# Catalytic Synthesis of Triarylmethane Derivatives via Friedel-Crafts Alkylation

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## Abstract

This article reviews the recent developments in and contributions to research related to triarylmethanes (TRAM) derivatives. TRAMs have attracted much attention from scientists and many of these compounds have widespread applications in synthetic, medicinal, and industrial chemistry. The catalytic Friedel-Crafts reaction of aromatic ring with aromatic aldehyde and their imine is emerging as a promising new approach to the synthesis of TRAM derivatives regioselectively under mild conditions. The catalytic Friedel-Crafts reactions are mediated by various Lewis acids that work in simpler, and more efficient, catalytic, and environmentally friendly ways.

**Keywords:** Catalytic Friedel-Crafts alkylation, Triarylmethanes, Lewis acids

## 1. Introduction

Triarylmethanes (TRAMs) have attracted considerable attention of many scientists due to their various biological activities [1], [2] such as antiviral, antitumor, antitubercular, antifungal, and anti-inflammatory agents (Figure 1). Moreover, these classes of compounds have found widespread application in the chemical industry (Figure 1) as leuco dyes, photochromic agents, protective groups in organic synthesis, suitable building blocks for generating dendrimers, and substrates for theoretical and biological studies [3].

Numerous methods of construction of triarylmethane frameworks have been developed. However, most of these methods are multi-step processes, or require harsh reaction conditions. As a result, there still exists a need for development of new approaches to the synthesis of TRAMs in simpler and more efficient, catalytic and environmentally friendly ways. Very recently, the catalytic Friedel-Crafts alkyalation of aromatic ring with aromatic aldehyde and imine using various Lewis acids promoting systems (Scheme 1) are emerging as effective methods for the synthesis of triaylmethanes, regioselectively, under mild conditions [4], [5]. The scope of this method and its application are described herein.

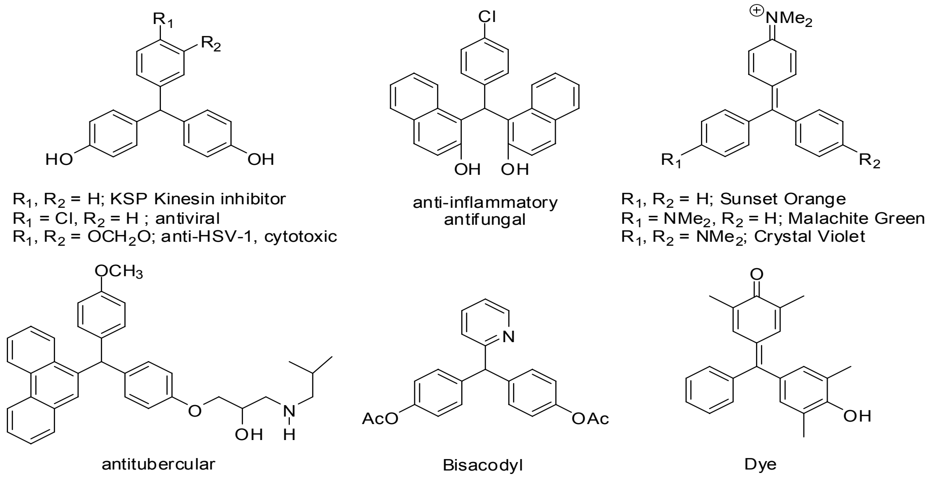
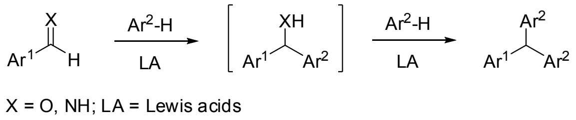


**Figure 1**

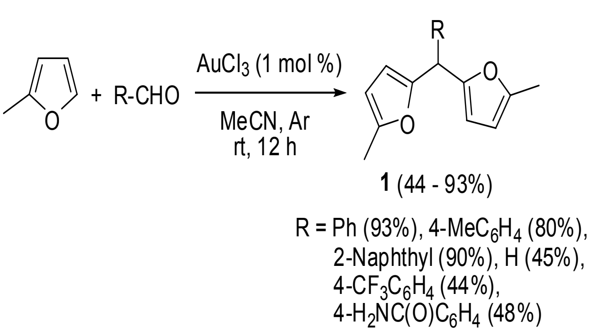


**Scheme 1**

## 2. Catalytic Friedel-Crafts reaction of aromatic ring with aldehyde

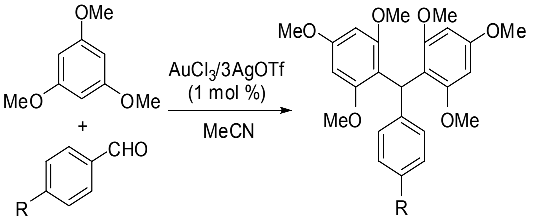
### 2.1 $AuCl_3$ and $AuCl_3$/3AgOTf-catalyzed Friedel-Crafts reaction

Nair et al. [6] developed a mild and practical methodology for the synthesis of triaryl- and triheteroarylmethanes using $AuCl_3$ or $AuCl_3$/3AgOTf-mediated Friedel-Crafts reaction of aromatic aldehyde with 1,3,5-trimethoxybenzene or heteroarenes, respectively. The reaction of 2-methylfuran with aromatic aldehyde in the presence of $AuCl_3$ (1 mol %) in $CH_3CN$ under argon atmosphere at room temperature for 12 h to afford the corresponding bis(furyl)arylmethanes **1** in 44-93% yields (Scheme 2).



**Scheme 2**

The electron-rich arene, 1,3,5-trimethoxybenzene, also condensed effectively with benzaldehyde, but it required a modified catalytic system ($AuCl_3$/3AgOTf) and a slightly elevated temperature (50 °C). With more electrophilic aldehyde, 4-nitrobenzaldehyde, the reaction took place at room temperature to provide the triarylmethane adduct **2** in high yield (Scheme 3).



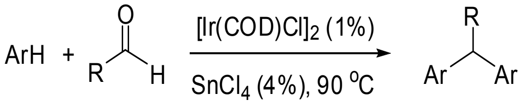
**2** (45 - 85%)

R = H, rt, 12 h, (% yield = 45%)
R = H, 50 °C, 12 h, (% yield = 85%)
R = $NO_2$, rt, 12 h, (% yield = 80%)

**Scheme 3**

### 2.2 $[Ir(COD)Cl]_2$-$SnCl_4$-catalyzed Friedel-Crafts reaction

Roy et al. [2] developed a facile protocol using a dual reagent catalysis concept for the bisarylation of aldehydes. Reactions of arenes and heteroarenes with aromatic or heteroaromatic aldehydes were carried out in the presence of a catalytic combination of $[Ir(COD)Cl]_2$-$SnCl_4$ at 90 °C to afford the corresponding triarylmethanes in moderate to high yields (Scheme 4). The reaction of aliphatic aldehyde was also employed in this reaction. The reactions of aromatic and heteroaromatic aldehydes having electron-withdrawing substituent on the aromatic ring were generally facile but those of aliphatic aldehydes were comparatively low in yield (30-37%).



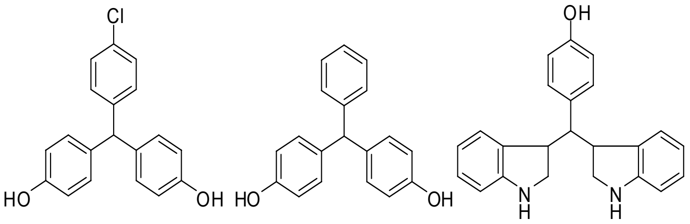
**3** (30 - 99%)

ArH = phenol, 1,3,5-trimethoxybenzene,
anisole, 1,2-dimethoxybenzene,
1,4-dimethoxybenzene,
1-methoxynaphthalene,
4-methylphenol, 4-chlorophenol,
thiophenol, 2,5-dimethylfuran

RCHO = $C_6H_5CHO$, 4-$O_2NC_6H_4CHO$,
4-$ClC_6H_4CHO$, 4-$MeC_6H_4CHO$,
p-formaldehyde, propanal

**Scheme 4**

Further bimetallic Ir-Sn catalyst combination could be employed for the preparation of three bioactive TRAMs **4-6** varying the aldehyde and arene motifs. In each case, the desired product was obtained in good yields and with excellent regioselectivity (Figure 2)



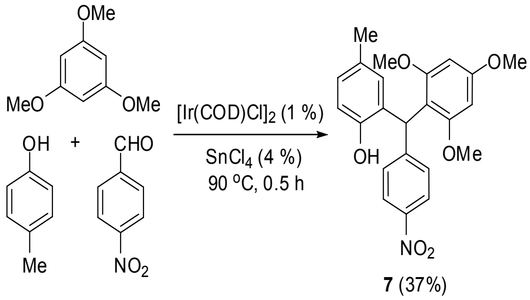
**4** (65%)
Antiviral

**5** (56%)
KSP Kinesin Inhibitor

**6** (82%)
Antimicrobial

**Figure 2**

Furthermore, the reaction of 4-nitrobenzaldehyde (1 mmol) with a mixture of 1,3,5-trimethoxybenzene (1 mmol) and 4-methylphenol (1 mmol) proceeded smoothly in the presence of a catalytic combination of $[Ir(COD)Cl]_2$-$SnCl_4$ at 90 °C to yield asymmetrical triarylmethane **7** in 37% yield (Scheme 5).

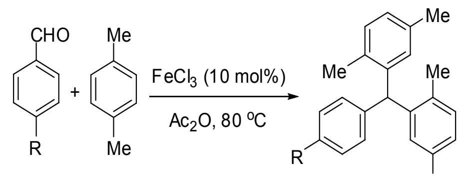


**7** (37%)

**Scheme 5**

### 2.3 $FeCl_3$-catalyzed Friedel-Crafts reaction

$FeCl_3$ have attracted the attention of synthetic organic chemists since iron is one of the most abundant metals on earth and consequently one of the most readily available, inexpensive, low toxic, and easily handled catalysts. Recently, Wu et al. [1] used $FeCl_3$ as a catalyst for Friedel-Crafts reaction of arenes with aromatic aldehydes under ‘open-flask’ and mild conditions. In the presence of acetic anhydride and stirring the reaction at 80°C, the reactions proceeded smoothly with both electron-rich and electron-poor aromatic aldehyde to provide a facile and direct acess to symmetrical triarylmethane derivatives, and acetylation of arenes was not observed in these reactions (Scheme 6). Longer reaction times were required (50 h) when highly electron-deficient *p*-nitrobenzaldehyde was used.

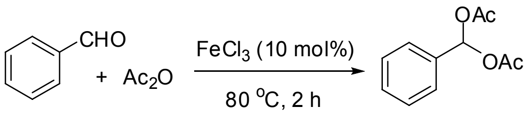


**8** (70-85%)

R = H, 22 h (% yield = 79%)
R = Cl, 22 h (% yield = 75%)
R = Br, 22 h (% yield = 78%)
R = Me, 10 h (% yield = 85%)
R = $NO_2$, 50 h (% yield = 70%)

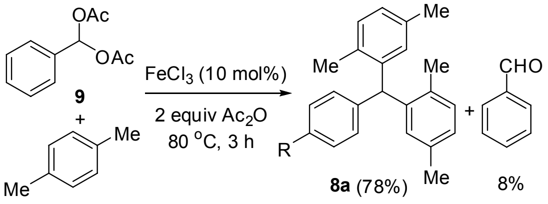
**Scheme 6**

The presence of acetic anhydride is crucial to this $FeCl_3$ catalyzed TRAMs formation. The role of $Ac_2O$ and $FeCl_3$ was proven through the experimentation with benzaldehyde and the reaction afforded diacetate **9** in 60% isolated yields (Scheme 7). The purified **8** was treated with *p*-xylene in the presence of $Ac_2O$ (2 equiv) and $FeCl_3$ leading to the triarylmethane adduct **8a** in 78% yield and a small amount of benzaldehyde.



**9** (60%)

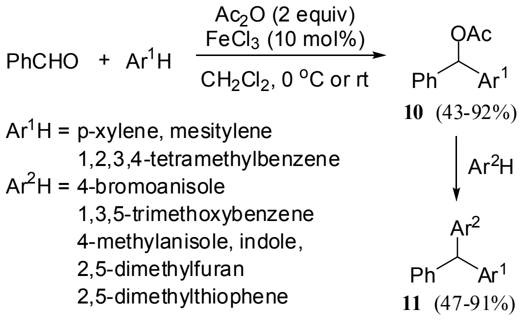
**Scheme 7**



**8a** (78%) 8%

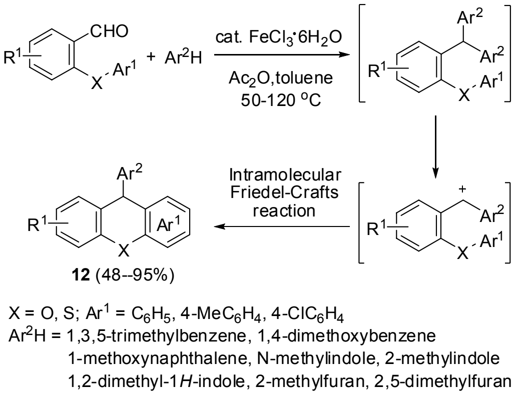
**Scheme 8**

Interestingly, mono Friedel-Crafts alkylation products **10** were isolated in moderate to high yields when the reaction was carried out at 0$^{O}$C or room tempearture depending on arene substrates (Scheme 9). The resulting mono-aromatic substitution products **10** without any purification could be further reacted with second arene substrate to give unsymmetric triarylmethane derivatives **11**. Under this sequential one-pot procedure, a variety of unsymmetrical TRAMs and thiophene, furan, and indole substituted heteroaryldiarylmethanes were produced.



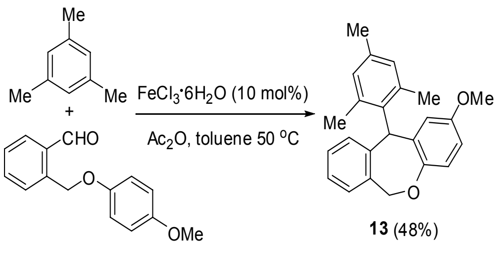
**Scheme 9**

One year later, Li et al. [8] succeeded in developing an efficient, general, and one-pot procedure for the synthesis of multi-substituted xanthene derivatives through $FeCl_3$-catalyzed reactions of 2-aryloxybenzaldehydes with electron-rich arenes (Scheme 10). This method offered several advantages such as high selectivity, mild reaction conditions, and easily accessible starting materials. A mechanistic study revealed that a C—C bond cleavage of a triarylmethane intermediate might be involved in the domino process.



**Scheme 10**

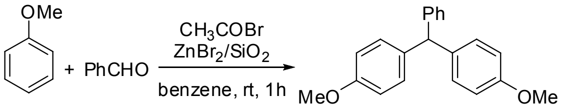
Moreover, the present method could be applied successfully to the synthesis of a biologically interesting 7-membered oxacycle **13** as shown in Scheme 11.



**Scheme 11**

### 2.4 $ZnBr_2/SiO_2$-catalyzed Friedel-Crafts reaction

Recently, a convenient and practical method for the preparation of triarylmethanes by the reaction of electron-rich arenes with acetyl bromide and aromatic aldehydes in the presence of $ZnBr_2/SiO_2$ has been developed [9]. The reaction of anisole with benzaldehyde afforded 4,4′-dimethoxy-triphenylmethane **14**, regioselectively, in an 84% yield (Scheme 12). It should be noted that the reaction under similar conditions but without acetyl bromide gave no reaction and anisole was recovered. Additionally, acetyanisole which is formed from Friedel-Crafts acylation of anisole with acetyl bromide was not detected. Toluene also is used as a solvent, whereas in polar solvent such as THF and dioxane the yield is very low.



**14** (84%)

**Scheme 12**

Although, polymethylbenzene such as *o*- and *m*-xylene and 1,2,3-trimethylbenzene required a slightly elevated temperature (50°C) to condense effectively with benzal- dehyde, other electron-rich arenes such as 1,2-dimethoxy- benzene (veratrole), 1,3,5-trimethoxy-benzene, 2- and 4-methoxytoluene and 1-methoxy-naphthalene reacted well to provide the corresponding triarylmethanes

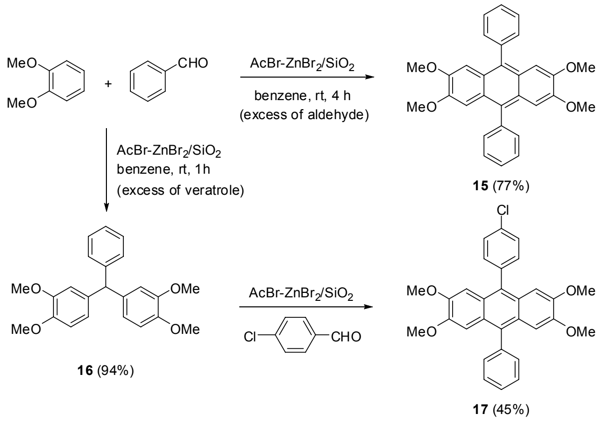
Interestingly, the reaction of veratrole (1 equiv) with benzaldeyde (3 equiv) and AcBr (4 equiv) in the presence of $ZnBr_2/SiO_2$ at room temperature for 4 h gave 9,10-diphenylanthracene **15** in a 77% yield (Scheme 13). Diveratrylphenylmethane **16** was presumed as an intermediate in the reaction, leading to **15**. To test this hypothesis, triarylmethane **16** was treated with 4-chlorobenzaldehyde under similar conditions. As it was expected, the unsymmetrically substituted antharcene **17** was obtained in a 45% yield.

Furthermore, reaction of tetrakis(veratrole) adduct **18** with benzaldehyde gave a molecule having two anthracene moieties **19** in a moderate yield (Scheme 14).

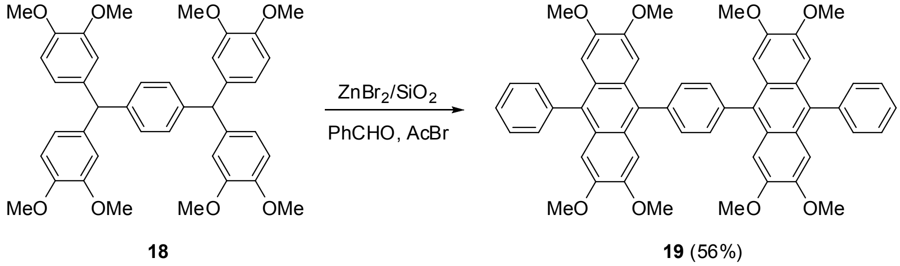
### 2.5 Iodine-Catalyzed Friedel-Crafts alkylation

Molecular iodine has received considerable attention in organic and pharmaceutical syntheses due to its inexpensive, non-toxic, and environmentally friendly characteristics [10]. Iodine has a high tolerance to air as well as moisture and can be easily removed from reaction systems. Moreover, the mild Lewis acidity associated with iodine has led to its use in various organic transformations in catalytic to stoichiometric amounts.

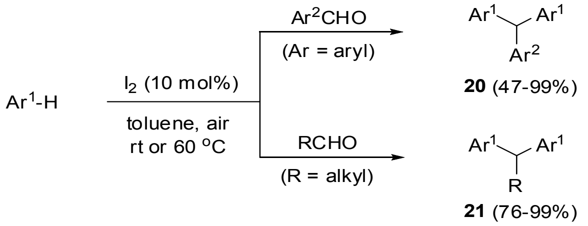
Recently, Jaratjaroonphong et al. [5] demonstrated an efficient molecular iodine catalyzed Friedel-Crafts alkylation of electron-rich arenes with a wide variety of aldehydes in toluene under 'open flask' and mild conditions. In the presence of 10 mol% of iodine, the reaction of arenes with aromatic aldehydes in toluene gave the corresponding triarylmethane derivatives, regioselectively, in good to excellent yields (Scheme 15). On the other hand, a series of diarylalkane derivatives was symthesized smoothly by reaction with aliphatic aldehydes under the present conditions.



Scheme 13



Scheme 14

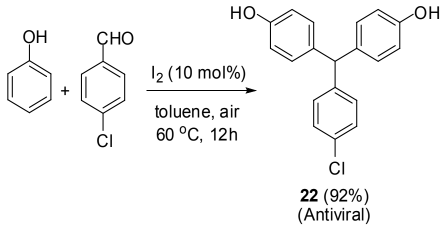


$Ar^1H$ = 1,2,4-trimethoxybenzene
1,3,5-trimethoxybenzene
1,2,3-trimethoxybenzene
1,2-dimethoxybenzene
anisole, phenol, 2-methylfuran

$Ar^2$ = $C_6H_5$, 4-$FC_6H_4$
4-$ClC_6H_4$, 4-$BrC_6H_4$
4-$O_2NC_6H_4$,
3,4-$(MeO)_2C_6H_3$
3-$MeOC_6H_4$
R = Et, $PhCH_2CH_2$
$Me_2CHCH_2$
$Me_2CH$
Ph(Me)CH
Cyclohexyl

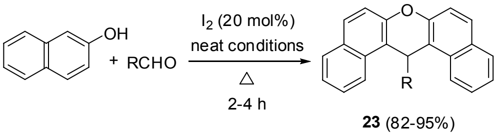
Scheme 15

Furthermore, compound **22** which has been reported to show significant antiviral activity was synthesized smoothly in an excellent 92% yield by condensation of phenol with 4-chlorobenzaldehyde employing iodine (10 mol%) as a catalyst (Scheme 16).



**Scheme 16**

Interestingly, treatment of 2-naphthol with various aldehydes including both aromatic and aliphatic aldehydes under neat conditions in the presence of iodine as a catalyst afforded the corresponding benzoxanthene derivatives in high yields as shown in Scheme 17 [11]. The aromatic aldehydes containing electron-donating as well as electron-withdrawing groups underwent the conversion equally. However, the reaction conducted with phenol instead of 2-naphthol did not afford any product. The experimental procedure of the present reaction was simple and the conversion was completed within a short period of time (2-5 h).



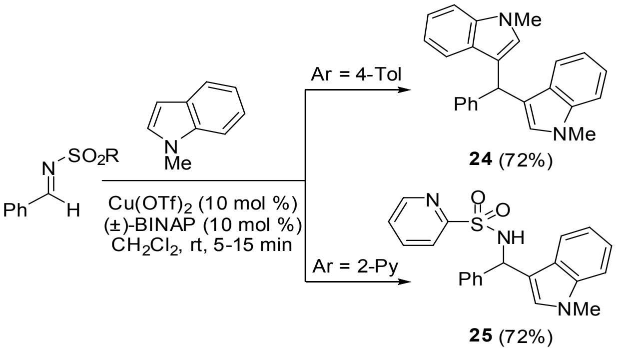
**Scheme 17**

## 3. Catalytic Friedel-Crafts reaction of aromatic ring with imine derivatives

The reaction of electron-rich aromatic compounds with imines in the presence of acidic catalyst known as aza-Friedel-Crafts reaction (AFCR) can generate benzylic amines, which further react with second electron-rich aromatic compounds to afford the corresponding triarylmethanes.

### 3.1 $Cu(OTf)_2$ catalyzed Aza-Friedel-Crafts alkylation

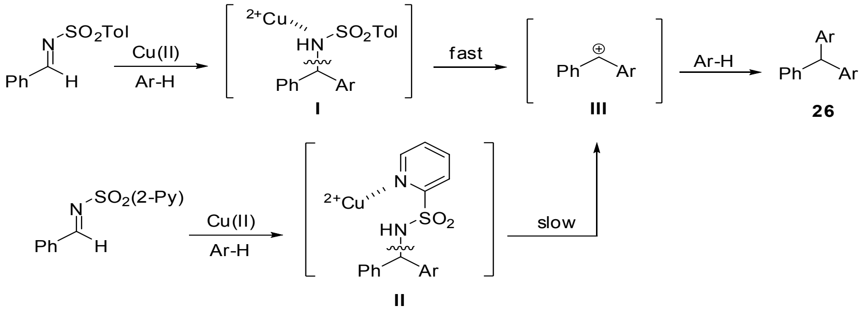
In recent years, Esquivias et al. [4] reported that $Cu(OTf)_2$-catalyzed aza-Friedel-Crafts reaction of *N*-methyl indole with the tosyl imine derived from benzaldehyde afforded the triarylmethane derivatives **24**, while the similar process using the 2-pryidyl-sulfonyl imine led selectively to the aza-Friedel-Crafts adduct **25** (Scheme 18).



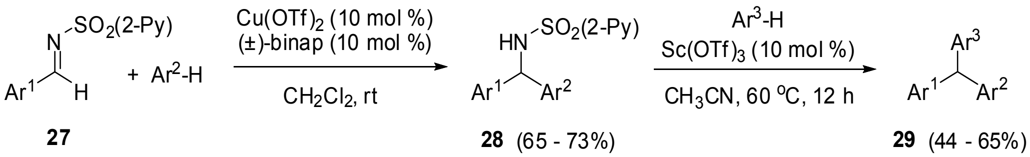
**Scheme 18**

The plausible mechanism for the formation of different products by tuning the *N*-protective group of imine substrates can be explained as shown in Scheme 19 [12]. The coordination of the Cu(II) catalyst to the sulfonamide nitrogen of the initial AFCR adduct resulting from tosyl imine (complex **I**) enhances the ability of the sulfonamide moiety as a leaving group, facilitating the formation of the highly stabilized carbocation intermediate **III**, required for the final Friedel-Crafts alkylation. In contrast, in the case of the 2-pyridyl analogue, it is reasonable to assume a preferential coordination of the Cu(II) atom to the pyridyl nitrogen atom (complex **II**), instead of the sulfonamide nitrogen, resulting in a lower leaving group capacity of the sulfonamide moiety which would make more difficult the cleavage of the C-N bond and formation of the carbocation intermediate. Moreover, DFT theoretical calculation of the mode of coordination on the second Friedel-Crafts reaction supported that the activation barrier of coordination of the copper atom to the tosyl unit is significantly higher than those of the 2-pyridyl-sulfonyl unit.

One-pot synthesis of unsymmetrical triaryl methanes by promoting a second electrophilic aromatic substitution with a different electron-rich arenes (Ar$^3$-H) to highlight the potential of the pyridylsulfo-namide adduct,. Gratifyingly, the resulting amine adducts **28** can be employed as a precursor for the synthesis of unsymmetrical triarylmethanes **29** by promoting a second electrophilic aromatic substitution with a different electron-rich arenes (Ar$^3$H) in the presence of Sc(OTf)$_3$ (10 mol %) in CH$_3$CN at 60 °C (Scheme 20).



**Scheme 19**

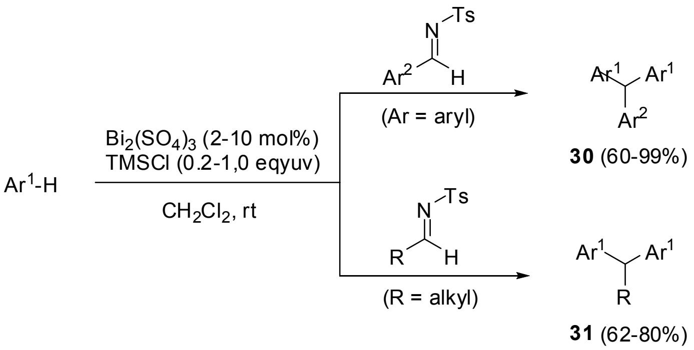


Ar$^1$ = Ph, 4-O$_2$N-C$_6$H$_4$, 1-Naphthyl, 3,4-(F)$_2$-C$_6$H$_3$
Ar$^2$ = 2-OMe, 4-NMe$_2$-C$_6$H$_4$, 1-OMe-Naphthyl
Ar$^3$ = 1,3,5-(OMe)$_3$-C$_6$H$_2$, 3-Methylindolyl, 2-Methylthiophenyl

**Scheme 20**

### 3.2 $Bi_2(SO_4)_3$-catalyzed Friedel-Crafts alkylation of imines

Recently, Tian et al. [13] developed a highly efficient catalytic Friedel-Crafts reaction of *N*-tosyl imines with anisol, phenol, thioanisole, and analogues at room temperature. In the presence of 2-10 mol% of $Bi_2(SO_4)_3$ and 0.20-1.0 equivalent of TMSCl, the reaction of a wide variety of *N*-tosyl aromatic and aliphatic imines with anisole, phenol, thioanisole and analogues afforded the corresponding symmetric diarylmethanes and triarylmethanes with high regioselectively and in good to excellent yields (Scheme 21)



$Ar^1H$ = anisole
phenol
thioanisole
2-methylanisole
1,2-dimethoxybenzene
2-methylphenol
1,3,5-trimethoxybenzene

$Ar^2$ = $C_6H_5$, 4-$MeC_6H_4$
4-$ClC_6H_4$, 4-$O_2NC_6H_4$
4-$MeO_2CC_6H_4$, 4-$HOC_6H_4$
3-$MeOC_6H_4$, 3-$O_2NC_6H_4$
2-$MeOC_6H_4$, 2-$O_2NC_6H_4$
2,4-$Cl_2C_6H_3$
R = Et, $Me_2CH$, Cyclohexyl

**Scheme 21**

## 4. Conclusion

Scope, limitation and application of the catalytic Friedel-Crafts reaction of aromatic ring with aromatic aldehydes or their imines leading to symmetric and asymmetric triarylmethanes are described herein. The attractive features of these protocols include high selectivity and yields, broad substrate scope, the use of an inexpensive and environmentally benign catalyst, mild reaction conditions, and experimental simplicity.

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