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$Fe(ClO_4)_3 \cdot \times H_2O$-Catalyzed direct C–C bond forming reactions between secondary benzylic alcohols with different types of nucleophiles

Ponnaboina Thirupathi, Sung Soo Kim *

Department of Chemistry, Inha University, Incheon 402-751, South Korea

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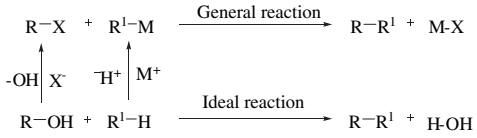
ABSTRACT

A mild and efficient $Fe(ClO_4)_3 \cdot \times H_2O$-catalyzed direct C–C bond coupling reactions of 1,3-dicarbonyl compounds, electron-rich arenes and heteroarenes and 4-hydroxycoumarin with secondary benzylic alcohols have been described. The benzylation of electron-rich arenes and heteroarenes leads to the synthesis of bis-symmetrical triarylmethanes. The present method is also applied to synthesis of an *anti*-coagulant compound, 4-hydroxy-3-(1,2,3,4-tetrahydronaphthalen-1-yl)-2*H*-chromen-2-one (Coumatetralyl (B)) from commercially available substrates was obtained in 85% yield. The advantages of this protocol are broad scope, mild conditions, use of inexpensive catalyst and simplicity of operation since water is the only side product.

1. Introduction

The formation of C–C bond is a fundamental reaction in organic synthesis. Accordingly the coupling reactions between reactive organometallics (R^1M) and halides (RX) are one of the most used strategies. The species R^1M and RX are often prepared from active methylenes (R^1H) and alcohols (ROH), respectively. Generally, the coupling reactions between R^1M and RX produce R-R^1 along with the large amount of salt as byproduct (Scheme 1). Thus, due to the increasing demand for economic and environmentally friendly processes, the development of direct catalytic carbon–carbon bond formation with alcohols is an important process for organic synthesis. Direct substitution of hydroxyl group of starting alcohols by nucleophiles could be considered as an ideal method because of the wide availability of the alcohols and the generation of H_2O as the only side product (Scheme 1). However, the catalytic substitution of hydroxyl group of alcohols is difficult due to their poor leaving ability, which requires equimolar or greater amount of reagents. Recently several workers have demonstrated that alcohols can react with



Scheme 1.

several nucleophiles, such as 1,3-dicarbonyl compounds,[1,2] amides,[3] allylsilanes,[1c,4] olefins,[1f] enolethers,[5] aromatic compounds[1a,1g,5,6] and 4-hydroxycoumarin[1h,7] leading to the corresponding alkylation products.

Recently, iron salts have attracted the attention from synthetic organic chemists since iron is one of the most abundant metal. Many iron salts are inexpensive and commercially available.[8] These iron salts have been found to show promising catalytic abilities in many organic transformations.[8] In continuation of the development of useful synthetic methodology for C–C bond forming reactions,[9] we report herein an efficient $Fe(ClO_4)_3 \cdot \times H_2O$-catalyzed alkylation of 1,3-dicarbonyl compounds, electron-rich heteroarenes, electron-rich arenes and 4-hydroxycoumarins.

2. Results and discussions

2.1. Benzylation of 1,3-dicarbonyl compounds

The functionalization of activated methylene unit of 1,3-dicarbonyl compounds is one of the most utilized types of carbon–carbon bond forming reactions. The α-benzylation of 1,3-dicarbonyl compounds are common procedures in organic synthesis. The traditional method for benzylation of 1,3-dicarbonyls is a stoichiometric reaction with benzyl halides in the presence of an equimolar amount of strong bases. Recently, several catalysts, such as trifluoromethanesulfonic acid,[1b] *p*-toluenesulfonic acid,[1b] polymer-supported *p*-toluenesulfonic acid,[1c] La, Yb, Sc and Hf triflate,[1d] $Bi(OTf)_3$,[1e] H-Montmorillonite[1f] and EMIOTf [2] have been used for nucleophilic substitution reactions of secondary benzylic alcohols

* Corresponding author. Fax: +82 32 867 5604.
E-mail address: sungsoo@inha.ac.kr (S.S. Kim).

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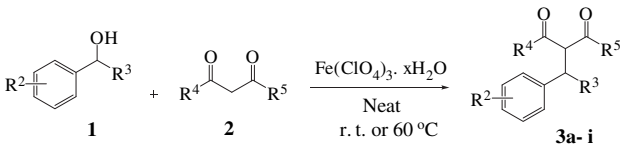
with 1,3-dicarbonyl compounds. However, many of these methods are associated with one or more drawbacks, such as elevated temperature and long reaction time. Only two of the Lewis acid catalyzed benzylation of 1,3-dicarbonyl compounds using secondary benzylic alcohol are known.[1a,1h] We herein report the $Fe(ClO_4)_3\cdot\times H_2O$-catalyzed reaction of secondary benzylic alcohols with various 1,3-diketones, β-ketoesters and 1,3-diesters involving active methylene.

We have examined the reaction of 1-phenylethanol (**1a**) with 2,4-pentadione (**2a**) under various reaction conditions employing various catalysts (Table 1). The reaction of 1-phenylethanol (**1a**) with 2,4-pentadione (**2a**) was treated in presence of 50 mg of Amberlyst-15 in CH_3NO_2 at rt for 24 h to afford the 3-(1-phenylethyl)pentane-2,4-dione (**3a**) in 26% yield. The remarkable improvement of the yield (78%) was observed by increasing the temperature up to 60 °C (entry 1). Then we have tried the reaction in the presence of Nafion Sac-13 (entry 2), $HClO_4\cdot SiO_2$ (entry 3) and various catalysts such as $In(ClO_4)_3$, $In(OTf)_3$, $Ce(OTf)_3$, $Cu(ClO_4)_2$, $Fe(ClO_4)_3\cdot\times H_2O$, $Fe(NO_3)_3\cdot 9H_2O$ and $FeBr_3$ (entries 4–11). Considering the amount of the 2,4-pentadione (**2a**) (entries 11–13), amount of the catalyst (entries 13–15), reaction time and yield, $Fe(ClO_4)_3\cdot\times H_2O$ is found to be the most effective (entry 14). The effects of various solvents, such as CH_3CN, CH_3NO_2, $CHCl_3$, CH_2Cl_2 and solvent-free condition have been also studied (entries 16–21). Solvent-free reaction at 60 °C is found to be the choice in terms of yield and reaction time (entry 21).

Table 2
Benzylation of 1,3-dicarbonyl compounds with various secondary benzylic alcohols[a]

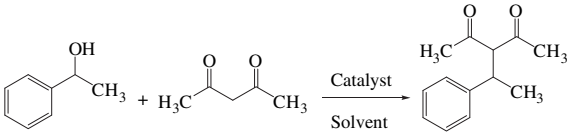


2a: $R^4=CH_3$, $R^5=CH_3$
2b: $R^4=CH_3$, $R^5=OCH_2CH_3$
2c: $R^4=R^5=$ Ethyl 2-cyclohexanone-carboxylate

Entry	**1**			**2**	Temperature (°C)	Reaction time (h)	Product **3**	Isolated yield[b] (%)
	R^2	R^3						
1	H	CH_3	**1a**	**2a**	60	3.5	**3a**	89[c]
2	4-CH_3O	CH_3	**1b**	**2a**	rt	3.0	**3b**	99
3	4-CH_3	CH_3	**1c**	**2a**	60	3.5	**3c**	91[c]
4	2-CH_3	CH_3	**1d**	**2a**	60	4.0	**3d**	88[c]
5	4-Cl	CH_3	**1e**	**2a**	60	4.0	**3e**	87[c]
6	H	CH_2CH_3	**1f**	**2a**	60	3.5	**3f**	85[c]
7	2-CH_3O	CH_2CH_3	**1g**	**2a**	rt	4.0	**3g**	93
8	4-CH_3O	CH_3	**1b**	**2b**	rt	3.5	**3h**	98[d]
9	4-CH_3O	CH_3	**1b**	**2c**	rt	4.5	**3i**	95

[a] Reaction condition: Secondary benzylic alcohol (1.0 mmol), 1,3-dicarbonyl compound (3.0 mmol) and 5 mol % of $Fe(ClO_4)_3\cdot\times H_2O$ were used at rt.
[b] Yield of isolated product after flash column chromatography.
[c] The reaction was carried out at 60 °C under solvent-free conditions.
[d] Mixture of diastereomers [1:1] was identified by NMR.

Table 1
Benzylation of 2,4-pentadione with 1-phenylethanol under various reaction conditions[a]



Entry	Catalyst (mg/mol %)	**2a** (equiv)	Solvent	Temperature	Reaction time (h)	Isolated yield[b] (%)
1	Amberlyst-15 (50)	1.5	CH_3NO_2	rt	24	26 (78)[c]
2	Nafion Sac-13 (50)	1.5	CH_3NO_2	rt	12	31
3	$HClO_4\cdot SiO_2$ (50)	1.5	CH_3NO_2	rt	24	18
4	$In(ClO_4)_3$ (10)	1.5	CH_3NO_2	rt	12	68
5	$In(OTf)_3$ (10)	1.5	CH_3NO_2	rt	12	79
6	$Ce(OTf)_3$ (10)	1.5	CH_3NO_2	rt	12	74
7	$Cu(ClO_4)_2$ (10)	1.5	CH_3NO_2	rt	12	69
8	$Fe(ClO_4)_3\cdot\times H_2O$ (10)	1.5	CH_3NO_2	rt	12	83
9	$Fe(NO_3)_3\cdot 9H_2O$ (10)	1.5	CH_3NO_2	rt	12	46
10	$FeBr_3$(10)	1.5	CH_3NO_2	rt	12	79
11	$Fe(ClO_4)_3\cdot\times H_2O$ (10)	1.5	CH_3NO_2	100	3.5	85
12	$Fe(ClO_4)_3\cdot\times H_2O$ (10)	2.0	CH_3NO_2	100	3.5	88
13	$Fe(ClO_4)_3\cdot\times H_2O$ (10)	3.0	CH_3NO_2	100	3.5	89
14	$Fe(ClO_4)_3\cdot\times H_2O$ (5)	3.0	CH_3CN	80	4.5	89
15	$Fe(ClO_4)_3\cdot\times H_2O$ (15)	3.0	CH_3CN	80	3.5	87
16	$Fe(ClO_4)_3\cdot\times H_2O$ (10)	3.0	CH_3CN	80	4.0	89
17	$Fe(ClO_4)_3\cdot\times H_2O$ (10)	3.0	CH_3NO_2	100	3.5	88
18	$Fe(ClO_4)_3\cdot\times H_2O$ (10)	3.0	$CHCl_3$	60	4.0	79
19	$Fe(ClO_4)_3\cdot\times H_2O$ (10)	3.0	CH_2Cl_2	45	4.0	82
20	$Fe(ClO_4)_3\cdot\times H_2O$ (5)	3.0	Solvent-free	50	5.0	84
21	$Fe(ClO_4)_3\cdot\times H_2O$ (5)	3.0	Solvent-free	60	3.5	89

[a] 1-Phenylethanol (1.0 mmol) is used under the reaction conditions indicated above.
[b] Yield of isolated product after column chromatography.
[c] The values in the parenthesis show the isolated yield of product at reflux temperature.

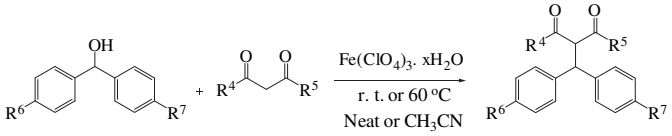
We then explored the generality of the $Fe(ClO_4)_3\cdot\times H_2O$-catalyzed reactions with various secondary benzylic alcohols and active methylene substrates including diketones, β-ketosters and diesters that proceed smoothly to give the corresponding benzylated products (Table 2). 1-(4-Methoxy phenyl) ethanol (**1b**), 1-(4-methylphenyl)ethanol (**1c**), 1-(2-methylphenyl)ethanol (**1d**) and 1-(4-chlorophenyl)ethanol (**1e**) react with 2,4-pentanedione (**2a**) to afford the benzylated products in 99, 91, 88 and 87%, respectively (entries 2–5). The reaction of 1-phenyl-propanol (**1f**) and 1-(2-methoxyphenyl)-1-propanol (**1g**) with 2,4-pentanedione (**2a**) gave the products in good yield (entries 6 and 7). The electron-donating methoxy group attached to the benzene ring of the alcohol moiety shows excellent reactivity towards benzylation and the reaction occurs at rt (entries 2, 7–9). This indicates that the methoxy group enhances the reactivity towards the benzylation. The reaction of 1-(4-methoxyphenyl)ethanol (**1b**) with ethyl 3-oxobutanoate (**2b**) can also give the

desired product in excellent yield (entry 8). It is noted that the cyclic β-ketoster, ethyl 2-cyclohexanonecarboxylate (**2c**) also displays a high reactivity to give the product in 95% yield (entry 9).

The reactions of benzhydrol derivatives with various 1,3-dicarbonyl compounds proceed smoothly to produce the benzylation products in excellent yield. The results are summarized in Table 3. When the reaction of benzhydrol with 2,4-pentanedione (**2a**) is carried out at rt, the desired product (62%) and 33% of dimeric ether were obtained (entry 1). The increase of reaction temperature up to 60 °C yields the benzylation product only (98%) without intervention of dimeric ether (entry 2). The reactions of benzhydrol (**4a**) with 1-phenylbutane-1,3-ione (**2d**) and 1,3-diphenyl-1,3-propanedione (**2e**) gave corresponding products in 99 and 98% yield, respectively (entries 3 and 4). 4,4′-Dichloro- (**4b**), 4,4′-diflouro- (**4c**) and 4,4′-dimethoxy-benzhydrol (**4d**) also react with 2,4-pentanedione (**2a**) to afford the benzylated products in excellent yield (entries 5–7). The benzylation of 1-phenylbutane-1,3-ione (**2d**) with 4,4′-dimethoxy-benzhydrol (**4d**) offer the product in 99% yield (entry 8). The reactions with 1,3-diketones (entries 1–8) give slightly higher yield than with keto esters and diester (entries 9–15). The reaction of benzhydrol (**4a**) with methyl 3-oxobutanoate (**2f**) and ethyl 3-oxobutanoate (**2b**) give rise to the product in high yields (entries 9 and 10). It is noted that the cyclic β-ketoster, ethyl 2-cyclohexanonecarboxylate (**2c**) displays high reactivity to generate the product in 91% yield (entry 11). The treatment of benzhydrol (**4a**) with diethyl malonate (**2h**) also produces the product in good yield (entry 12). 4,4′-Dichloro- (**4b**) and 4,4′-diflourobenzhydrol (**4c**) react with ethyl 3-oxobutanoate (**2b**) to bring about the benzylated products in 91 and 93%, respectively (entries 13 and 14). The benzylation of ethyl 3-oxo-3-phenylpropanoate (**2g**) with 4,4′-dimethoxy-benzhydrol (**4d**) entails the product with 94% yield (entry 15).

The mechanism for direct C–C bond coupling reaction of secondary benzylic alcohols with 1,3-dicarbonyl compounds catalyzed by $Fe(ClO_4)_3\cdot\times H_2O$ have been proposed in Scheme 2. The first step is the formation of the complex **A** by coordination of the 1,3-dicarbonuyl compound **2** to Fe(III) ion.[10] Complex **A** is planar and stabilized by π-delocalization. Fe(III) centre has 17 valence electrons in an octahedron and the coordination sphere is kinetically labile. Alcohol **1** is coordinated at a vacant site to form species **B**. The function of the Fe(III) is not only to hold the alcohol **1** in proximity to the alkylating agent but also alcohol **1** is activated by the Lewis acid of Fe(III) (**B**). Subsequently, the nucleophilic carbon atom of **B** undergoes alkylation at coordinating alcohol to form **3** or **5** via **C**. Alternatively the coordinating alcohol of **B** is attacked by alcohol **1** to produce **D** through which ether **E** is obtained. Ether **E** is able to attack on vacant site of complex **A** to give **F**. Finally, **F** is alkylated at coordinating alcohol to obtain **3** or **5**. The effective activation of 1,3-dicarbonyl compounds by Fe(III) in (**B**) or (**F**) could promote higher selectivity towards benzylation compared to other catalysts.[1b–f,2]

Table 3
Benzylation of 1,3-dicarbonyl compounds with various benzhydrol derivatives[a]



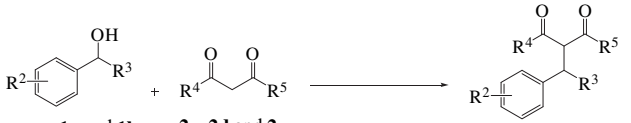
4 **2** **5a-m**

2a: $R^4=CH_3$, $R^5=CH_3$
2b: $R^4=CH_3$, $R^5=OCH_2CH_3$
2c: $R^4=R^5=$ Ethyl 2-cyclohexanone-carboxylate
2d: $R^4=Ph$, $R^5=CH_3$
2e: $R^4=Ph$, $R^5=Ph$
2f: $R^4=CH_3$, $R^5=OCH_3$
2g: $R^4=Ph$, $R^5=OCH_2CH_3$
2h: $R^4=OCH_2CH_3$, $R^5=OCH_2CH_3$

Entry	**4**		**2**	Temperature (°C)	Reaction time (h)	Product **5**	Isolated yield[b] (%)
1	H	H **4a**	**2a**	rt	8.0	**5a**	62 (33)[d]
2	H	H **4a**	**2a**	60	2.5	**5a**	98
3	H	H **4a**	**2d**	60	3.5	**5b**	99[c]
4	H	H **4a**	**2e**	60	3.5	**5c**	98[c]
5	Cl	Cl **4b**	**2a**	60	3.0	**5d**	96
6	F	F **4c**	**2a**	60	3.5	**5e**	97
7	CH_3O	CH_3O **4d**	**2a**	rt	3.0	**5f**	99
8	CH_3O	CH_3O **4d**	**2d**	rt	2.5	**5g**	99[c]
9	H	H **4a**	**2f**	60	4.5	**5h**	95
10	H	H **4a**	**2b**	60	4.5	**5i**	94
11	H	H **4a**	**2c**	60	4.5	**5j**	91
12	H	H **4a**	**2h**	60	4.5	**5k**	91
13	Cl	Cl **4b**	**2b**	60	4.0	**5l**	91
14	F	F **4c**	**2b**	60	4.0	**5m**	93
15	CH_3O	CH_3O **4d**	**2g**	rt	4.5	**5o**	94

[a] Reaction condition: Benzhydrol derivative (1.0 mmol) and 1,3-dicarbonyl compound (3.0 mmol) were used at rt.
[b] Yield of isolated product after flash column chromatography.
[c] 1.5 mmol of 1,3-dicarbonyl compound and 2 mL of CH_3CN is used.
[d] The values in the parenthesis show the isolated yield of dimerization of benzhydrol.

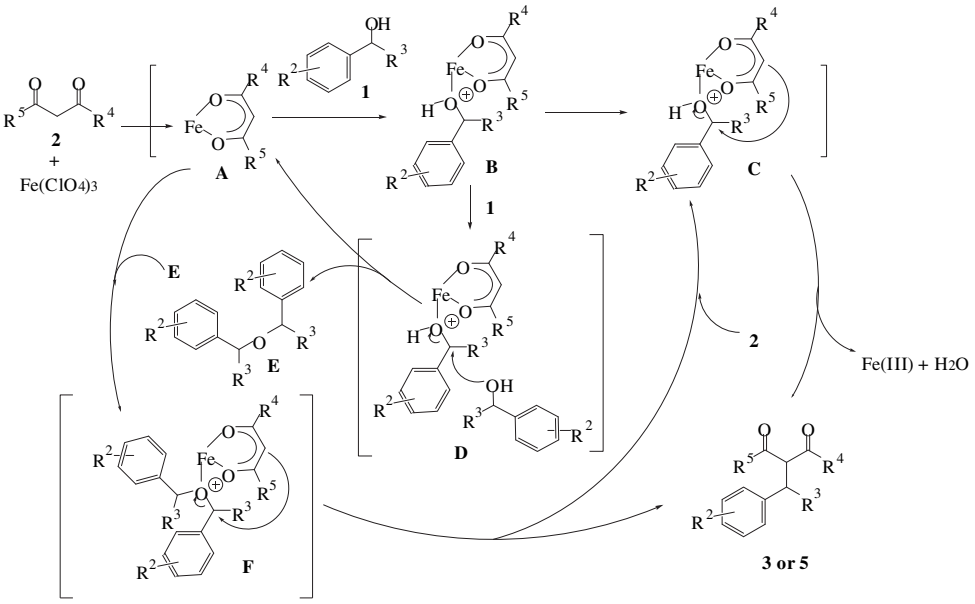
Table 4
$Fe(ClO_4)_3\cdot\times H_2O$-catalyzed benzylation of 1,3-dicarbonyl compounds with secondary benzylic alcohols in comparison with other literatures



1a and **1b** **2a, 2d** and **2c** **3a, 3b** and **3g**

Entry	Catalyst/(mol %)	**1**	**2**	Solvent	Temperature (°C)	Reaction time (h)	Isolated yield[a] (%)	Reference
1	$InCl_3$/(5)	**1a**	**2a**	Toluene	80	15	87	1a
2	PTSA/TfOH (5)	**1a**	**2a**	CH_3NO_2	100	1	88	1b
3	$Sc(OTf)_3$/(5)	**1a**	**2a**	CH_3NO_2	70	21	83	1d
4	$Bi(OTf)_3$/(1)	**1a**	**2a**	CH_3NO_2	100	3	91	1e
5	H-Mont (0.15 g)	**1a**	**2a**	*n*-Heptane	100	1	90	1f, 1g
7	EMIOTf (Ionicliquid)/(5)	**1a**	**2a**	Neat	100	3	77	1i
8	$Fe(ClO_4)_3$/(5)	**1a**	**2a**	Neat	60	3.5	89	Present method
9	$Hf(OTf)_3$/(5)	**1b**	**2d**	CH_3NO_2	20	7	89[b] (96)[c]	1d
10	$Hf(OTf)_3$/(5)	**1b**	**2c**	CH_3NO_2	20	24	84[d] (90)[c]	1d

[a] Yield of isolated product after column chromatography.
[b] 1-Phenylethanol (**1a**) (1.0 mmol) and 2,4-pentadione (**2a**) (3.0 mmol) are used; [b]1-(4-methoxyphenyl)ethanol (**1b**) (1.0 mmol) and 1-phenylbutane-1,3-ione (**2d**) (3.0 mmol) are used.
[c] The values in the parenthesis show the isolated yield of present method.
[d] 1-(4-Methoxyphenyl)ethanol (**1b**) (1.0 mmol) and ethyl 2-cyclohexanone-carboxylate (**2c**) (3.0 mmol) are used.



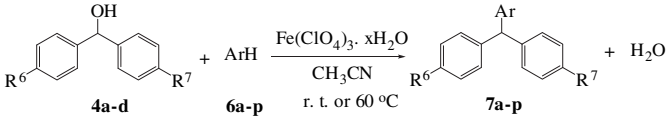
Scheme 2. $Fe(ClO_4)_3 \cdot \times H_2O$-catalyzed mechanism for the direct C–C bond coupling reaction of secondary benzylic alcohols with 1,3-dicarbonyl compounds.

2.2. Synthesis of triarylmethanes

The functionalization of the arenes and heteroarenes is of great synthetic importance for the preparation of pharmaceuticals, agrochemicals and fine chemicals. Hence, the development of environmentally benign C–C coupling reactions of arenes is an important topic of organic synthesis. Recently, few methods have been reported for the preparation of bis-symmetrical triarylmethanes from different substrates with good to moderate yield.[9a,11] Deutsch et al. have investigated the synthesis of triarylmethanes through amidoalkylation of arenes with poor yield (18–22%).[11] Previously we have also reported the synthesis of triarylmethanes from α-amido sulfones in two steps with moderate yield (56–67%).[9a] In continuation of our interest in the synthesis of triarylmethanes, single step synthesis has been developed. We herein demonstrate an efficient $Fe(ClO_4)_3 \cdot \times H_2O$-catalyzed Friedel–Crafts type alkylations of electron-rich arenes or heteroarenes with benzhydrol derivatives that lead to the desired products in very good yield (Table 5). The synthesis of bis-symmetrical triarylmethanes using benzhydrol derivatives is achieved in excellent yield compared to other methods.[9a,11,12] Triarylmethanes display interesting properties and have received a great deal of attention as leuco dyes,[13] photochromic agents,[14] suitable building blocks for generating dendrimers,[15] and substrates for theoretical[14] and biological studies.[16]

Benzhydrol reacts with indole in presence of 5 mol% of $Fe(ClO_4)_3 \cdot \times H_2O$ in CH_3CN at rt that gives the corresponding product in 32% yield along with 56% of the dimeric ether. The improvement of 92% yield without formation the dimeric ether is attained by

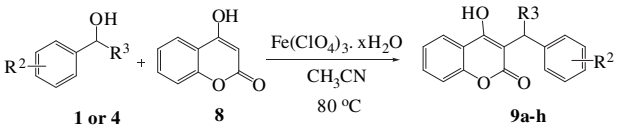
Table 5
Synthesis of triarylmethanes via nucleophilic substitution of benzhydrol derivatives with electron-rich heteroarenes or arenes[a]



Entry	Benzhydrol **4**		Ar **6**	Temperature (°C)	Reaction time (h)	Product **7**	Isolated yield[b] (%)
	R^6	R^7					
1	H	H **4a**	Indole **6a**	60	4	**7a**	92
2	CH_3O	CH_3O **4d**	Indole **6a**	rt	6	**7b**	94
3	CH_3O	CH_3O **4d**	*N*-Methyl indole **6b**	rt	6	**7c**	91
4	CH_3O	CH_3O **4d**	5-Methoxy indole **6c**	rt	5	**7d**	96
5	CH_3O	CH_3O **4d**	5-Bromo indole **6d**	rt	5	**7e**	94
6	CH_3O	CH_3O **4d**	2-Methyl indole **6e**	rt	6	**7f**	90
7	CH_3O	CH_3O **4d**	6-Carboxymethyl Indole **6f**	rt	6	**7g**	92
8	H	H **4a**	1,2,3-Trimethoxy benzene **6g**	60	2	**7h**	91
9	H	H **4a**	1,2,4-trimethoxy benzene **6h**	60	8	**7i**	96
10	Cl	Cl **4b**	1,2,4-Trimethoxy benzene **6h**	60	2	**7j**	93
11	F	F **4c**	1,2,4-Trimethoxy benzene **6h**	60	2	**7k**	95
12	CH_3O	CH_3O **4d**	1,2,4-Trimethoxy benzene **6h**	rt	4.5	**7l**	99
13	CH_3O	CH_3O **4d**	1,3,5-Trimethoxybenzene **6i**	rt	4.5	**7m**	94
14	CH_3O	CH_3O **4d**	1,3-Dimethoxy benzene **6j**	rt	3.5	**7n**	90
15	CH_3O	CH_3O **4d**	1,4-Dimethoxy benzene **6k**	rt	4.5	**7o**	87
16	CH_3O	CH_3O **4d**	Anisole **6l**	rt	7.0	**7p**	76

[a] Reaction condition: Benzhydrol derivative (1.0 mmol) and electron-rich arene or heteroarene (1.1 mmol) are used.
[b] Yield of isolated product after column chromatography.

Table 6
C3-Benzylation of 4-hydroxycoumarin with various secondary benzylic alcohols[a]



1 or 4 8 9a-h

Entry	Alcohol **1** or **4**		Reaction time (h)	Product **9**	Isolated yield[b] (%)
	R^2	R^3			
1	H	H **1a**	4.0	**9a**	86
2	4-CH_3O	CH_3 **1b**	3.5	**9b**	92
3	4-CH_3	CH_3 **1c**	4.0	**9c**	89
4	2-CH_3O	CH_2CH_3 **1g**	3.5	**9d**	90
5	H	C_6H_5 **4a**	3.0	**9e**	91
6	Cl	4-ClC_6H_5 **4b**	2.5	**9f**	93
7	F	4-FC_6H_5 **4c**	2.5	**9g**	95
8	CH_3O	4-$CH_3OC_6H_5$ **4d**	2.0	**9h**	98

[a] Reaction condition: Secondary benzylic alcohols (1.0 mmol) and 4-hydroxycoumarin (1.0 mmol) are used.
[b] Yield of isolated product after column chromatography.

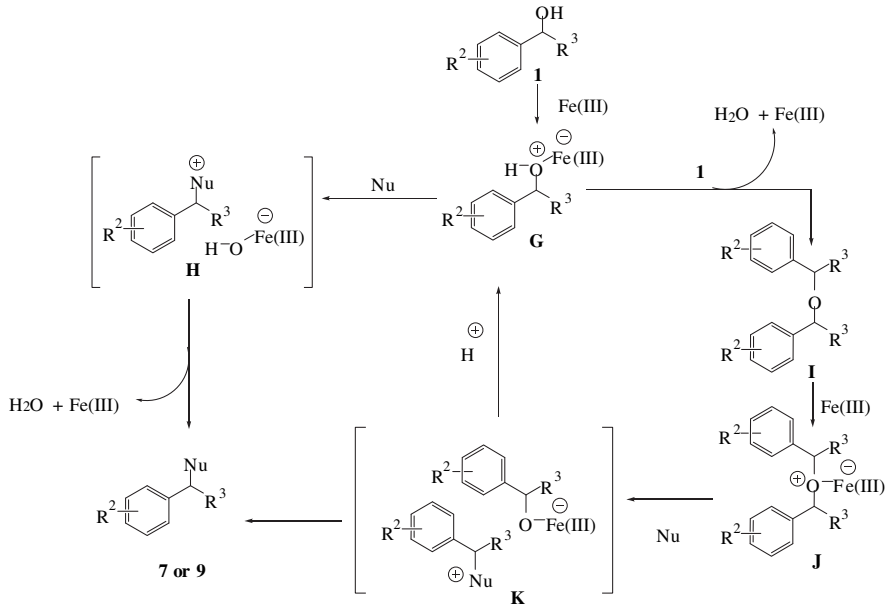
increasing the reaction temperature up to 60 °C (entry 1). The reactions of 4,4′-dimethoxybenzhydrol with various indole derivatives gave the corresponding bis-symmetrical triarylmethanes in excellent yield (entries 2–7). Under similar reaction conditions benzhydrol reacts with electron-rich 1,2,3- and 1,2,4-trimethoxy benzenes to produce the product in 91 and 96%, respectively (entries 8 and 9). The reactions of 4,4′-diflouro-, 4,4′-dichloro and 4,4′-dimethoxybenzhydrol with 1,2,4-trimethoxy benzene also gave corresponding products in 93, 95 and 99% yield, respectively (entries 10–12). 4,4′-Dimethoxybenzhydrol reacts with other activated aromatics, such as 1,3,5-trimethoxybenzene, 1,3- and 1,4-dimethoxybenzenes to afford the bis-symmetrical triarylmethanes in good yields (entries 12–15). The reaction of 4,4′-dimethoxybenzhydrol with anisole gave corresponding *p*-benzylated product (symmetrical triarylmethane) and *o*-benzylated (bis-symmetrical triarylmethanes) product in 76 and 7% yield, respectively (entry 16). However anisole takes longer reaction time and affords much less yield (entry 16).

2.3. C3-Alkylation of 4-hydroxycoumarins

Coumarin and its derivatives are one of the important classes of heterocyclic compounds and known to possess a wide range of biological activities including *anti*-HIV, *anti*-biotic, *anti*-fungal, *anti*-bacterial, *anti*-viral, *anti*-cancer, *anti*-clotting activity and especially as *anti*-coagulants.[17–24] Among the various substituted coumarins, 3-(benzyl)-substituted 4-hydroxycoumarins represent a significant class of the compounds because of the frequent existence of such structures in clinical pharmaceuticals,[25] such as Warfarin, Coumatetralyl, Bromadialone and Difenacoum. Some of the 3-(benzyl)-substituted 4-hydroxycoumarins were employed as synthetic intermediates for the synthesis of various biological active molecules.[26] Recently, several reports are available in the literature for the alkylation of 4-hydroxycoumarins with alcohols in the presence of strong acids,[7a,b] $Yb(OTf)_3$,[7c] Amberlyst IR-120 [7d] and Iodine (Table 6).[7e]

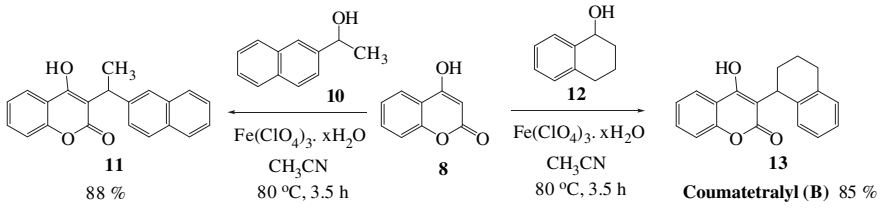
The scope of benzylation reactions have been studied using secondary benzylic alcohols with 4-hydroxycoumarin. The results are summarized in Table 4. We have examined the reactions of 1-phenylethanol (**1a**), 1-(4-methoxyphenyl)ethanol (**1b**) and 1-(4-methylphenyl)ethanol (**1c**) with 4-hydroxycoumarin (**8**) that give rise to the 3-benzylated 4-hydroxycoumarins in good yield (entries 1–3). Under similar reaction conditions 1-(2-methoxyphenyl)-1-propanol (**1g**) reacts with 4-hydroxycoumarin (**8**) to generate the product in 90% yield (entry 4). The efficiency of benzhydrylic alcohols, such as unsubstituted, 4,4′-diflouro-, 4,4′-dichloro and 4,4′-dimethoxybenzhydrol with 4-hydroxycoumarins is examined that proceed smoothly to give the corresponding C3-benzylated products 91, 94, 95 and 98% yield, respectively (entries 5–8).

The sterically hindered alcohol 1-(2-napthyl)ethanol (**10**) is also a good substrate for this reaction. 1-(2-Napthyl)ethanol (**10**) reacts with 4-hydroxycoumarin (**8**) in presence of 5 mol% of $Fe(ClO_4)_3\cdot\times H_2O$ in CH_3CN at 80 °C producing the 4-hydroxy-3-(1-(naphthalene-2-yl)ethyl)-2*H*-chromen-2-one (**11**) in 88% yield (Scheme 2). Finally, the application of the present method is applied to synthesis of an *anti*-coagulant compound 4-hydroxy-3-(1,2,3,4-tetrahydronaphthalen-1-yl)-2*H*-chromen-2-one (Coumatetralyl (B)) (**13**) from 1,2,3,4-tetrahydro-1-naphanol **12** that gives 85% yield (Scheme 4).



Nu= Electron-rich heteroarenes, arenes or 4-hydroxycoumarin

Scheme 3. $Fe(ClO_4)_3\cdot\times H_2O$-catalyzed mechanism for the direct C–C bond coupling reaction of secondary benzylic alcohols with electron-rich heteroarenes, arenes or 4-hydroxycoumarin.



Scheme 4. Synthesis of 4-hydroxy-3-(1-(naphthalene-2-yl)ethyl)-2*H*-chromen-2-one and Coumatetralyl (B).

The probable mechanism for the direct C–C bond coupling reaction of secondary benzylic alcohols with electron-rich heteroarenes, arenes or 4-hydroxycoumarin catalyzed $Fe(ClO_4)_3\cdot\times H_2O$ have been explained in Scheme 3. The catalytic amount of Fe(III) reacts with secondary benzylic alcohols rapidly to produce **G**.[27] The nucleophilic carbon atom attacks on **G** to result in the formation of **7** or **9** by elimination of water molecule through **H**. Similarly, the secondary benzylic alcohols are reacting with **G** to form dimeric ether **I**. The dimeric ether **I** is polarized by Fe(III) to yield **J**. The nucleophilic attack of carbon atom on **J** and subsequent aromatization of **K** leads to the final product **7** or **9**.

3. Summary

$Fe(ClO_4)_3\cdot\times H_2O$ as a highly effective catalyst for benzylation of 1,3-dikones, β-ketoesters, 1,3-diesters, electron-rich arenes and heteroarenes and 4-hydroxycoumarin with various benzylic alcohols is described. The usefulness of this procedure is shown by a synthesis of bis-symmetrical triarylmethanes and one step synthesis of an *anti*-coagulant compound 4-hydroxy-3-(1,2,3,4-tetrahydronaphthalen-1-yl)-2*H*-chromen-2-one (Coumatetralyl (B)). The advantages of this protocol are broad scope, mild conditions, use of inexpensive catalyst and simplicity of operation since water is the only side product.

4. Experimental section

4.1. General experimental procedure for the benzylation of 1,3-dicarbonyl compounds

To a mixture of secondary benzyl alcohol (1 mmol) and 1,3-dicarbonyl compound (3.0 mmol) under solvent-free condition or in CH_3CN (2 mL), $Fe(ClO_4)_3\cdot\times H_2O$ (5 mol %) was added that stirred at rt or 60 °C for 2.5–4.5 h. The progress of the reaction mixture was monitored by TLC. After completion of the reaction, the mixture was quenched with distilled water (5 mL) and extracted with EtOAc (5 mL). The combined organic portions were washed with water (5 mL), saturated aqueous NH_4Cl (5 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was subject to column chromatography to obtain the pure product.

4.2. Experimental procedures for synthesis of bis-symmetrical triarylmethanes and C3-benzylation of 4-hydroxycoumarin

$Fe(ClO_4)_3\cdot\times H_2O$ (5 mol %) was added to a mixture of secondary benzyl alcohol (1 mmol) and electron-rich heteroarene or arene (1.1 mmol) in CH_3CN (2 mL). The resulting solution was stirred for 2.0–7.0 h at rt or 60 °C. The progress of the reaction mixture was monitored by TLC. After completion of the reaction, the mixture was quenched with distilled water (5 mL) and extracted with EtOAc (5 mL). The combined organic portions were washed with water (5 mL), saturated aqueous NH_4Cl (5 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was subject to flash column chromatography (silica gel, hexane–EtOAc, 3:1) to obtain the pure product.

The products were characterized by ^1H and ^{13}C NMR data that are consistent with literature values.[1a–i,2,7a–e] Melting point, HRMS–FAB, ^1H and ^{13}C NMR values for new products are given below.

Compound **3a**. White solid, ^1H NMR (400 MHz, $CDCl_3$) δ: 7.24–7.22 (m, 2H), 7.15–7.12 (m, 3H), 3.99 (d, J=7.8 Hz, 1H), 3.60–3.54 (m, 1H), 2.20 (s, 3H), 1.77 (s, 3H), 1.15 (d, J=7.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 203.3, 143.0, 128.7, 127.2, 126.9, 76.5, 49.4, 29.8, 20.8.

Compound **3b**. White solid, ^1H NMR (400 MHz, $CDCl_3$) δ: 7.07 (d, J=7.6 Hz, 2H), 6.79 (d, J=7.6 Hz, 2H), 3.95 (d, J=7.8 Hz, 1H), 3.73 (s, 3H), 3.57–3.48 (m, 1H), 2.22 (s, 3H), 1.80 (s, 3H), 1.15 (d, J=7.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 203.7, 158.4, 134.9, 128.2, 114.1, 76.9, 55.1, 39.7, 29.8, 20.9.

Compound **3c**.White solid, ^1H NMR (400 MHz, $CDCl_3$) δ: 7.07–7.03 (m, 4H), 3.99 (d, J=7.6 Hz, 1H), 3.58–3.48 (m, 1H), 2.27 (s, 3H), 2.24 (s, 3H), 1.82 (s, 3H), 1.16 (d, J=7.5 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 203.6, 139.9, 136.5, 129.5, 127.1, 76.5, 40.1, 29.7, 20.9.

Compound **3d**. White solid, ^1H NMR (400 MHz, $CDCl_3$) δ; 7.16–7.05 (m, 4H), 4.17 (d, J=11.0 Hz, 1H), 3.94–3.86 (m, 1H), 2.40 (s, 3H), 2.29 (s, 3H), 1.82 (s, 3H), 1.13 (d, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.3, 203.2, 141.3, 135.3, 130.8, 126.5, 126.4, 125.4, 75.9, 34.9, 29.7, 29.3, 20.5, 19.5.

Compound **3e**. White solid, ^1H NMR (400 MHz, $CDCl_3$) δ; 7.26 (d, J=8.4 Hz, 2H), 7.13 (d, J=8.4 Hz, 2H), 3.99 (d, J=11.3 Hz, 1H), 3.63–3.55 (m, 1H), 2.26 (s, 3H), 1.86 (s, 3H), 1.18 (d, J=7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 203.1, 203.0, 141.5, 132.7, 128.9, 128.6, 76.6, 39.8, 29.8, 29.6, 20.7.

Compound **3f**. White solid, ^1H NMR (400 MHz, $CDCl_3$) δ; 7.31–7.26 (m, 2H), 7.22–7.19 (m, 1H), 7.15 (d, J=7.6 Hz, 2H), 4.11 (d, J=11.0 Hz, 1H), 3.35 (td, J=11.0, 3.0 Hz, 1H), 2.27 (s, 3H), 1.80 (s, 3H), 1.62–154 (m, 1H), 1.52–1.44 (m, 1H), 0.69 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.5, 204.2, 141.4, 129.5, 129.1, 127.9, 77.0, 48.5, 30.7, 30.5, 21.5.

Compound **3g**. White solid, ^1H NMR (400 MHz, $CDCl_3$) δ; 7.20–7.15 (m, 1H), 7.07 (d, J=7.6 Hz, 2H), 6.90–6.84 (q, J=7.6 Hz, 2H), 4.31 (d, J=11.0 Hz, 1H), 3.83 (s, 3H), 2.26 (s, 3H), 1.85 (s, 3H), 1.60–1.51 (m, 2H), 0.68 (t, J=7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 204.2, 203.6, 157.5, 129.4, 128.4, 128.0, 120.6, 110.9, 74.5, 55.2, 41.5, 30.4, 28.3, 26.7, 11.5; HRMS–FAB (m/z): $[M]^+$ calcd for $C_{15}H_{20}O_3$: 248.1412, found: 248.1412.

Compound **3h**. White solid, ^1H NMR (400 MHz, $CDCl_3$) δ; 7.06 (d, J=7.5 Hz, 2H), 6.74 (d, J=7.5 Hz, 2H), 4.14 (t, J=7.6 Hz, 2H), 3.68 (s, 3H), 3.67 (d, J=11.0 Hz, 1H), 2.21 (s, 3H), 1.27 (t, J=7.6 Hz, 3H), 1.14 (d, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.3, 202.3, 168.5, 168.0, 140.1, 139.9, 136.3, 136.1, 129.2, 128.9, 127.1, 127.0, 67.5, 66.9, 61.3, 60.9, 39.5, 39.2, 29.6, 29.3, 20.8, 20.5, 20.2, 13.9, 13.6.

Compound **3i**. White solid, ^1H NMR (400 MHz, $CDCl_3$) δ; 7.13 (d, J=8.4 Hz, 2H), 6.79 (d, J=8.4 Hz, 2H), 4.23 (t, J=7.0 Hz, 2H), 3.77 (s, 3H), 2.45–242 (m, 2H), 2.10–2.05 (m, 1H), 1.96–1.89 (m, 1H), 1.70–1.65 (m, 1H), 1.56–1.49 (m, 2H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 208.1, 171.7, 158.8, 134.7, 131.0, 113.6, 65.2, 61.6, 55.7, 42.3, 36.2, 28.1, 23.3, 18.5, 14.7.

Compound **5a**. White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.27–7.24 (m, 8H), 7.18–7.13 (m, 2H), 4.81 (d, J=12.0 Hz, 1H), 4.81 (d, J=12.0 Hz, 1H), 4.73 (d, J=12.5 Hz, 1H), 2.0 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.9, 141.2, 128.8, 127.6, 126.9, 74.4, 51.1, 29.6.

Compound **5a**. (Dimeric ether) White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.99 (d, J=8.0 Hz, 4H), 7.56–754 (m, 2H), 7.51–7.49 (m, 4H), 6.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 186.3, 136.1, 133.0, 129.3, 127.7, 93.7.

Compound **5b**. White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.95 (d, J=8.4 Hz, 2H), 7.50–7.54 (m, 1H), 7.41 (d, J=6.5 Hz, 2H), 7.37 (d, J=7.0 Hz, 2H), 7.32–7.28 (m, 2H), 7.26–7.20 (m, 3H), 7.15–7.11 (m, 2H), 7.05–7.02 (m, 1H), 5.02 (d, J=12.0 Hz, 1H), 5.11 (d, J=12.0 Hz, 1H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.9, 194.2, 141.6, 141.2, 136.8, 133.6, 128.9, 128.7, 128.6, 128.0, 127.7, 127.0, 126.6, 68.8, 51.4, 27.8.

Compound **5c**. White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.83 (d, J=8.4 Hz, 4H), 7.58–7.44 (m, 3H), 7.53–7.44 (m, 3H), 7.35–7.30 (m, 4H), 7.25 (d, J=8.4 Hz, 4H), 7.17–7.12 (m, 4H), 7.07–7.01 (m, 2H), 6.35 (d, J=12.0 Hz, 1H), 5.36 (d, J=12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.1, 141.7, 136.9, 133.2, 132.4, 128.6, 128.3, 127.2, 126.6, 62.3, 52.4.

Compound **5d**. White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.23 (d, J=8.5 Hz, 4H), 7.15 (d, J=8.5 Hz, 4H), 4.80 (d, J=12.5 Hz, 1H), 4.59 (d, J=12.0 Hz, 1H), 2.0 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.0, 139.3, 133.0, 129.1, 129.0, 74.3, 49.5, 29.6.

Compound **5e**. White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.20 (d, J=8.6 Hz, 2H), 7.18 (d, J=8.6 Hz, 2H), 6.95 (d, J=8.6 Hz, 4H), 4.80 (d, J=12.5 Hz, 1H), 4.64 (d, J=12.0 Hz, 1H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.0, 164.8, 159.8, 137.5, 129.9, 129.7, 116.7, 116.3, 75.4, 50.1, 30.2.

Compound **5f**. White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.15 (d, J=8.4 Hz, 4H), 6.78 (d, J=8.6 Hz, 4H), 4.70 (d, J=12.0 Hz, 1H), 4.63 (d, J=12.0 Hz, 1H), 2.72 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.3, 158.3, 133.7, 128.6, 114.3, 74.9, 55.1, 49.7, 29.7.

Compound **5g**. White solid, mp 107–108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.95 (d, J=8.4 Hz, 2H), 7.54–7.52 (m, 1H), 7.44–7.39 (m, 2H), 7.26 (d, J=8.8 Hz, 2H), 7.13 (d, J=8.8 Hz, 2H), 6.84 (d, J=8.8 Hz, 2H), 6.67 (d, J=8.8 Hz, 2H), 5.52 (d, J=11.7 Hz, 1H), 5.02 (d, J=12.0 Hz, 1H), 3.75 (s, 3H), 3.65 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 203.2, 194.4, 158.4, 158.0, 136.9, 134.2, 133.6, 133.5, 129.0, 128.7, 128.5, 114.3, 113.9, 69.3, 55.1, 55.0, 49.9, 27.6.

Compound **5h**. White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.27–7.25 (m, 8H), 7.18–7.14 (m, 2H), 4.77 (d, J=12.0 Hz, 1H), 4.54 (d, J=12.0 Hz, 1H), 3.53 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.7, 168.1, 141.4, 141.0, 128.8, 128.6, 127.8, 127.5, 126.9, 126.8, 64.9, 52.5, 50.8, 30.0.

Compound **5i**. White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.30–7.22 (m, 8H), 7.17–7.12 (m, 2H), 4.77 (d, J=12.0 Hz, 1H), 4.52 (d, J=12.0 Hz, 1H), 3.96 (q, J=7.0 Hz, 4H), 2.08 (s, 3H), 0.98 (t, J=7.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.7, 167.6, 141.5, 141.2, 128.7, 128.5, 127.7, 127.6, 126.9, 126.7, 65.1, 61.4, 50.8, 29.9, 13.7.

Compound **5j**. White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.43–7.93 (m, 4H), 7.23–7.19 (m, 4H), 7.16–7.13 (m, 2H), 3.89–3.87 (m, 1H), 3.80–3.76 (m, 1H), 2.65–2.58 (m, 1H), 2.45–2.32 (m, 2H), 1.89–1.82 (m, 1H), 1.77–1.64 (m, 2H), 1.57–1.42 (m, 2H), 0.89 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.1, 170.5, 140.7, 140.4, 130.5, 130.1, 127.8, 126.4, 126.2, 65.7, 61.1, 54.0, 41.7, 34.7, 26.6, 22.6, 13.3.

Compound **5k**. White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.29 (d, J=7.0 Hz, 4H), 7.25–7.21 (m, 4H), 7.16–7.12 (m, 4H), 4.75 (d, J=12.0 Hz, 1H), 4.33 (d, J=12.0 Hz, 1H), 4.19 (q, J=7.0 Hz, 4H), 1.26 (t, J=7.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.5, 141.2, 128.4, 127.6, 126.7, 61.3, 57.3, 41.4, 13.8.

Compound **5l**. White solid, mp 98–99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.26–7.15 (m, 8H), 4.73 (d, J=12.0 Hz, 1H), 4.43 (d, J=12.0 Hz, 1H), 4.00 (q, J=7.0 Hz, 4H), 2.11 (s, 3H), 1.04 (t, J=7.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 200.8, 167.2, 139.6, 139.4, 133.0, 132.9, 129.1, 129.0, 128.9, 128.8, 64.8, 61.7, 49.2, 30.1, 13.8; HRMS–FAB (m/z): $[M]^+$ calcd for $C_{19}H_{19}Cl_2O_3$: 365.0711, found: 365.0711.

Compound **5m**. Viscous, ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.27–7.21 (m, 4H), 6.95 (t, J=8.8 Hz, 4H), 4.79 (d, J=12.0 Hz, 1H), 4.46 (d, J=12.0 Hz, 1H), 4.00 (q, J=7.0 Hz, 4H), 2.11 (s, 3H), 1.03 (t, J=7.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 201.1, 167.3, 162.8, 160.4, 137.1, 136.9, 129.1, 129.0, 115.7, 115.4, 65.3, 61.6, 49.1, 29.9, 13.7; HRMS–FAB (m/z): $[M]^+$ calcd for $C_{19}H_{19}F_2O_3$: 333.1304, found: 333.1302.

Compound **5n**. White solid, mp 101–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 8.02 (d, J=7.3 Hz, 2H), 7.54 (t, J=7.3 Hz, 1H), 7.43 (t, J=7.3 Hz, 2H), 7.29 (d, J=8.4 Hz, 2H), 7.14 (d, J=8.8 Hz, 2H), 6.83 (d, J=8.8 Hz, 2H), 6.68 (d, J=8.8 Hz, 2H), 5.34 (d, J=11.7 Hz, 1H), 5.01 (d, J=11.7 Hz, 1H), 3.95–3.85 (m, 2H), 3.75 (s, 3H), 3.65 (s, 3H), 0.97 (t, J=7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 192.9, 167.7, 157.2, 157.9, 136.6, 134.1, 133.4, 129.0, 128.6, 128.5, 113.9, 113.8, 61.4, 59.8, 55.1, 55.0, 49.3, 13.7; HRMS–FAB (m/z): $[M]^+$ calcd for $C_{26}H_{26}O_5$: 418.1780, found: 418.1778.

Compound **7a**. White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.89 (br s, 1H), 7.32 (d, J=8.4 Hz, 1H), 7.29–7.13 (m, 12H), 6.97 (t, J=8.0 Hz, 1H), 6.54 (d, J=2.0 Hz, 1H), 5.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.9, 136.7, 129.0, 128.2, 126.9, 126.2, 124.0, 122.1, 119.9, 119.4, 111.0, 48.8.

Compound **7b**. White solid, mp 117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.90 (br s, 1H), 7.32 (d, J=8.4 Hz, 2H), 7.23 (d, J=8.4 Hz, 4H), 7.11–7.06 (m, 1H), 7.23 (d, J=8.4 Hz, 4H), 6.91 (m, 1H), 6.56 (s, 1H), 5.67 (s, 1H), 3.84 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.8, 136.6, 136.5, 129.7, 126.8, 123.8, 121.9, 120.3, 119.8, 119.1, 113.5, 111.0, 55.1, 47.0; HRMS–FAB (m/z): $[M]^+$ calcd for $C_{23}H_{21}NO_2$: 343.1572, found: 343.1572.

Compound **7c**. White solid, mp 116–117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.43 (d, J=7.8 Hz, 2H), 7.37 (d, J=6.7 Hz, 1H), 7.34 (d, J=8.0 Hz, 4H), 7.16 (t, J=8.4 Hz, 1H), 7.00 (d, J=8.4 Hz, 4H), 6.59 (s, 1H), 5.78 (s, 1H), 3.89 (s, 6H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.7, 137.3, 136.5, 129.6, 128.4, 127.2, 121.4, 119.9, 118.8, 118.6, 113.4, 108.9, 54.9, 47.0, 32.2; HRMS–FAB (m/z): $[M]^+$ calcd for $C_{24}H_{23}NO_2$: 357.1729, found: 357.1729.

Compound **7d**. White solid, mp 129–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.90 (br s, 1H), 7.20 (d, J=9.0 Hz, 1H), 7.18 (d, J=8.8 Hz, 4H), 6.86 (d, J=8.8 Hz, 5H), 6.70 (d, J=2.0 Hz, 1H), 6.54 (d, J=2.0 Hz, 1H), 5.56 (s, 1H), 3.80 (s, 6H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.8, 153.6, 136.4, 131.8, 129.7, 127.3, 124.6, 120.1, 113.5, 111.9, 111.6, 102.0, 55.7, 55.1, 47.1; HRMS–FAB (m/z): $[M]^+$ calcd for $C_{24}H_{23}NO_3$: 373.1678, found: 373.1678.

Compound **7e**. White solid, mp 132–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 8.04 (br s, 1H), 7.04 (d, J=1.8 Hz, 1H), 7.25(dd, J=7.0, 1.8 Hz, 1H), 7.16 (d, J=8.4 Hz, 1H), 7.12 (d, J=8.8 Hz, 4H), 6.84 (d, J=8.8 Hz, 4H), 6.54 (d, J=1.8 Hz, 1H), 5.53 (s, 1H), 3.78 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.9, 136.0, 135.2, 129.6, 128.6, 125.1, 124.8, 122.2, 120.1, 113.6, 112.5, 112.5, 55.1, 46.8; HRMS–FAB (m/z): $[M]^+$ calcd for $C_{23}H_{20}BrNO_2$: 421.0677, found: 421.0677.

Compound **7f**. White solid, mp 166–167 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.72 (br s, 1H), 7.21 (d, J=7.8 Hz, 1H), 7.12 (d, J=8.4 Hz, 4H), 7.06–7.02 (m, 2H), 6.90 (t, J=8.4 Hz, 2H), 6.81 (d, J=8.4 Hz, 4H), 5.64 (s, 1H), 3.74 (s, 6H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.7, 136.3, 135.1, 131.8, 129,7, 128.3, 120.6, 119.5, 119.0, 114.4, 113.5, 110.1, 55.2, 46.0, 12.3; HRMS–FAB (m/z): $[M]^+$ calcd for $C_{24}H_{23}NO_2$: 357.1729, found: 357.1729.

Compound **7g**. White solid, mp 129–130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.93 (br s, 1H), 7.20 (d, J=8.4 Hz, 4H), 6.88 (d, J=8.8 Hz, 4H), 6.73 (d, J=2.5 Hz, 1H), 6.54 (d, J=2.1 Hz, 1H), 5.58 (s, 1H), 3.81 (s, 6H), 3.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.8, 153.5, 136.4, 131.8, 129.7, 127.3, 124.6, 120.0, 113.5, 111.8, 111.7, 101.9, 55.7, 55.1, 47.0; EI (m/z): $[M]^+$ calcd for $C_{25}H_{23}NO_4$: 401.1627, found: 401.18, 400.16, 2677.09, 228.16, 227.12, 105.04.

Compound **7h**. White solid, mp 124–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.30–7.26 (m, 4H), 7.22–7.20 (m, 2H), 7.12 (d, J=7.4 Hz,

4H), 6.57 (d, *J*=8.8 Hz, 1H), 6.53 (d, *J*=8.4 Hz, 1H), 5.85 (s, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.3, 151.7, 144.0, 142.3, 130.6, 129.4, 128.1, 128.0, 126.1, 124.3, 106.6, 60.6, 60.5, 55.8, 49.9; HRMS–FAB (*m*/*z*): $[M]^+$ calcd for $C_{22}H_{22}O_3$: 334.1569, found: 334.1569.

Compound **7j**. White solid, mp 125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.28–7.24 (m, 4H), 7.20–7.17 (m, 2H), 7.11 (d, *J*=7.0 Hz, 4H), 6.55 (s, 1H), 6.46 (s, 1H), 5.89 (s, 1H), 3.87 (s, 3H), 3.66 (s, 3H), 3.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.3, 148.1, 144.0, 142.7, 129.2, 128.0, 125.9, 124.2, 114.7, 98.0, 56.6, 56.5, 56.0, 49.1; HRMS–FAB (*m*/*z*): $[M]^+$ calcd for $C_{22}H_{22}O_3$: 334.1569, found: 334.1569.

Compound **7j**. White solid, mp 147–148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.23 (d, *J*=8.4 Hz, 4H), 6.99 (d, *J*=8.4 Hz, 4H), 6.53 (s, 1H), 6.35 (s, 1H), 5.77 (s, 1H), 3.88 (s, 3H), 3.67 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.3, 148.6, 142.8, 142.1, 132.0, 130.5, 128.3, 123.0, 114.4, 97.8, 56.7, 56.5, 56.1, 48.0; HRMS–FAB (*m*/*z*): $[M]^+$ calcd for $C_{22}H_{20}Cl_2O_3$: 402.0791, found: 402.0790.

Compound **7k**. White solid, mp 126–127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 6.99 (d, *J*=8.4 Hz, 4H), 6.79 (d, *J*=8.8 Hz, 4H), 6.53 (s, 1H), 6.44 (s, 1H), 5.76 (s, 1H), 3.86 (s, 3H), 3.76 (s, 6H), 3.66 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.4, 160.0, 151.2, 148.4, 142.7, 139.5, 139.4, 130.4, 130.5, 123.7, 114.9, 114.7, 114.4, 97.8, 56.5, 56.4, 55.9, 47.7; HRMS–FAB (*m*/*z*): $[M]^+$ calcd for $C_{22}H_{20}F_2O_3$: 370.1381, found: 370.1379.

Compound **7l**. White solid, mp 127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.03 (d, *J*=8.8 Hz, 2H), 7.02 (d, *J*=8.0 Hz, 2H), 6.94 (t, *J*=8.4 Hz, 4H), 6.55 (s, 1H), 6.37 (s, 1H), 5.81 (s, 1H), 3.87 (s, 3H), 3.66 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.7, 151.3, 148.0, 142.7, 136.5, 130.0, 125.0, 114.6, 113.4, 98.1, 56.7, 56.6, 56.0, 55.1, 47.4; HRMS–FAB (*m*/*z*): $[M]^+$ calcd for $C_{24}H_{26}O_5$: 394.1780, found: 394.1779.

Compound **7m**. White solid, mp 108–109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.13 (d, *J*=8.8 Hz, 4H), 6.79 (d, *J*=8.8 Hz, 4H), 6.17 (s, 2H), 5.98 (s, 1H), 3.81 (s, 3H), 3.79 (s, 6H), 3.62 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.8, 159.0, 157.3, 136.5, 130.0, 114.0, 112.8, 91.6, 55.7, 55.2, 55.1, 43.5; HRMS–FAB (*m*/*z*): $[M]^+$ calcd for $C_{24}H_{26}O_5$: 394.1780, found: 394.1779.

Compound **7n**. White solid, mp 94–95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.06 (d, *J*=8.4 Hz, 4H), 6.86 (d, *J*=8.0 Hz, 4H), 6.82 (d, *J*=8.4 Hz, 1H), 6.53 (d, *J*=2.2 Hz, 1H), 6.45 (dd, *J*=8.4, 2.2 Hz, 1H), 5.81 (s, 1H), 3.82 (s, 3H), 3.81 (s, 6H), 3.74 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.2, 157.8, 157.6, 136.6, 130.4, 130.0, 125.7, 113.3, 103.6, 98.5, 55.4, 55.1, 55.0, 47.3; HRMS–FAB (*m*/*z*): $[M]^+$ calcd for $C_{23}H_{24}O_4$: 364.1675, found: 364.1675.

Compound **7o**. White solid, mp 102–103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 6.99 (d, *J*=8.4 Hz, 4H), 6.79 (d, *J*=8.8 Hz, 5H), 6.70 (dd, *J*=8.4, 3.0 Hz, 1H), 6.45 (d, *J*=3.0 Hz, 1H), 5.78 (s, 1H), 3.76 (s, 6H), 3.66 (s, 3H), 3.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.8, 153.3, 151.5, 136.1, 134.7, 130.2, 129.6, 117.2, 113.7, 113.4, 111.8, 110.8, 56.4, 55.5, 55.1, 48.0; HRMS–FAB (*m*/*z*): $[M]^+$ calcd for $C_{23}H_{24}O_4$: 364.1675, found: 364.1675.

Compound **7p**. Viscous, (*p*-benzylated product) White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.08 (d, *J*=8.5 Hz, 6H), 6.88 (d, *J*=8.5 Hz, 6H), 5.43 (s, 1H), 3.82 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 157.8, 136.7, 130.1, 113.5, 55.1, 54.3; HRMS–FAB (*m*/*z*): $[M]^+$ calcd for $C_{22}H_{22}O_3$: 334.1569, found: 334.1569.

Compound **7p**. Viscous, (*o*-benzylated product) White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.01–6.95 (m, 6H), 6.80–6.78 (m, 5H), 6.72 (d, *J*=8.5 Hz, 1H), 5.79 (s, 1H), 3.78 (s, 6H), 3.68 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 157.7, 157.6, 155.3, 136.9, 136.2, 136.1, 132.8, 131.5, 130.1, 130.0, 113.4, 113.3, 55.6, 55.1, 47.8; HRMS–FAB (*m*/*z*): $[M]^+$ calcd for $C_{22}H_{22}O_3$: 334.1569, found: 334.1569.

Compound **9a**. White solid, mp 202 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.67 (d, *J*=8.5 Hz, 1H), 7.58–7.18 (m, 8H), 4.76 (q, *J*=7.5 Hz, 1H), 1.67 (d, *J*=7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 161.0, 152.9, 143.9, 131.4, 127.5, 127.0, 125.4, 123.2, 123.0, 116.3, 115.8, 109.6, 33.6, 16.5.

Compound **9b**. White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.88 (d, *J*=7.8 Hz, 1H), 7.50 (t, *J*=8.0 Hz, 1H), 7.36 (d, *J*=9.0 Hz, 2H), 7.29–7.25 (m, 2H), 6.83 (d, *J*=8.8 Hz, 2H), 4.58 (q, *J*=7.3 Hz, 1H), 3.77 (s, 3H), 1.71 (d, *J*=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.5, 160.4, 157.6, 152.1, 135.2, 131.2, 128.1, 123.5, 122.7, 166.3, 116.0, 113.3, 109.8, 54.8, 33.1, 16.4.

Compound **9c**. White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.63 (d, *J*=7.8 Hz, 1H), 7.46 (t, *J*=8.4 Hz, 1H), 7.34 (d, *J*=7.8 Hz, 2H), 7.26 (d, *J*=8.4 Hz, 1H), 7.23–7.16 (m, 3H), 4.68 (q, *J*=7.3 Hz, 1H), 2.36 (s, 3H), 1.64 (d, *J*=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.5, 159.9, 152.5, 138.3, 137.6, 131.7, 130.4, 127.2, 123.7, 122.9, 116.3, 116.2, 110.0, 34.2, 21.0, 16.5.

Compound **9d**. White solid, mp 206–207 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.81 (d, *J*=8.4 Hz, 1H), 7.77 (dd, *J*=7.6, 1.8 Hz, 1H), 7.42 (td, *J*=8.4, 1.8 Hz, 1H), 7.23–7.19 (m, 3H), 7.01 (t, *J*=7.6 Hz, 1H), 6.88 (d, *J*=8.0 Hz, 1H), 4.28 (t, *J*=7.6 Hz, 1H), 3.96 (s, 3H), 2.44–2.40 (m, 1H), 2.31–2.22 (m, 1H), 0.89 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.2, 160.7, 155.1, 152.6, 131.3, 130.2, 129.8, 127.7, 123.5, 123.3, 122.4, 116.3, 116.0, 110.6, 107.3, 56.0, 36.8, 23.8, 13.0; HRMS–FAB (*m*/*z*): $[M+H]^+$ calcd for $C_{19}H_{19}O_4$: 311.1284, found: 311.1283.

Compound **9e**. White solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ; 7.74 (dd, *J*=9.5, 1.5 Hz, 1H), 7.50 (td, *J*=8.4, 1.5 Hz, 1H), 7.37–7.20 (m, 12H), 5.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.3, 160.9, 152.6, 140.0, 132.0, 129.3, 128.7, 127.6, 123.8, 123.1, 116.3, 115.9, 107.6, 47.2.

Compound **9f**. White solid, mp 210–212 °C; ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD) δ; 7.83 (dd, *J*=8.0, 1.0 Hz, 1H), 7.52 (td, *J*=8.4, 1.0 Hz, 1H), 7.29–7.19 (m, 9H), 7.11 (t, *J*=8.4 Hz, 1H), 5.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ: 163.5, 162.1, 152.6, 139.3, 132.6, 132.1, 130.1, 128.7, 123.9, 123.1, 116.5, 116.2, 107.0, 45.3; HRMS–FAB (*m*/*z*): $[M+H]^+$ calcd for $C_{22}H_{15}Cl_2O_3$: 397.0402, found: 397.0398.

Compound **9g**. White solid, mp 198–199 °C; ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD) δ; 7.75 (dd, *J*=8.0, 1.5 Hz, 1H), 7.49 (td, *J*=8.4, 1.5 Hz, 1H), 7.25–7.17 (m, 6H), 6.98 (t, *J*=8.8 Hz, 4H), 5.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ: 163.1, 161.1, 160.6, 152.6, 136.0, 132.3, 130.2, 124.0, 123.0, 116.5, 115.9, 115.7, 107.5, 45.4; HRMS–FAB (*m*/*z*): $[M+H]^+$ calcd for $C_{22}H_{15}F_2O_3$: 365.0992, found: 365.0989.

Compound **9h**. Red solid, mp 202–203 °C; ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD) δ; 7.74 (dd, *J*=8.4, 1.4 Hz, 1H), 7.50 (td, *J*=8.4, 1.5 Hz, 1H), 7.30–7.21 (m, 2H), 7.18 (d, *J*=8.8 Hz, 4H), 6.88 (d, *J*=8.8 Hz, 4H), 5.83 (s, 1H), 3.79 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ: 163.3, 161.0, 152.7, 132.2, 131.9, 129.8, 123.8, 123.1, 116.2, 114.6, 107.8, 55.2, 45.7 HRMS–FAB (*m*/*z*): $[M+H]^+$ calcd for $C_{24}H_{21}O_5$: 389.1388, found: 389.1389.

Compound **11**. White solid, mp 171–172 °C; ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD) δ; 7.94 (s, 1H), 7.82 (d, *J*=7.3 Hz, 1H), 7.80–7.76 (m, 2H), 7.67 (d, *J*=9.5 Hz, 1H), 7.43–7.51 (m, 4H), 7.25 (d, *J*=8.0 Hz, 1H), 7.17 (t, *J*=7.3 Hz, 1H), 4.86 (q, *J*=7.3 Hz, 1H), 1.77 (t, *J*=7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ: 163.3, 161.2, 152.2, 140.9, 133.1, 131.8, 131.2, 127.4, 127.2, 127.1, 126.2, 125.5, 125.0, 124.8, 123.5, 122.7, 116.4, 116.0, 109.4, 34.0, 16.1 HRMS–FAB (*m*/*z*): $[M+H]^+$ calcd for $C_{21}H_{17}O_3$: 317.1180, found: 317.1178.

Compound **12**. White solid, mp 189–190 °C; ^{1}H NMR (400 MHz, $CDCl_3$+CD_3OD) δ; 7.74 (d, *J*=7.5 Hz, 1H), 7.39 (t, *J*=7.3 Hz, 1H), 7.18–7.10 (m, 2H), 6.96 (d, *J*=8.0 Hz, 4H), 4.44 (t, *J*=7.0 Hz, 1H), 2.89–2.81 (m, 1H), 2.01–1.86 (m, 4H), 1.75–1.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$+CD_3OD) δ: 164.0, 162.6, 152.4, 137.4, 131.2, 129.2, 127.6, 126.1, 123.5, 123.1, 117.1, 116.0, 108.6, 35.7, 29.6, 27.9, 22.6.

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