Catalytic selective bis-arylation of imines with anisole, phenol, thioanisole and analogues†

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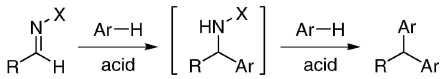
The first highly efficient double Friedel–Crafts reaction of *N*-tosyl imines with anisole, phenol, thioanisole and analogues has been developed to produce the corresponding symmetric diarylmethanes and triarylmethanes with high regioselectivity in the presence of a catalytic amount of $Bi_2(SO_4)_3$–TMSCl at room temperature.

The reaction of imines with aromatic compounds is an important carbon–carbon bond-forming reaction. In the presence of acidic catalysts, the addition of electron-rich aromatic compounds to imines can generate benzylic amines, which are intrinsically unstable under acidic reaction conditions and can further undergo the substitution of amino groups with the remaining electron-rich aromatic compounds to produce symmetric diarylmethanes (R = alkyl) and triarylmethanes (R = aryl) (Scheme 1) that have found widespread applications in synthetic, medicinal and industrial chemistry.[1] To our knowledge, only indoles,[2] pyrroles[3] and amino-substituted arenes[4] have recently been explored as reactive aromatic compounds for this type of double Friedel–Crafts reaction, and most of the reported methods are restricted by the formation of a multitude of products, high catalyst loading and at times drastic reaction conditions. Herein we report, for the first time, a highly efficient catalytic bis-arylation of *N*-tosyl imines with much less activated aromatic compounds such as anisole, phenol, thioanisole and analogues at room temperature.

Inspired by our recent discovery that a number of Lewis acids in combination with chlorotrimethylsilane (TMSCl) are powerful in promoting the addition of nucleophilic species to *N*-alkoxycarbonyl imines formed *in situ* at room temperature,[5,6] we decided to utilize these catalyst systems to promote the double Friedel–Crafts reaction of imines with aromatic compounds such as anisole, phenol and thioanisole, which are much less activated than indoles, pyrroles and amino-substituted arenes. The bis-arylation of *N*-tosyl imine **1a** with anisole (**2a**) was selected as a model reaction to evaluate the catalytic activity of Lewis acid in combination with TMSCl at room temperature. As summarized in Table 1, a number of Lewis acids (2 mol%) in combination with TMSCl (0.20 equiv.) were found to catalyze this reaction to give symmetric triarylmethane **3aa** selectively in good to excellent yields, though neither a single Lewis acid nor TMSCl was effective in doing so.[7] The best yield (90%) and regioselectivity (20 : 1)[8] were obtained with bismuth sulfate [$Bi_2(SO_4)_3$], an environmentally benign catalyst (entry 8, Table 1).[9] Further efforts to decrease the loading of $Bi_2(SO_4)_3$ and/or TMSCl resulted in lower yields. Notably, during the reaction of *N*-tosyl imine **1a** with anisole (**2a**) we observed no intermediate resulting from mono Friedel–Crafts reaction by ^{1}H NMR analysis of the reaction mixture.

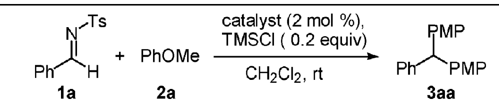
The replacement of the tosyl group in imine **1a** with another group was further examined. In the presence of 2 mol% of $Bi_2(SO_4)_3$ and 0.20 equiv. of TMSCl, the double Friedel–Crafts reaction of PhCH=NSOPh with anisole (**2a**) proceeded smoothly to give product **3aa** in a slightly lower yield (86%) in 6 h. In contrast, no desired product was obtained at all when PhCH=NAc, PhCH=NCOPh, PhCH=NPh, PhCH=NBn or PhCH=NOH were treated with anisole (**2a**) under the same reaction conditions. Thus, the tosyl group was chosen to activate the C=N double bond in the bis-arylation of imines.

Using $Bi_2(SO_4)_3$–TMSCl as the catalyst system, a wide variety of alkoxy-, hydroxy-, or methylmercapto-substituted



Scheme 1 Acid-catalyzed double Friedel–Crafts reaction of imines with aromatic compounds.

Table 1 Survey of catalysts[a]



Entry	Catalyst	Time/h	Yield (%)[b]
1	None	48	ND[c]
2	CF_3SO_3H	4	55
3	$FeCl_3$	1.5	60
4	$Fe_2(SO_4)_3 \cdot 5H_2O$	3	64
5	$ZnCl_2$	1.5	72
6	$AlCl_3$	1	58
7	$BiCl_3$	1.5	67
8	$Bi_2(SO_4)_3$	1.5	90

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (3.0 mmol), catalyst (2 mol%), TMSCl (0.20 mmol), CH_2Cl_2 (0.2 mL), rt. PMP = 4-methoxyphenyl. [b] Isolated yield. [c] No desired product was detected by TLC analysis.

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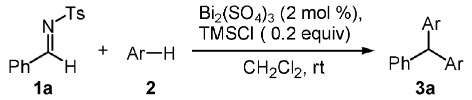
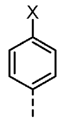
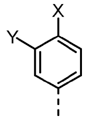
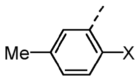
† Electronic supplementary information (ESI) available: General information, experimental procedures and characterization data for the products. See DOI: 10.1039/b800066b

Table 2 Bismuth-catalyzed bis-arylation of *N*-tosyl imine **1a** with anisole, phenol, thioanisole and analogues[a]



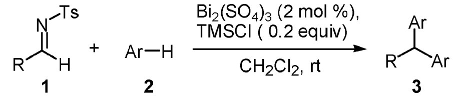
Entry	2	Ar		Product	Time/h	Yield (%)[b]
1	**2a**		X = OMe	**3aa**	1.5	90
2[c]	**2b**		X = $\mathrm{OCH_2CH_2OAc}$	**3ab**	15	60
3[d]	**2c**		X = $\mathrm{OCH_2OCH_2OH}$	**3ac**	48	80
4	**2d**		X = OH	**3ad**	1	76
5[e]	**2e**		X = SMe	**3ae**	32	81
6	**2f**		X = OMe, Y = Me	**3af**	3	93
7	**2g**		X = OMe, Y = OMe	**3ag**	5	86
8	**2h**		X = OH, Y = Me	**3ah**	2	85
9	**2i**		X = OH, Y = *i*-Pr	**3ai**	1	83
10[e]	**2j**		X = OH, Y = Cl	**3aj**	48	86
11	**2k**		X = OMe	**3ak**	26	74
12	**2l**		X = OH	**3al**	1	84
13	**2m**	4-Methoxynaphthyl		**3am**	2	95
14	**2n**	2,4,6-Trimethoxyphenyl		**3an**	0.3	99

[a] Reaction conditions: **1a** (1.0 mmol), **2** (3.0 mmol), $\mathrm{Bi_2(SO_4)_3}$ (2 mol%), TMSCl (0.20 mmol), $\mathrm{CH_2Cl_2}$ (0.20 mL), rt. [b] Isolated yield. [c] 5 mol% of $\mathrm{Bi_2(SO_4)_3}$ was used. [d] 5 mol% of $\mathrm{Bi_2(SO_4)_3}$ and 1.0 equiv. of TMSCl were used. [e] 10 mol% of $\mathrm{Bi_2(SO_4)_3}$ and 1.0 equiv. of TMSCl were used.

arenes were found to react well with *N*-tosyl imine **1a** at room temperature to give the corresponding symmetric triarylmethanes selectively in good to excellent yields (Table 2).[10] Due to their electron-donating nature, alkoxy, hydroxy, and methylmercapto groups not only activate arenes toward the double Friedel–Crafts reaction of *N*-tosyl imine **1a**, but also dominate the regioselectivity thereof. In the presence of 2 mol% of $\mathrm{Bi_2(SO_4)_3}$ and 0.20 equiv. of TMSCl, the reaction of *N*-tosyl imine **1a** with most of the alkoxy- or hydroxy-substituted arenes proceeded completely within hours. In contrast, the reaction with 2-phenoxyethanol (**2c**), thioanisole (**2e**) or 4-chlorophenol (**2j**), proceeded much slower, and 5–10 mol% of $\mathrm{Bi_2(SO_4)_3}$ and 1.0 equiv. of TMSCl were required to accelerate the rate of the reaction (entries 3, 5 and 10, Table 2). As to the regioselectivity, the *para*-position of the aromatic ring in the nucleophile, if available, was alkylated predominantly by *N*-tosyl imine **1a**. Alternatively, the *ortho*-position was the choice if the *para*-position was occupied by another group.

Next, a range of *N*-tosyl imines were found to undergo double Friedel–Crafts reaction with anisole (**2a**), phenol (**2d**) or thioanisole (**2e**) at room temperature (Table 3). In the

Table 3 Bismuth-catalyzed bis-arylation of various *N*-tosyl imines with anisole, phenol and thioanisole[a]



Entry	1	R	2	Product	Time/h	Yield (%)[b]
1	**1b**	4-$\mathrm{MeC_6H_4}$	**2a**	**3ba**	48	85
2	**1c**	4-$\mathrm{ClC_6H_4}$	**2a**	**3ca**	1	94
3	**1c**	4-$\mathrm{ClC_6H_4}$	**2d**	**3cd**	1	82
4[c]	**1c**	4-$\mathrm{ClC_6H_4}$	**2e**	**3ce**	36	70
5	**1d**	4-$\mathrm{O_2NC_6H_4}$	**2a**	**3da**	6	84
6	**1e**	4-$\mathrm{MeO_2CC_6H_4}$	**2a**	**3ea**	1.5	96
7	**1f**	4-$\mathrm{HOC_6H_4}$	**2d**	**3fd**	12	80
8	**1g**	3-$\mathrm{MeOC_6H_4}$	**2a**	**3ga**	3	70
9	**1h**	3-$\mathrm{O_2NC_6H_4}$	**2a**	**3ha**	3	94
10[d]	**1i**	2-$\mathrm{MeOC_6H_4}$	**2a**	**3ia**	12	63
11	**1j**	2-$\mathrm{O_2NC_6H_4}$	**2a**	**3ja**	6	79
12	**1k**	2,4-$\mathrm{Cl_2C_6H_3}$	**2d**	**3kd**	0.5	77
13[c]	**1k**	2,4-$\mathrm{Cl_2C_6H_3}$	**2e**	**3ke**	30	60
14	**1l**	Et	**2a**	**3la**	5	62
15	**1m**	$\mathrm{Me_2CH}$	**2a**	**3ma**	6	77
16	**1n**	Cyclohexyl	**2a**	**3na**	6	80

[a] Reaction conditions: **1** (1.0 mmol), **2** (3.0 mmol), $\mathrm{Bi_2(SO_4)_3}$ (2 mol%), TMSCl (0.20 mmol), $\mathrm{CH_2Cl_2}$ (0.20 mL), rt. [b] Isolated yield. [c] 5 mol% of $\mathrm{Bi_2(SO_4)_3}$ and 1.0 equiv. of TMSCl were used. [d] 5 mol% of $\mathrm{Bi_2(SO_4)_3}$ was used.

presence of 2–5 mol% of $Bi_2(SO_4)_3$ and 0.20 equiv. of TMSCl, anisole (**2a**) or phenol (**2d**) could react with a number of *N*-tosyl aromatic imines bearing either electron-withdrawing groups (Cl, NO_2 and COOMe) or electron-donating groups (Me, OH and OMe) on the *ortho*-, *meta*- or *para*-positions of aromatic rings, and gave the corresponding symmetric triarylmethanes with high regioselectivity and in good to excellent yields (entries 1–3, 5–12, Table 3). Due to the low reactivity of thioanisole (**2e**), 1.0 equiv. of TMSCl was required to promote its reaction with *N*-tosyl imines (entries 4 and 13, Table 3). Furthermore, *N*-tosyl aliphatic imines were found to be suitable substrates to synthesize diarylmethanes (entries 14–16, Table 3).

In summary, we have developed, for the first time, a highly efficient catalytic bis-arylation of *N*-tosyl imines with anisole, 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 equiv. of TMSCl, the double Friedel–Crafts reaction of a wide variety of *N*-tosyl aromatic and aliphatic imines with anisole, phenol, thioanisole and analogues proceeded smoothly to give the corresponding symmetric triarylmethanes and diarylmethanes with high regioselectivity and in good to excellent yields. The attractive features of this protocol 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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8 For the activation of imines with $Yb(OTf)_3–Me_3SiCl$, see: (*a*) M. Yamanaka, A. Nishida and M. Nakagawa, *J. Org. Chem.*, 2003, **68**, 3112; (*b*) M. Yamanaka, A. Nishida and M. Nakagawa, *Org. Lett.*, 2000, **2**, 159.

9 For a study on the enhancement of the catalytic activity of Lewis acids with TMSCl, see: (*a*) Y. Onishi, T. Ito, M. Yasuda and A. Baba, *Tetrahedron*, 2002, **58**, 8227; (*b*) T. Saito, Y. Nishimoto, M. Yasuda and A. Baba, *J. Org. Chem.*, 2006, **71**, 8516.

10 A small portion (about 5 μL) of the reaction mixture was directly dissolved in $CDCl_3$ and subject to ^1H NMR analysis. Based on the ^1H NMR analysis of the reaction mixture, only one minor isomer of **3aa** was detected and identified as (2-methoxyphenyl)(4-methoxyphenyl)phenylmethane (**3aa′**) by comparing the ^1H NMR spectrum with that of an authentic sample prepared from (2-methoxyphenyl)phenylmethanol and anisole (**2a**) in the presence of $Bi_2(SO_4)_3$ at room temperature. The regioselectivity was determined to be 20 : 1 by integration of the signals at δ 5.44 ppm (CH of **3aa**) and δ 5.86 ppm (CH of **3aa′**).

11 For a review on catalysis with bismuth(III) salts, see: N. M. Leonard, L. C. Wieland and R. S. Mohan, *Tetrahedron*, 2002, **58**, 8373.

12 Mercapto-substituted arenes were also found to react with *N*-tosyl imine **1a**, but the reaction gave the corresponding thioacetals instead of triarylmethanes. For example, the reaction of *N*-tosyl imine **1a** with 2-methylthiophenol in the presence of 2 mol% of $Bi_2(SO_4)_3$ and 0.20 equiv. of TMSCl proceeded smoothly to give benzaldehyde bis(2-methylphenyl)dithioacetalin 93% yield. And under the same reaction conditions, the reaction of *N*-tosyl imine **1a** with 4-chlorothiophenol gave benzaldehyde bis(4-chlorophenyl)dithioacetal in 92% yield. For details, see the ESI†.