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Brönsted acid-catalyzed synthesis of diarylmethanes under non-genotoxic conditions

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Dedicated to Professor Harry Wasserman on the occasion of his 90th birthday

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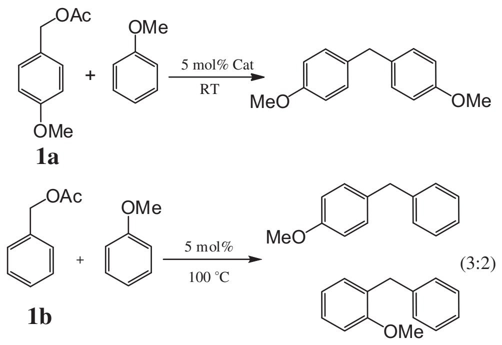
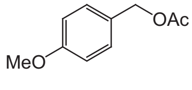
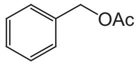
ABSTRACT

Triflic acid and triflimide were found to efficiently catalyze the formation of a wide diversity of diarylmethanes from the non-genotoxic benzylic acetates and electron-rich arenes or heteroarenes. The reaction worked best with acetates capable of generating a stabilized benzylic cationic species. In most cases, the reactions were conveniently run in the absence of solvent under mild conditions.

The benzylation of arenes is an important reaction for the construction of diarylmethanes, which are found in a substantial number of biologically active compounds and are useful synthetic intermediates. Many groups have reported useful and reliable metal-catalyzed Friedel–Crafts alkylation of aromatic compounds for the construction of diarylmethane derivatives. Syntheses of diarylmethanes based on organozinc[1] or organoboron[2] derivatives catalyzed by Pd have also been reported. The traditional Friedel–Crafts reaction of arenes has many drawbacks, such as the requirement of fairly drastic conditions incompatible with many functional groups, the generation of large amounts of undesirable by-products or the use of genotoxic benzylating agents (e.g., benzyl chlorides or bromides).[3] The increasing concern about health and environmental protection has stimulated the search for new procedures for the synthesis of diarylmethanes. In this context benzylations of arenes using the cheap, non-genotoxic but less electrophilic benzyl alcohols or esters have attracted the attention of several research groups. Several heavy metal-derived catalysts[4] and in particular rare earth triflates[5] have been successfully used but these methods often require more complex work-up procedures to remove residues of heavy metals. Recently, Beller and co-workers[6] showed that iron catalysts efficiently catalyze the arylation of benzyl alcohols and benzyl carboxylates under mild conditions. An important fea-

Table 1
Benzylation and *p*-methoxybenzylation of anisole



Entry	Electrophile	Cat. (5 mol %)	Yield[a] (%)
1		H_3PO_4	0
2		CF_3COOH	0
3		HCl	6–9
4		HOTf	100
5		$HNTf_2$	100
6		H_2SO_4	100
7		CH_3SO_3H	25
8		HOTf	100
9		$HNTf_2$	100
10		H_2SO_4	5

[a] Yields determined by ^1H NMR.

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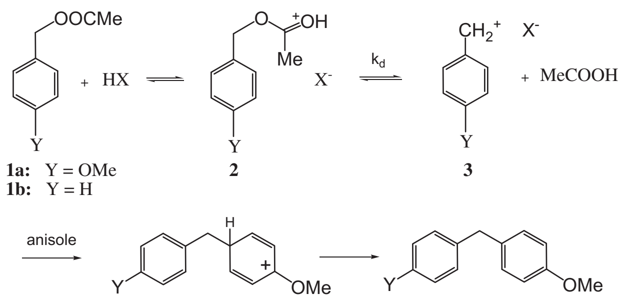


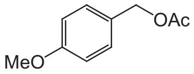
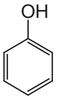
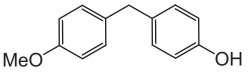
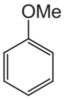
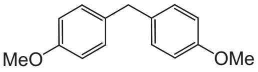
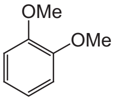
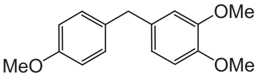
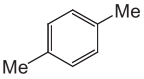
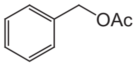
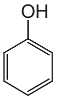
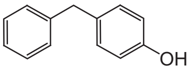
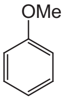
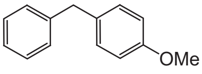
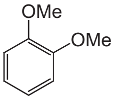
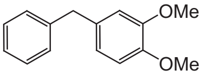
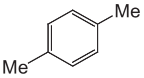
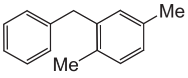
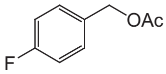
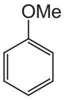
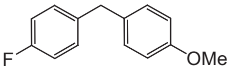
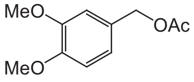
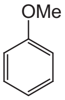
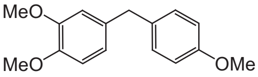
Scheme 1.

ture of this process was the tolerance of a wide variety of functional groups.

In this context, the observation by Sun and Wang[7] that molecular iodine efficiently catalyzed the benzylation of arenes with benzyl alcohols is also of particular interest. A last approach which will probably appeal to industrial chemists involves the use of solid heterogeneous Brönstedt and Lewis acid catalysts.[8]

In 1997 we,[9] and Mikami's group[10] independently introduced trialkylsilyl triflimides as a new class of non-metallic Lewis acid catalysts. These silylating agents are stronger Lewis acids than the corresponding triflates and catalyze a variety of reactions involving Lewis acid activated carbonyl derivatives.[12] More recently, Martin and co-workers reported an elegant approach to an array of substituted β-heteroaryl propionates by coupling silyl ketene acetals and other π-nucleophiles with alcohols and acetates derived from electron-rich heterocycles in the presence of trimethylsilyl trifluoromethanesulfonate.[13] However, with less activated benzyl acetates, trialkylsilyl triflimides were again found to be largely superior to the corresponding triflates.[12] In their seminal report, Mikami and co-workers[10] had claimed that TMS-ethers derived from benzyl alcohols could alkylate anisole in the presence of catalytic amounts of $TMSNTf_2$. However, in these reactions, 1 equiv of $HNTf_2$ is produced as a result of the aromatization of the tetrahedral intermediate. It was, therefore, not excluded that $HNTf_2$ could take part in the catalytic process.[11] This was debatable in as much as Beller and co-workers[6] had reported that HCl, HOAc and *p*-toluenesulfonic acid did not catalyze the reaction of *o*-xylene with 1-phenylethylacetate while Lachter and co-workers[14] and more recently Sarca and Laali[15] reported the successful benzylation of arenes promoted by amberlyst 15, niobic acid, or triflic acid in ionic solvents.

Table 2
Reaction of arenes with benzyl acetates **1a–d**

Entry	Electrophile	Nucleophile	Main product	*T* (°C)	*t*	Cat.	Solvent	Yield[a,b] (%)
1	 **1a**			rt	20 min	HOTf	No	95
2				rt	20 min	HOTf	No	98
3				rt	1 h	HOTf	No	90
4			decomposition	rt	20 min	HOTf	No	0
5	 **1b**		 (3:2)	100	1 h	HOTf	No	99
6			 (3:2)	100	1 h	HOTf	No	91
7			 (3:1)	100	1 h	HOTf	No	86
8				100	1 h	HOTf	No	89
9	 **1c**		 (3:2)	100	1 h	HOTf	No	71
10	 **1d**			rt	20 min	HOTf	No	81

[a] Only the major isomer is shown. When two isomers are formed, ratios are indicated in brackets.

[b] Yields were determined by GLC.