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Trifluoromethanesulfonic Acid Catalyzed Friedel–Crafts Alkylations of 1,2,4-Trimethoxybenzene with Aldehydes or Benzylic Alcohols

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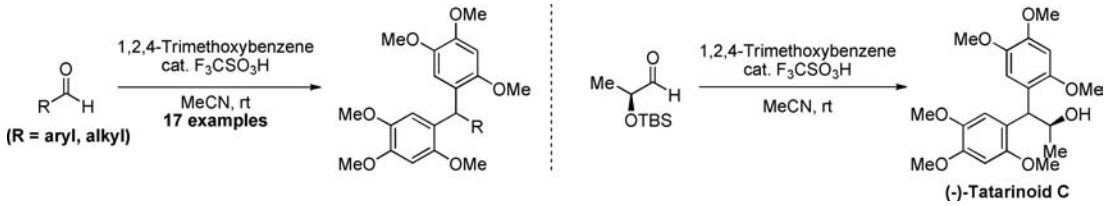
ABSTRACT



Trifluoromethanesulfonic acid in acetonitrile was found to efficiently catalyze Friedel–Crafts alkylations of 1,2,4-trimethoxybenzene with a variety of simple or functionalized aldehydes to provide di- or triarylmethanes in high yields. The operationally simple protocol allowed a short synthesis of the phenylpropanoid natural product (–)-tatarinoid C establishing its absolute configuration. Under the developed reaction conditions a benzylic alcohol instead of an aldehyde also underwent reactions with 1,2,4-trimethoxybenzene and other nucleophiles to afford unsymmetrically substituted compounds.

As part of our research program toward the synthesis of rubromycins,[1] we studied the spiroketalization of ketone **1** and unexpectedly isolated diarylmethane derivative **3** as an inseparable mixture of two diastereomers (Scheme 1). Notably, the formation of **3** only started at slightly elevated temperatures (~0 °C), converting *rac*-**2** into **3**. It is likely that this transformation involves a Friedel–Crafts type alkylation of spiroketal *rac*-**2** with the methoxy-substituted carbenium ion as an electrophile generated from the MOM-ether moieties. Formation of compound **3** very likely proceeds *via* benzylic ether **4a**, with subsequent displacement of methanol under generation of reactive intermediate **4b** which undergoes a regioselective Friedel–Crafts type alkylation with the second equivalent of *rac*-**2** by **4b** to afford "dimer" **3**.

Motivated by this observation we had a closer look to reactions of this type leading to diarylmethanes. Generally, the structural motif of symmetrically substituted di- and triarylmethanes is of great interest since they are part of several biologically active compounds[2] and dyes.[3] Various protocols for the synthesis of methoxy-substituted di- and triarylmethanes have been reported so far; however, they often depend on multistep synthesis or require either stoichiometric amounts of promoters (e.g., Lewis or Brønsted acids) or harsh reaction conditions, hence leading to reduced functional group tolerance.[4] Recently, an

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(1) (a) Sörgel, S.; Azap, C.; Reissig, H.-U. *Org. Lett.* **2006**, *8*, 4875–4878. (b) Venkatesh, C.; Reissig, H.-U. *Synthesis* **2008**, 3605–3614. (c) Review: Brasholz, M.; Sörgel, S.; Azap, C.; Reissig, H.-U. *Eur. J. Org. Chem.* **2007**, 3801–3814. (d) Recent micoreview on spiroketalizations: Wilsdorf, M.; Reissig, H.-U. *Angew. Chem.* **2012**, *124*, 9624–9626. *Angew. Chem., Int. Ed.* **2012**, *51*, 9486–9488.

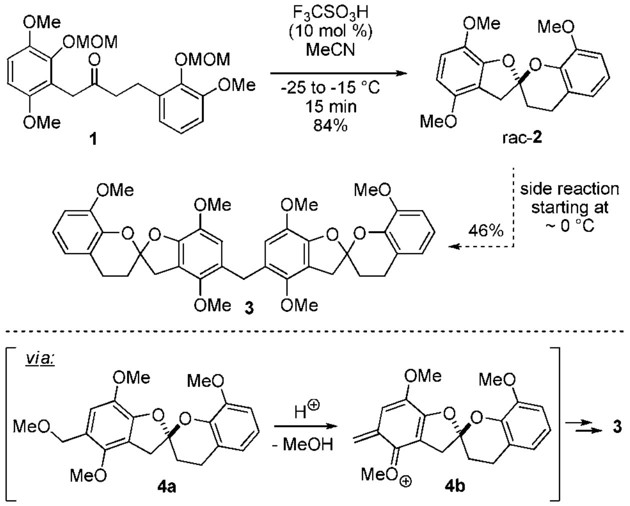
(2) (a) Mibu, N.; Yokomizo, K.; Uyeda, M.; Sumoto, K. *Chem. Pharm. Bull.* **2005**, *53*, 1171–1174. (b) Podder, S.; Choudhury, J.; Roy, U. K.; Roy, S. *J. Org. Chem.* **2007**, *72*, 3100–3101. (c) Parai, M. K.; Panda, G.; Chaturvedi, V.; Manju, Y. K.; Sinha, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 289–292.

(3) Review on the synthesis and application of triarylmethanes; see: Nair, V.; Thomas, S.; Mathew, S. C.; Abhilash, K. G. *Tetrahedron* **2006**, *62*, 6731–6747.

(4) For selected recent examples, see: (a) Barbero, M.; Cadamuro, S.; Dughera, S.; Magistris, C.; Venturello, P. *Org. Biomol. Chem.* **2011**, *9*, 8393–8399. (b) Leng, Y.; Chen, F.; Zuo, L.; Duan, W. *Tetrahedron Lett.* **2010**, *51*, 2370–2372. (c) Mohammadpoor-Baltork, I.; Moghadam, M.; Tangestaninejad, A.; Mirkhani, V.; Mohammadiannejad-Abbasabadi, K.; Khavasi, R. H. *Eur. J. Org. Chem.* **2011**, 1357–1366. (d) Thirupathi, P.; Kim, S. S. *J. Org. Chem.* **2009**, *74*, 7755–7761. (e) Thirupathi, P.; Kim, S. S. *Eur. J. Org. Chem.* **2010**, 1798–1808. (f) Kodomari, M.; Nagamatsu, M.; Akaike, M.; Aoyama, T. *Tetrahedron Lett.* **2008**, *49*, 2537–2540.

10.1021/ol400972m

Scheme 1. Unexpected Formation of Bisspiroketal **3** from *rac*-**2**



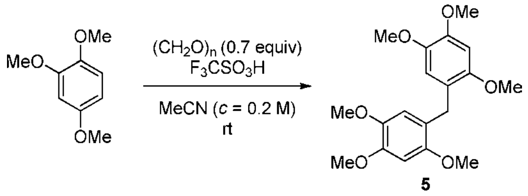
iodine catalyzed Friedel–Crafts alkylation has been reported;[5] however, long reaction times (usually 72 h) are needed for full conversion. We here report an operationally simple protocol for the double arylation of a variety of functionalized aldehydes with 1,2,4-trimethoxybenzene employing trifluoromethanesulfonic acid as the catalyst, which has already been recognized as an efficient promoter for Friedel–Crafts type acylations of arenes.[6]

The screening of the reaction conditions disclosed that as little as 0.1 mol % of F_3CSO_3H was sufficient to promote the formation of bis(1,2,4-trimethoxy)phenylmethane (**5**) in excellent yield from 1,2,4-trimethoxybenzene and paraformaldehyde (Table 1).

We then evaluated the scope of this Friedel–Crafts reaction with respect to the aldehyde component (Table 2). The reactions were generally run in acetonitrile with 10 mol % of F_3CSO_3H; although the conversion was complete within several hours in many cases, the reactions were routinely quenched only after 24 h by the addition of a saturated aqueous sodium bicarbonate solution.

Electron-poor and -rich aromatic aldehydes were well tolerated giving compounds **6a**–**e** generally in high yields. Notably, vanillin, 4-formylphenylboronic acid, and nicotinaldehyde were also suitable electrophiles thus affording the triarylmethane derivatives **6f**–**h** in excellent yields and with high purity. The reaction also proceeded with enolizable aliphatic aldehydes, albeit slightly lower yields were obtained for **7a** and **7b**. Even cyclohexyl- and pivalaldehyde as sterically fairly demanding precursors furnished diarylalkanes **7c** and **7d** in acceptable yields. α-Functionalized acetals instead of aldehydes can also be applied: bromo-, diethoxyphosphono-, and cyanoalkyl-substituted diarylalkanes (**7e**–**g**) were isolated in moderate yields. These compounds are suitable starting materials for further transformations. Most importantly, ketones do not react under the conditions employed as exemplified with 4,4-dimethoxybutan-2-one (**8**) affording diarylated butan-2-one **7h** in good yield. We also used donor–acceptor-substituted cyclopropane **9**,[7] serving as a masked 4-oxobutane acid equivalent, which cleanly provided the diaryl-substituted methyl butanoate **7i** in excellent yield (Scheme 2).

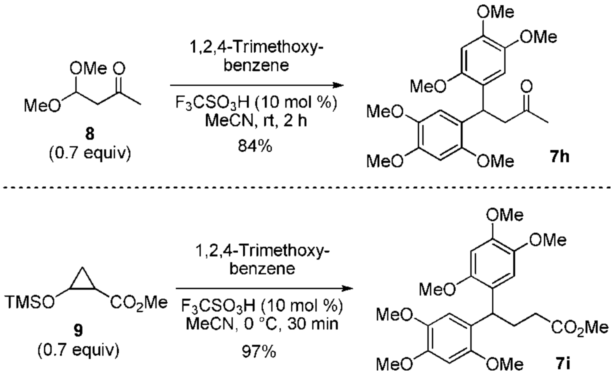
Table 1. Screening of the Catalyst Loading[a]



entry	F_3CSO_3H (mol %)	t (h)	yield (%)[b]
1	10.0	1	99
2	1.0	16	96
3	0.1	16	96
4	–	16	–

[a] Conditions: 1,2,4-Trimethoxybenzene (2.00 mmol), paraformaldehyde (1.40 mmol), acetonitrile (5.0 mL). [b] Yield of purified product.

Scheme 2. Synthesis of Functionalized Diarylalkanes



By employing α-chiral aldehyde (−)-**10**, easily prepared from (*S*)-methyl lactate in two steps,[8] we could obtain the phenylpropanoid natural product (−)-tatarinoid C[9] in a single step with moderate yield. The simultaneous desilylation was unavoidable and may partially occur prior to the

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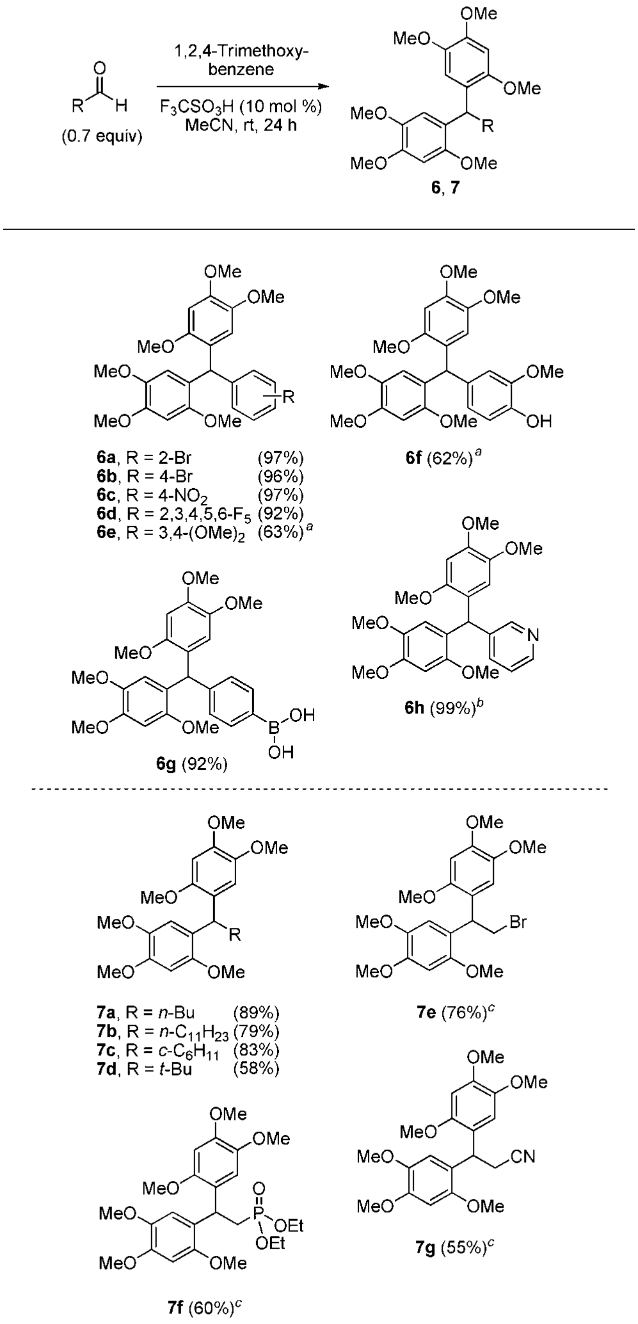
(5) Jaratjaroonphong, J.; Sathalalai, S.; Techasauvapak, P.; Reutrakul, V. *Tetrahedron Lett.* **2009**, *50*, 6012–6015.

(6) For selected examples, see: (a) Epple, G.; Effenberger, F. *Angew. Chem.* **1972**, *84*, 295–296. *Angew. Chem., Int. Engl.* **1972**, *11*, 300–301. (b) Hwang, J. P.; Prakash, G. K. S.; Olah, G. A. *Tetrahedron* **2000**, *56*, 7199–7203. (c) Prakash, G. K. S.; Yan, P.; Török, B.; Olah, G. A. *Catal. Lett.* **2003**, *87*, 109–112. (d) Murai, Y.; Hashidoko, Y.; Hashimoto, M. *Biosci. Biotechnol. Biochem.* **2011**, *75*, 352–354. (e) Anderson, K. W.; Tepe, J. J. *Tetrahedron* **2002**, *58*, 8475–8481. (f) Fillion, E.; Fishlock, D.; Wilsily, A.; Goll, J. M. *J. Org. Chem.* **2005**, *70*, 1316–1327. For recent related Friedel–Crafts alkylations, see: (g) Prakash, G. K. S.; Paknia, F.; Mathew, T.; Mlostoń, G.; Joschek, J. P.; Olah, G. A. *Org. Lett.* **2011**, *13*, 4128–4131. (h) O'Connor, M. J.; Boblak, K. N.; Topinka, M. J.; Kindelin, P. J.; Briski, J. M.; Zheng, C.; Klumpp, D. A. *J. Am. Chem. Soc.* **2010**, *132*, 3266–3267. (i) Ramulu, B. V.; Reddy, A. G. K.; Satyanarayan, G. *Synlett* **2013**, *24*, 868–872.

Table 2. Scope with Respect to the Aldehyde Component



6, **7**

6a, R = 2-Br (97%)
6b, R = 4-Br (96%)
6c, R = 4-NO_2 (97%)
6d, R = 2,3,4,5,6-F_5 (92%)
6e, R = 3,4-$(OMe)_2$ (63%)[a]

6f (62%)[a]

6g (92%)

6h (99%)[b]

7a, R = *n*-Bu (89%)
7b, R = *n*-$C_{11}H_{23}$ (79%)
7c, R = *c*-C_6H_{11} (83%)
7d, R = *t*-Bu (58%)

7e (76%)[c]

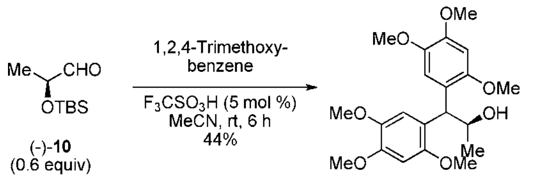
7f (60%)[c]

7g (55%)[c]

[a] Incomplete conversion. [b] 1.1 equiv of F_3CSO_3H was used. [c] Instead of aldehydes the corresponding acetals were used as precursors.

Friedel–Crafts alkylation. This may lead to oligomerization of the aldehyde and hence to a reduced yield of the product (Scheme 3). Remarkably, no racemization was noticed as confirmed by derivatization of (−)-tatarinoid C as a Mosher ester.[10]

Scheme 3. Synthesis of (−)-Tatarinoid C



(-)-**10**
(0.6 equiv)

(-)-Tatarinoid C
(ee > 96%)
$[\alpha]_D$ = - 6.2 (*c* = 2.50, $CHCl_3$)

On the basis of quantum mechanical calculations it was originally proposed that (−)-tartarinoid C should have an *R*-configuration.[11] A previous report[12] on the synthesis of (−)-tatarinoid C assumed an *R*-configuration; however, we suggest that the stereogenic center of this natural product has to be correctly assigned as *S*-configured due to the agreement of the sense of optical rotation of our synthetic sample with the originally reported value for the natural product.

As demonstrated above in many examples, 1,2,4-trimethoxybenzene readily reacts with a variety of aldehydes or acetals. As expected, 1,2-dimethoxybenzene was already significantly less reactive: the reaction with *p*-bromobenzaldehyde remained incomplete after 24 h and triarylmethane derivative **11** was isolated only in 34% yield (Scheme 4). Following this trend of decreased nucleophilicity, the conversion of anisole into **12** proceeded to be less than 25%, even after a prolonged reaction time (48 h). Harsher reaction conditions have not been examined, but may lead to a reasonable yield. Currently, the standard protocol seems to be limited to electron-rich arenes such 1,2,4-trimethoxybenzene or (hetero)arenes of similar nucleophilicity.[13]

The described double arylation of aldehydes proceeds *via* an intermediate benzylic alcohol, and we therefore also studied anisaldehyde derived benzylic alcohol **13**. Numerous methods for the alkylations and arylations of benzylic alcohols are known, frequently relying on Lewis acid catalysis.[14] Therefore, precursor **13** was reacted with various nucleophiles, such as 1,2,4-trimethoxybenzene and

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(7) Reviews: (a) Reissig, H.-U. *Top. Curr. Chem.* **1988**, *144*, 73–135. (b) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151–1196. (c) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321–347. (d) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051–3060. For selected reports on donor–acceptor cyclopropanes for *in situ* generation of carbonyl groups and direct subsequent functionalization in one-pot procedures, see: (e) Grimm, E. L.; Reissig, H.-U. *J. Org. Chem.* **1985**, *50*, 242–244. (f) Ullmann, A.; Schnaubelt, J.; Reissig, H.-U. *Synthesis* **1998**, 1052–1066. (g) Özbek, H.; Veljkovic, I. S.; Reissig, H.-U. *Synlett* **2008**, 3145–3148. (h) Beyzavi, M. H.; Lentz, D.; Reissig, H.-U.; Wiehe, A. *Eur. J. Org. Chem.* **2013**, 269–282.

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(9) Ganjewala, D.; Srivastava, A. K. *Asian J. Plant Sci.* **2011**, *10*, 182–189.

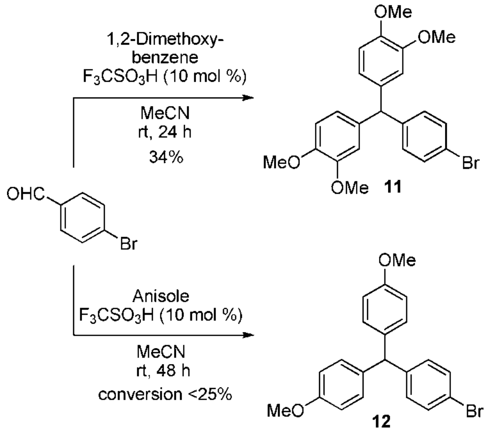
(10) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nat. Protoc.* **2007**, *2*, 2451–2458. For experimenal details, see Supporting Information.

(11) Tong, X.-G.; Wu, G.-S.; Huang, C.-G.; Lu, Q.; Wang, Y.-H.; Long, C.-L.; Luo, H.-R.; Zhu, H.-J.; Cheng, Y.-X. *J. Nat. Prod.* **2010**, *73*, 1160–1163.

(12) Slutskyy, Y.; Jewell, W. T.; Lucero, C. G. *Tetrahedron Lett.* **2013**, *54*, 210–212. The authors did not report the $[\alpha]_D$ value for their synthetic sample.

(13) Ofial, A. R.; Mayr, H. *Pure Appl. Chem.* **2005**, *77*, 1807–1821.

Scheme 4. Reactions with other Alkoxy-Substituted Benzene Derivatives



indole, furnishing the arylated products **14a** and **14b**, respectively (Scheme 5).[15] Acetylacetone as well as allyltrimethylsilane and tosylsulfonamide were found to be suitable nucleophiles (**14c**–**e**) under the reaction conditions employed. These examples demonstrate that trifluoromethanesulfonic acid should also be a suitable promoter of many other Friedel–Crafts type alkylations.

In conclusion, a mild protocol was developed for the double arylation of aldehydes and for substitutions of benzylic alcohols promoted by trifluoromethanesulfonic acid in acetonitrile.[16]

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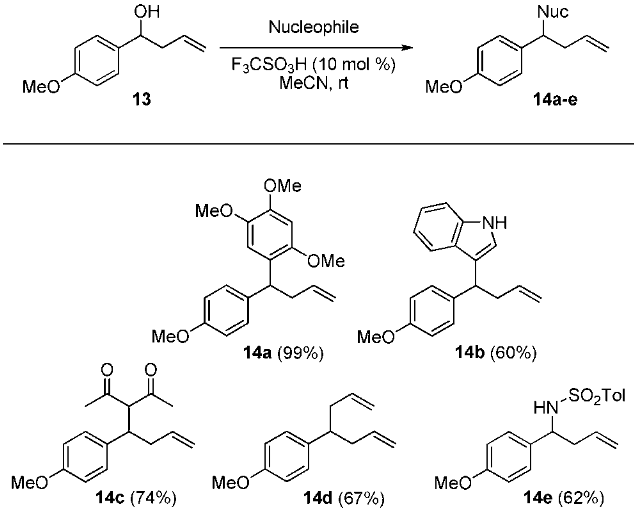
Scheme 5. Reactions of Benzylic Alcohol **13** with Nucleophiles



Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Review on recent developments in the Friedel–Crafts alkylation: (a) Nachtheim, B. J.; Rueping, M. *Beilstein J. Org. Chem.* **2010**, *6*, 6. (b) Nachtheim, B. J.; Rueping, M. *Top Curr. Chem.* **2012**, *311*, 115–142 and references therein.

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