMR and UV–vis spectroscopic data and GC–MS, no loss of catalyst or fluorous solvent to the organic phases can be detected. Use of fluorous phase, recycled without purification was equally effective. For example, in the $Yb(OPf)_3$-catalyzed reaction of acetophenone, aniline, and benzaldehyde, the yields of reaction from the first run to the fifth run are 96, 94, 94, 93, and 92%, respectively.

3. Experimental

3.1. General

MPs were obtained with Shimadzu DSC-50 thermal analyzer. IR spectra were recorded on a Bumem MB154S infra-red analyzer. ^1H NMR and ^{19}F NMR spectra were measured on Bruker Advance RX500. UV–vis spectra was achieved by UV-1601 apparatus. Mass spectra were recorded with a Saturn 2000GC/MS instrument. Inductively coupled plasma (ICP) spectra were measured on Ultima2C apparatus. Elemental analyses were performed on a Yanagimoto MT3CHN corder. Commercially available reagents were used without further purification.

3.2. Typical procedure for preparation of $RE(OPf)_3$

$RE(OPf)_3$ was prepared according to the literatures [10]. (Method A): The mixture of PfOH solution (aqueous) and $YbCl_3{\cdot}6H_2O$ solution (aqueous) was stirred at room temperature. (Method B): The mixture of PfOH solution (aqueous) and Yb_2O_3 powder was stirred at boiling. In both methods, the

resulting gelatin-like solid was collected, washed and dried at 150 °C in vacuo to give a white solid, which does not have a clear melting point up to 500 °C, but shrinks around 380 and 450 °C. IR (KBr) υ 1237 (CF_3), 1152 (CF_2), 1081 (SO_2), 1059 (SO_2), 747 (S–O) and 652 (C–S) cm^{-1}. ICP: calcd for $C_{24}O_9F_{51}S_3Yb$: Yb, 10.30%. Found: Yb, 9.88%. Anal. calcd for $C_{24}O_9F_{51}S_3Yb{\cdot}H_2O$: C, 17.21%; H, 0.10%. Found: C, 17.03%; H, 0.18%.

3.3. Typical procedure for the Mannich reaction of aldehydes, ketones, and amines

A mixture of $Yb(OPf)_3$ (34 mg, 0.02 mmol), benzaldehyde (0.50 ml, 5 mmol), acetophenone (0.58 ml, 5 mmol), aniline (0.46 ml, 5 mmol), toluene (4 ml), and perfluorodecalin ($C_{10}F_{18}$, *cis* and *trans*-mixture, 2.0 ml). The mixture was stirred at 60 °C for 12 h. Then, the fluorous layer on the bottom was separated for the next condensation. The reaction mixture (organic phase) was cooled to 0 °C. The crystalline product was further washed cold ethanol (10 ml) and dried to give the product 1,3-diphenyl-3-phenylamino-1-propanone (1.45 g, 96%).

3.3.1. 1,3-Diphenyl-3-phenylamino-1-propanone (production for Table 1)

A white solid; mp 169–170 °C (literature [3d] 169–171 °C) IR (KBr) υ 3200, 1681, 1610, 1500, 1300, 756, 512 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 3.47 (d, J = 4.8 Hz, 2H), 5.03 (t, J = 6.1 Hz, 1H), 6.58 (s, 2H), 6.68 (s, 1H), 7.09 (s, 2H), 7.20 (s, 2H), 7.32 (s, 2H), 7.45 (s, 4H), 7.56 (s, 1H), 7.92 (d, 2H). MS (EI) m/z 301 (M^+).

3.3.2. 1,3-Diphenyl-3-(p-nitrophenylamino)-1-propanone (Table 2, entry 1)

A yellow solid; mp 183–185 °C (literature [3d] 184–186 °C) IR (KBr) υ 3381, 1710, 1454, 1600, 1210 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 3.57 (d, J = 5.0 Hz, 2H), 5.13 (t, J = 6.2 Hz, 1H), 5.58 (brs, 2H), 6.58 (d, 2H), 7.27 (t, 1H), 7.30 (t, 2H), 7.42 (d, 2H), 7.47 (t, 2H), 7.42 (d, 2H), 7.47 (t, 2H), 7.58 (t, 1H), 7.88 (d, 2H), 7.99–8.10 (m, 2H). MS (EI) m/z 346 (M^+).

3.3.3. 1,3-Diphenyl-3-(p-methylphenylamino)-1-propanone (Table 2, entry 2)

A white solid; mp 168–170 °C (literature [3d] 170–171 °C) IR (KBr) υ 3400, 1682, 1520, 807 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 3.50 (d, J = 5.0 Hz, 2H), 5.03 (t, J = 5.3 Hz, 1H), 6.66 (d, 2H), 6.80 (d, 2H), 7.24 (t, 1H), 7.32 (t, 2H), 7.46 (t, 4H), 7.57 (t, H), 7.92 (d, 2H). MS (EI) m/z 315 (M^+).

3.3.4. 1,3-Diphenyl-3-(p-chlorophenylamino)-1-propanone (Table 2, entry 3)

A white solid; mp 170–171 °C (literature [3d] 170–171 °C) IR (KBr) υ 3380, 1680, 1611, 1532, 812 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 3.47–3.49 (m, 2H), 4.93 (t, J = 6.4 Hz, 1H), 6.48 (d, 2H), 7.02 (d, 2H), 7.27 (t, 1H), 7.31 (t, 2H), 7.39–7.49 (m, 4H), 7.57 (t, 1H), 7.90 (d, 2H). MS (EI) m/z 336–338 (M^+).

3.3.5. 1,3-Diphenyl-3-(p-methoxyphenylamino)-1-propanone (Table 2, entry 4)

A yellowlish solid; mp 166–167 °C (literature [3d] 184–186 °C) IR (KBr) υ 3390, 1675, 1500, 1287, 812, 709 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 2.42 (s, 3H), 3.38–3.55 (m, 2H), 4.93 (t, J = 6.4 Hz, 1H), 6.48 (d, 2H), 6.85 (d, 2H), 7.23 (t, 1H), 7.33 (t, 2H), 7.42–7.47 (m, 4H), 7.52 (t, 1H), 7.91 (d, 2H). MS (EI) m/z 331 (M^+).

3.3.6. 1,3-Diphenyl-3-(p-carboxylphenylamino)-1-propanone (Table 2, entry 5)

A yellow solid; mp 162–163 (literature [6] 162–163 °C) IR (KBr) υ 3379, 1701, 1280, 815 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 3.65–3.71 (q, J = 9.0 Hz, 1H), 5.05–5.11 (m, 1H), 6.52 (d, 2H), 7.00 (d, 1H), 7.22 (t, 1H), 7.30 (t, 2H), 7.47 (d, 2H), 7.50 (t, 2H), 7.58 (d, 2H), 7.62 (t, 1H), 7.88 (d, 2H). MS (EI) m/z 345 (M^+).

3.3.7. 1,3-Diphenyl-3-(p-carbethoxyphenylamino)-1-propanone (Table 2, entry 6)

A white solid; mp 150–152 °C (literature [6] 150–151 °C) IR (KBr) υ 3406, 1679, 1521, 712 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 3.45–3.57 (m, 4H), 3.82 (t, J = 4.3 Hz, 3H), 5.10 (t, J = 6.3 Hz, 1H), 5.78 (br, 1H), 6.82–6.86 (m, 1H), 7.20 (t, 2H), 7.29–7.34 (m, 3H), 7.42–7.47 (m, 5H), 7.62 (t, 1H), 7.81 (d, 2H). MS (EI) m/z 373 (M^+).

3.3.8. 1,3-Diphenyl-3-(3-nitrophenylamino)-1-propanone (Table 2, entry 7)

A yellow solid; mp 140–142 °C (literature [6] 138–139 °C) IR (KBr) υ 3406, 1679, 1521, 712 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 3.44–3.57 (m, 2H), 5.10 (s, 1H), 6.80–6.85 (m, 1H), 7.20 (t, 1H), 7.27 (t, 2H), 7.32–7.36 (m, 3H), 7.42–7.47 (m, 5H), 7.62 (t, 1H), 7.90 (d, 2H). MS (EI) m/z 346 (M^+).

3.3.9. 1-Phenyl-3-(p-methylphenyl)-3-phenylamino-1-propanone (Table 2, entry 10)

A white solid; mp 131–132 °C (literature [6] 131–132 °C) IR (KBr) υ 3400, 1678, 1600, 1520, 810 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 3.47–3.59 (m, 2H), 3.73 (s, 3H), 5.78 (t, J = 6.8 Hz, 1H), 6.52 (d, 2H), 6.69 (t, 1H), 6.85 (d, 2H), 7.09 (t, 2H), 7.39 (d, 2H), 7.45 (t, 2H), 7.57 (t, 1H), 7.90 (d, 2H). MS (EI) m/z 316 (M^+).

3.3.10. 1-Phenyl-3-(p-methoxyphenyl)-3-phenylamino-1-propanone (Table 2, entry 11)

A white solid; mp 151–152 °C (literature [3d] 150–152 °C) IR (KBr) υ 3380, 1680, 1598, 803 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 3.37–3.52 (m, 2H), 3.70 (s, 3H), 5.02 (t, J = 6.7 Hz, 1H), 6.58 (d, 2H), 6.69 (t, 1H), 6.85 (d, 2H), 7.12 (t, 2H), 7.38 (d, 2H), 7.43 (t, 2H), 7.58 (t, 1H), 7.89 (d, 2H). MS (EI) m/z 332 (M^+).

3.3.11. 1-Phenyl-3-(p-nitrophenyl)-3-phenylamino-1-propanone (Table 2, entry 12)

A white solid; mp 107–110 °C (literature [3c] 108–109 °C) IR (KBr) υ 3410, 1623, 1605, 1512, 748 cm^{-1}. ^1H NMR (500

MHz, TMS, $CDCl_3$) δ 3.52 (d, J = 6.1 Hz, 2H), 5.12 (t, J = 6.1 Hz, 1H), 6.72 (d, 2H), 6.70 (t, 1H), 7.11 (t, 2H), 7.49 (t, 2H), 7.59 (t, 1H), 7.65 (d, 2H), 7.87 (d, 2H), 8.18 (d, 2H). MS (EI) m/z 346 (M^+).

3.3.12. 1-Phenyl-3-(p-chloroophenyl)-3-phenylamino-1-propanone (Table 2, entry 13)

A white solid; mp 117–118 °C (literature [3h] 118–119 °C) IR (KBr) υ 3390, 1688, 1604, 1510, 792 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 3.48 (d, J = 5.8 Hz, 2H), 5.18 (t, J = 5.9 Hz, 1H), 6.60 (d, 2H), 6.68 (t, 1H), 7.12 (t, 2H), 7.52 (t, 2H), 7.54 (t, 1H), 7.60 (d, 2H), 7.82 (d, 2H), 7.90 (d, 2H). MS (EI) m/z 336–338 (M^+).

3.3.13. 1-(p-Methylphenyl)-3-phenyl-3-phenylamino-1-propanone (Table 2, entry 15)

A white solid; mp 138–139 °C (literature [3i] 139–140 °C) IR (KBr) υ 3380, 1625, 1600, 1502, 758 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 2.40 (s, 3H), 3.42 (d, J = 5.9 Hz, 1H), 3.49 (d, 1H), 4.91 (d, J = 6.1 Hz, 1H), 6.42 (d, 2H), 6.79 (d, 2H), 7.12–7.42 (m, 7H), 7.79 (d, 2H). MS (EI) m/z 316 (M^+).

3.3.14. 1-(p-Nitrophenyl)-3-phenyl-3-phenylamino-1-propanone (Table 2, entry 16)

A yellow solid; mp 144–146 °C (literature [3d]) IR (KBr) υ 3400, 1678, 1510, 808 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 3.44–3.57 (m, 2H), 5.10 (s, 1H), 6.80–6.83 (m, 1H), 7.20 (t, 1H), 7.30 (t, 2H), 7.32–7.39 (m, 3H), 7.42–7.50 (m, 5H), 7.62 (t, 1H), 7.92 (d, 2H). MS (EI) m/z 346 (M^+).

3.3.15. 1-(p-Chlorophenyl)-3-phenyl-3-phenylamino-1-propanone (Table 2, entry 17)

A yellowish solid; mp 119–120 °C (literature [3d] 119–120 °C) IR (KBr) υ 3380, 1685, 1610, 1520, 808 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 3.47–3.50 (m, 2H), 4.92 (t, J = 6.3 Hz, 1H), 6.48 (d, 2H), 7.08 (d, 2H), 7.27 (t, 1H), 7.34 (t, 2H), 7.39–7.49 (m, 4H), 7.60 (t, 1H), 7.89 (d, 2H). MS (EI) m/z 336–338 (M^+).

3.3.16. 2-[1″-(N-phenylamino)-1′-phenyl]methylcyclohexane (Table 2, entry 18)

A white solid; mp 139–140 °C (literature [3c] 138–140 °C) IR (KBr) υ 3380, 1685, 1610, 1520, 808 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 1.61–1.88 (m, 6H), 2.31–2.45 (m, 2H), 2.71 (m, 1H), 4.51 (br, 1H), 4.68 (d, J = 7.3 Hz, 5H), 6.49 (m, 2H), 6.63 (m, 2H), 7.19–7.40 (m, 5H). MS (EI) m/z 309 (M^+).

3.3.17. 2-[1′-(N-p-methylphenylamino)-1′-phenyl]methylcyclohexane (Table 2, entry 19)

A white solid; mp 116–118 °C (literature [3c] 116–118 °C) IR (KBr) υ 3382, 1680, 1610, 1509, 800 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 1.60–1.91 (m, 6H), 2.29–2.42 (m, 2H), 2.70 (m, 1H), 3.60 (s, 3H), 4.52 (br, 1H), 4.65 (d, J = 5.2 Hz, 5H), 6.50 (m, 2H), 6.63 (m, 2H), 7.19–7.35 (m, 5H). MS (EI) m/z 323 (M^+).

3.3.18. 2-[1′-(N-p-chlorophenylamino)-1′-phenyl]methylcyclohexane (Table 2, entry 20)

A yellowish solid; mp 137–138 °C (literature [3c] 136–138 °C) IR (KBr) υ 3378, 1676, 1609, 1510, 800 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 1.60–1.92 (m, 6H), 2.29–2.32 (m, 2H), 2.65 (m, 1H), 3.54 (s, 3H), 4.57 (br, 1H), 4.67 (d, J = 5.5 Hz, 5H), 6.51 (m, 2H), 6.60 (m, 2H), 7.21–7.55 (m, 5H). MS (EI) m/z 343–345 (M^+).

3.3.19. 2-[1′-(N-p-chlorophenylamino)-1′-(p-methoxyphenyl)]methylcyclohexane (Table 2, entry 21)

A yellowish solid; mp 133–134 °C (literature [3c] 132–134 °C) IR (KBr) υ 3321, 1702, 1610, 1510, 800 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 1.14–2.65 (m, 9H), 3.08 (s, 1H), 3.61 (s, 3H), 4.62 (d, J = 4.9 Hz, 1H), 6.31–6.82 (m, 3H), 7.09–7.35 (m, 5H). MS (EI) m/z 374–376 (M^+).

3.3.20. 2-[1′-(2-Furyl)-1′-N-phenylamino]methylcyclohexane (Table 2, entry 22)

A white solid (literature [4]); mp 107–108 °C. IR (KBr) υ 3362, 2938, 1673, 1597, 1500 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 1.60–2.40 (m, 8H), 2.89–2.96 (m, 1H), 4.57 (br, 1H), 4.85 (d, J = 5.0 Hz, 1H), 6.21 (m, 2H), 6.65 (m, 3H), 7.11–7.30 (m, 3H). MS (EI) m/z 269 (M^+).

3.3.21. 2-[1′-N-phenylamino-1′-(2-pyridyl)]methylcyclohexane (Table 2, entry 23)

A white solid (literature [4]); mp 141–142 °C. IR (KBr) υ 3390, 2924, 1692, 1590, 1486 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 1.61–2.51 (m, 8H), 3.21–3.33 (m, 1H), 4.78 (d, J = 3.9 Hz, 1H), 5.09 (br, 1H), 6.63 (d, 2H), 6.65 (t, 1H), 7.11–7.40 (m, 4H), 7.59 (t, 1H), 8.59 (d, 1H). MS (EI) m/z 280 (M^+).

3.3.22. 2-[1′-(N-phenylamino)-1′-phenyl]methylcyclopentanone (Table 2, entry 24)

A white solid; mp 164–165 °C (literature [3c] 164–166 °C) IR (KBr) υ 3411, 1730, 1690, 1608, 1521, 806 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 1.61–2.41 (m, 7H), 3.66 (s, 1H), 4.41 (d, J = 4.8 Hz, 1H), 6.51–6.66 (m, 3H), 6.82–7.19 (m, 7H). MS (EI) m/z 295 (M^+).

3.3.23. 2-[1′-(N-p-chlorophenylamino)-1′-phenyl]methylcyclopentanone (Table 2, entry 25)

A yellow solid; mp 144–147 °C (literature [3c] 144–146 °C) IR (KBr) υ 3410, 1728, 1688, 1608, 1513, 800 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 1.63–2.44 (m, 7H), 3.69 (s, 1H), 4.40 (d, J = 5.2 Hz, 1H), 6.58–6.76 (m, 3H), 6.92–7.32 (m, 6H). MS (EI) m/z 329–311 (M^+).

3.3.24. 2-[1′-(N-3-nitrophenylamino)-1′-phenyl]methylcyclopentanone (Table 2, entry 26)

A yellow solid; mp 165–166 °C (literature [3c] 166–168 °C) IR (KBr) υ 3397, 1736, 1708, 1600, 1510, 796 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 1.43–2.94 (m, 7H), 3.49 (s, 1H), 4.30 (d, J = 5.3 Hz, 1H), 6.33–6.76 (m, 3H), 6.88–7.22 (m, 6H). MS (EI) m/z 340 (M^+).

3.3.25. 2-[1′-(N-p-nitrophenylamino)-1′-(p-methoxyphenyl)]methylcyclopentanone (Table 2, entry 27)

A yellow solid; mp 127–129 °C (literature [3c] 127–128 °C). IR (KBr) υ 3418, 1726, 1678, 1600, 1510, 803 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 1.46–2.64 (m, 7H), 3.31 (s, 1H), 3.60 (s, 1H), 4.45 (d, J = 4.9 Hz, 1H), 6.39–6.68 (m, 2H), 6.92–7.42 (m, 6H). MS (EI) m/z 329–311 (M^+).

3.3.26. 2-Methyl-1,3-diphenyl-3-(p-chlorophenylamino)-1-propanone (Table 2, entry 28)

A white solid; mp 170–171 °C (literature [3a]) IR (KBr) υ 3379, 1676, 1613, 1528, 809 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 3.25 (d, J = 7.0 Hz, 3H), 3.47–3.49 (m, 1H), 4.90 (t, J = 5.5 Hz, 1H), 6.34 (d, 2H), 7.06 (d, 2H), 7.25 (t, 1H), 7.28 (t, 2H), 7.39–7.51 (m, 4H), 7.56 (t, 1H), 7.90 (d, 2H). MS (EI) m/z 350–352 (M^+).

3.3.27. 1-Ethyl-3-phenyl-3-phenylamino-1-propanone (Table 2, entry 29)

A white solid; mp 110–112 °C (literature [3e] 112–114 °C) IR (KBr) υ 3200, 1681, 1610, 1500, 1300, 756, 512 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 1.24–2.55 (m, 5H), 3.50 (d, J = 4.6 Hz, 2H), 5.02 (t, J = 5.9 Hz, 1H), 6.54 (s, 2H), 6.66 (s, 1H), 7.09 (s, 2H), 7.32 (s, 1H), 7.45 (s, 2H), 7.56 (s, 1H), 7.90 (d, 2H). MS (EI) m/z 253 (M^+).

3.3.28. 1-Propyl-3-phenyl-3-phenylamino-1-propanone (Table 2, entry 30)

A white solid; mp 87–88 °C (literature [3e] 87–88 °C) IR (KBr) υ 3219, 1680, 1613, 1505, 1308, 756 cm^{-1}. ^1H NMR (500 MHz, TMS, $CDCl_3$) δ 0.72 (t, 3H), 1.43 (m, 2H), 2.20 (t, 2H), 2.80 (d, 2H), 3.63 (br, J = 5.8 Hz, 1H), 6.54 (s, 2H), 6.66 (s, 1H), 7.10 (s, 2H), 7.24 (s, 1H), 7.36 (s, 1H), 7.44 (s, 2H), 7.76 (s, 1H). MS (EI) m/z 267 (M^+).

4. Conclusions

In conclusion, $RE(OPf)_3$ are demonstrated to be new and highly effective catalysts for the one-pot Mannich-type reactions of methyl ketones with aromatic aldehydes and aromatic amines in fluorous media. By simple separation of the fluorous phase containing only catalyst, reaction can be repeated several times. The simple procedures as well as easy recovery and reuse of this novel catalytic system are expected to contribute to the development of more benign Mannich reaction.

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References

[1] (a) M. Tramontini, Synthesis (1973) 703–775;
(b) E.F. Kleinnmann, in: B.M. Trost (Ed.), Comprehensive Organic Synthesis, vol. 2, Pergamon Press, New York, 1991, Chapter 4.1 and references cited therein;
(c) M. Arend, B. Westermann, N. Risch, Angew. Chem. Int. Ed. 37 (1998) 1044–1070, and references cited therein.

[2] (a) M. Onaka, R. Ohno, N. Yanagiya, Y. Izumi, Synlett (1993) 141–143;
(b) O. Ishihra, M. Funahashi, N. Hanaki, M. Miyata, H. Yamamoto, Synlett (1994) 963–966;
(c) S. Kobayashi, M. Araki, M. Yasuda, Tetrahedron Lett. 36 (1995) 5773–5776;
(d) P.G. Cozzi, B.D. Simone, A. Umani-Ronchi, Tetrahedron Lett. 37 (1996) 1691–1694;
(e) K. Manabe, Y. Mori, S. Kobayashi, Synlett (1999) 1401–1402;
(f) T.-P. Loh, Sarah.B.K.W. Liung, K.-L Tan, L.-L Wei, Tetrahedron 56 (2000) 3227–3237;
(g) K. Manabe, S. Kobayashi, Tetrahedron Lett. 40 (1999) 3773–3776;
(h) H. Ishitani, M. Ueno, S. Kobayashi, J. Am. Chem. Soc. 119 (1997) 10049–10053;
(i) M. Shi, S.-C. Cui, Y.-H. Liu, Tetrahedron 61 (2005) 4965–4970.

[3] HCl-catalyzed, HCl-catalyzed cases in EtOH have been reported.
(a) A.H. Blatt, N. Gross, J. Org. Chem. 29 (1964) 3306–3311;
(b) X.-J. Xu, G.-X. Chen, Acta Chim. Sinica 40 (1982) 463–468;
(c) L. Yi, J.-H. Zou, H.-S. Lei, X. Lin, M. Zhang, Org. Prep. Proced. Int. 23 (1991) 673–676;
(d) L. Yi, H.-S. Lei, J.-H. Zou, X.-J. Xu, Synthesis (1991) 717–718;
(e) J.-H. Zou, Synth. Commun. 28 (1996) 618–622;
(f) J.-H. Zou, Org. Prep. Proced. Int. 28 (1996) 618–622;
(g) J.-H. Zou, Chin. J. Org. Chem. 16 (1996) 218–222;
(h) S.Y. Xiao, Q.-W. Zeng, Z.-T. Chen, Z.-N. Xia, Z.-L. Li, J. Chongqing Univ. (Nat. Sci.) 23 (2000) 65–69;
(i) D.-C. Yang, G.-L. Zhang, N. Yang, Y.-G. Zhong, Chem. J. Chin. Univ. 21 (2000) 1694–1695.

[4] K. Manabe, S. Kobayashi, Org. Lett. 1 (1999) 1965–1967.

[5] S. Limura, D. Nobutou, K. Manabe, S. Kobayashi, Chem. Commun. (2003) 1644–1645.

[6] L.-M. Wang, J.-W. Han, J. Sheng, Z.-Y. Fan, H. Tian, Chin. J. Org. Chem. 25 (2005) 591–594.

[7] (a) S. Kobayashi, I. Hachiya, T. Takahori, M. Araki, M. Ishitani, Tetrahedron Lett. 33 (1992) 6815–6818;
(b) S. Kobayashi, H. Ishitani, I. Hachiya, M. Araki, Tetrahedron 50 (1994) 11623–11636;
(c) T. Hanamoto, Y. Sugimoto, Y.Z. Jin, J. Inanaga, Bull. Chem. Soc. Jpn. 70 (1997) 1421–1426;
(d) K. Manabe, H. Oyamada, K. Sugita, S. Kobayashi, J. Org. Chem. 64 (1999) 8054–8057;
(e) T. Kitazume, H. Nakano, Green Chem. (1999) 179–181;
(f) S. Kobayashi, A. Kawada, S. Mitamura, J. Matsuo, T. Suchiya, Bull. Chem. Soc. Jpn. 73 (2000) 2325–2333;
(g) S. Kobayashi, I. Komoto, J. Matsuo, Adv. Synth. Catal. 343 (2001) 71–74;
(h) M. Shi, S.-C. Cui, Chem. Commun. (2002) 994–995;
(i) M. Shi, S.-C. Cui, J. Fluorine Chem. 116 (2002) 143–147.

[8] (a) D.W. Zhu, Synthesis (1993) 953–954;
(b) E.D. Wolf, G.V. Koten, B. Deelman, J. Chem. Soc. Rev. 28 (1999) 37–41.

[9] (a) I.T. Horvath, J. Rabai, Science 266 (1994) 72–75;
(b) R.P. Huhges, H.A. Trujillo, Organometllics 15 (1996) 286–294;
(c) G. Pozzi, F. Montanari, S. Quici, Chem. Commun. (1997) 69–70;
(d) R.H. Fish, Chem. Eur. J. 5 (1999) 1677–1680;
(e) J.J.J. Juliette, I.T. Horvath, J.A. Gladysz, Angew. Chem. Int. Ed. Engl. 36 (1997) 1610–1612;
(f) J. Otera, A. Orita, Angew. Chem. Int. Ed. Engl. 40 (2001) 3670–3674;

(g) X.-H. Hao, A. Yoshida, J. Nishikido, Tetrahedron Lett. 46 (2005) 2697–2700;
(h) X.-H. Hao, A. Yoshida, J. Nishikido, J. Fluorine Chem. 127 (2006) 193–199.
[10] (a) W.-B. Yi, C. Cai, J. Fluorine Chem. 126 (2005) 831–833;
(b) W.-B. Yi, C. Cai, J. Fluorine Chem. 126 (2005) 1191–1195;
(c) W.-B. Yi, C. Cai, J. Fluorine Chem. 126 (2005) 1553–1558;
(d) W.-B. Yi, C. Cai, Chin. J. Org. Chem. 25 (2005) 1434–1436.
[11] J.A. Dean, Lange's Handbook of Chemistry, 13th ed., McGraw-Hill, New York, 1985, pp. 5–14.