Organocatalytic Friedel–Crafts Benzylation of Heteroaromatic and Aromatic Compounds via an S_N1 Pathway

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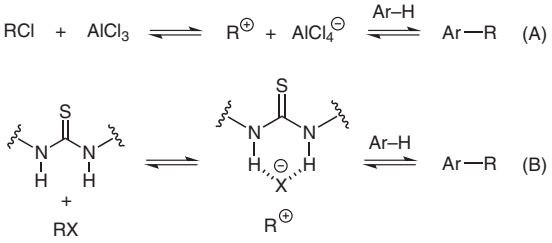
Abstract: The Friedel–Crafts-type benzylation of various π-excessive heteroaromatic and aromatic compounds with trityl or benzhydryl halides was efficiently promoted by a thiourea catalyst. This is a novel example of thiourea catalysis of aromatic alkylation by way of an S_N1 pathway.

Key words: benzylation, catalysis, heterocycles, arenes

Since its discovery over 130 years ago, the Friedel–Crafts alkylation of aromatic compounds has been widely recognized as a basic tool for the construction of the organic frameworks of valuable pharmaceuticals and functional materials.[1] Conventionally, the Friedel–Crafts alkylation of aromatic compounds has been performed by using alkyl halides as electrophiles in the presence of a strong Lewis acid such as aluminum(III) chloride or iron(III) chloride under strictly anhydrous conditions, where carbocation species are believed to form a tight ion pair or to complex with a counteranion such as tetrachloroaluminate ($AlCl_4^-$) (Scheme 1, A).[2]

Recent studies on green chemical transformations have been devoted to the development of readily handled, nonmetallic, and catalytic methods for effecting Friedel–Crafts alkylation.[3] Accordingly, considerable attention has been focused on the synthetic versatility of organocatalytic variants.[4] Unfortunately, however, most of these can be classified as conjugate addition-based Friedel–Crafts alkylation reactions.[3] Only recently have McCubbin and co-workers[5] described exceptions to this norm with regard to organocatalytic Friedel–Crafts alkylations. In these reactions, allylic, benzylic, or propargylic alcohols served as reactive electrophiles and (pentafluorophenyl)boronic acid was used as a Brønsted acid catalyst (pK_a 8.9 for phenylboronic acid itself).[6]

In our own efforts in this field, we have been interested in the use of thiourea and urea derivatives because of their ability to bind anions through double hydrogen bonding (Scheme 1, B).[7,8] We expected that halophilic thiourea catalysts might effectively induce ionization of alkyl halides as electrophiles to generate carbocation intermediates in an S_N1-type Friedel–Crafts alkylation. In view of the weakly acidic nature of the thiourea functionality (pK_a 8.5 for thiourea catalyst **1**),[9] the overall process would constitute a new and mild method for organocatalytic Friedel–Crafts alkylation.



Scheme 1 Friedel–Crafts alkylation strategy

Here we describe the realization of this expectation through development of an organocatalytic Friedel–Crafts alkylation of π-excessive heteroaromatic and aromatic compounds in the presence of a thiourea as an organocatalyst.

First, we evaluated the tritylation of furan with trityl chloride (**5**)[10] in dichloromethane containing various thioureas and related organocatalysts **1**–**4** (Figure 1) at room temperature as a model system. The results are summarized in Table 1.[11]

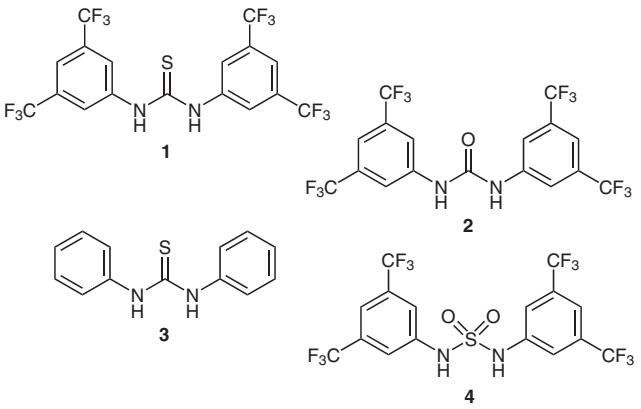


Figure 1 Urea-related organocatalysts examined in Friedel–Crafts alkylation

As expected, stirring of trityl chloride (**5**) in neat furan as a solvent in the presence of thiourea **1** (100 mol%) for 3.5 hours at room temperature gave a mixture of monosubstituted and 2,5-disubstituted products **6** and **7** in excellent yield (**6**/**7** = 62:38) (Table 1, entry 1). Next, we examined the catalytic effect of **1** in the presence of an appropriate

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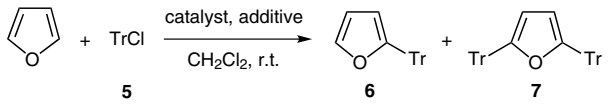
Table 1 Alkylation of Furan with Trityl Chloride



5 **6** **7**

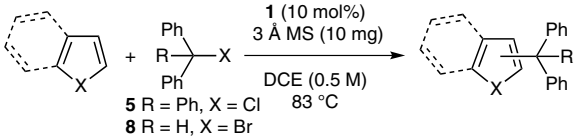
Entry[a]	Catalyst (mol%)	Additive	Time (h)	Yield[b] (%)	Ratio **6**/**7**
1[c]	**1** (100)	–	3.5	99	62:38
2	**1** (10)	cyclohexene[d]	3	63[e]	86:14
3	**1** (25)	3 Å MS[f]	3.5	99	63:37
4	**1** (10)	3 Å MS[f]	4	99	60:40
5	**1** (5)	3 Å MS[f]	5	79[g]	72:28
6	**1** (1)	3 Å MS[f]	6	75[g]	65:35
7	–	3 Å MS[f]	12	71[e]	94:6
8	**2** (10)	3 Å MS[f]	41	96	62:38
9	**3** (10)	3 Å MS[f]	120	trace	–
10	**4** (10)	3 Å MS[f]	34	88	62:38

[a] Unless otherwise noted, all reactions were performed at 0.5 M with 5.0 equiv of furan at r.t., and quenched after consumption of Ph_3CCl (**5**).
[b] Isolated yield based on **5**.
[c] Furan served as the solvent.
[d] 100 mol%.
[e] Unidentified byproducts were formed.
[f] 10 mg/1.0 mmol of **5**.
[g] Highly polar substances were formed.

acid scavenger. Whereas a combination of 10 mol% of **1** and 100 mol% of cyclohexene was ineffective, the use of powdered 3 Å molecular sieves as an acid scavenger was found to be satisfactory for the present purpose (entries 2–4).[12,13] Treatment of 5.0 equiv of furan with trityl chloride (**5**) in the presence of 10 mol% of thiourea **1** and 3 Å molecular sieves (10 mg/1.0 mmol of **5**) in dichloromethane gave **6** and **7** in almost quantitative yield after four hours at room temperature (**6**/**7** = 60:40; entry 4). Reducing the catalyst loading to 5 mol% or 1 mol% retarded the reaction and led to lower product yields (entries 5 and 6). It became clear that there was a significant catalytic effect; under catalyst-free conditions, twelve hours were needed to obtain substantial amounts of the products, with high monosubstitution selectivity (entry 7).[14] Urea **2**, thiourea **3**, and the sulfamide analogue **4** were all less efficient catalysts than thiourea **1** (entries 8–10).[15]

Having identified the optimal conditions, we next examined a variety of π-excessive heteroaromatic compounds to establish the general utility of our synthetic procedure. To facilitate the desired alkylation, all reactions were performed in refluxing 1,2-dichloroethane (DCE) containing 10 mol% of catalyst **1** and powdered 3 Å molecular sieves (10 mg/1.0 mmol of **5** or **8**) unless otherwise mentioned (Table 2).[16]

Table 2 Alkylation of π-Excessive Heteroaromatics with a Range of Benzylic Halides



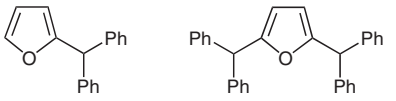
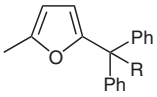
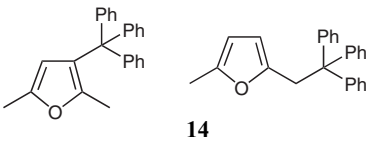
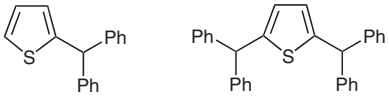
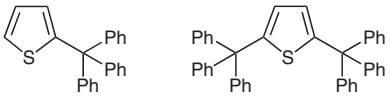
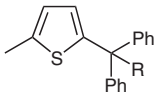
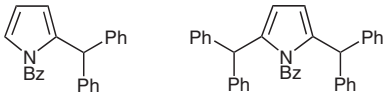
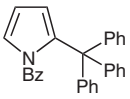
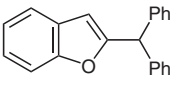
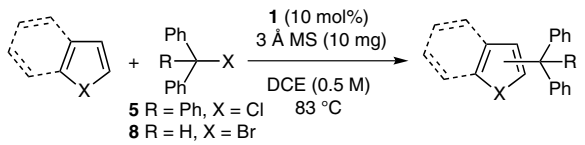
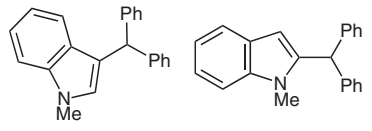
Entry[a]	Product(s)	Time (h)	Yield[b] (%)
1	 **9** **10**	0.5	40 + 59
2[c]	 **11** (R = H)	1.5	37[d]
3[c]	**12** (R = Ph)	0.2	98
4[e]	 **13** **14**	12	49 + 19[f]
5[e]	 **15** **16**	2	44 + 55
6[e]	 **17** **18**	6	43 + 56
7	 **19** (R = H)	36	95
8[g]	**20** (R = Ph)	24	99
9[h]	 **21** **22**	2	37 + 28
10[h]	 **23**	2	–[d]
11[h]	 **24**	2	78

Table 2 Alkylation of π-Excessive Heteroaromatics with a Range of Benzylic Halides (continued)



Entry[a]	Product(s)	Time (h)	Yield[b] (%)
12[h]	 **25** **26**	2	30 + 20[d]

[a] Unless otherwise noted, all reactions were performed at 0.5 M with 5 equiv of the nucleophile and 3 Å MS (10 mg/1.0 mmol of **5** or **8**) in refluxing DCE, and quenched after consumption of **5** or **8**.
[b] Isolated yield based on **5** or **8**, except for entries 9–12.
[c] At 0 °C in CH_2Cl_2.
[d] Unidentified complex byproducts were formed.
[e] 30 mol% of catalyst **1** and 30 mg of 3 Å MS were used.
[f] Along with 10% of Ph_3CH.
[g] At r.t.
[h] 40 mol% of catalyst **1** and 40 mg of 3 Å MS with 1.0 equiv of the substrate were used; yields are based on the substrate.

The reaction of furan with 1,1′-(bromomethylene)dibenzene (**8**) was completed within 30 minutes to afford the monosubstituted product **9** and the 2,5-disubstituted product **10** in yields of 40% and 59%, respectively (Table 2, entry 1).[17] 2-Methylfuran was also reactive under these conditions. Although its reaction with bromide **8** gave product **11** in only 37% yield as a result of undesired decomposition (entry 2), tritylation occurred quite smoothly at 0 °C to give the tritylated product **12** in almost quantitative yield (entry 3). 2,5-Dimethylfuran reacted slowly with trityl chloride (**5**) to give the expected product **13** in 49% yield (entry 4). Interestingly, in this case, we also observed the formation of the novel side-chain-alkylated product **14** in 19% yield, along with 10% of triphenylmethane. To account for the formation of these byproducts, it is conceivable that free-radical coupling at the furanylmethyl carbon might also occur as a competing pathway.[18]

The alkylation of thiophene or 2-methylthiophene with chloride **5** or bromide **8** proceeded efficiently in the presence of 30 or 10 mol% of catalyst **1** to give the desired products **15**–**20** in high yields (Table 2, entries 5–8). *N*-Benzoyl-1*H*-pyrrole also served as a moderately reactive heteroaromatic substrate and its reaction with bromide **8** gave adducts **21** and **22** in yields of 37% and 28%, respectively; however, attempts at tritylation of this substrate were unsuccessful (entries 9 and 10). Finally, we examined the reactions of 1-benzofuran and 1-methyl-1*H*-indole as substrates. Heating these substrates for two hours in the presence of 1.0 equiv of bromide **8** gave adduct **24** and a regioisomeric mixture of adducts **25** and **26**, respectively, in yields of 78% and 50% (entries 11 and 12).

Next, we examined the application of our method to the alkylation of reactive aromatic compounds with bromide **8** as the electrophile.[19] We hoped that this would provide a rapid route to triarylmethane derivatives of industrial importance.[20] The results are summarized in Table 3.

Unfortunately, anisole and *p*-xylene as representative aromatic substrates did not react, even under harsh conditions (refluxing DCE for 24 h). However, the reaction of 1,4-dimethoxybenzene with **8** proceeded in the presence of 10 mol% of **1** to afford the disubstituted product **27** and the monosubstituted product **28** in yields of 34% and 17%, respectively (Table 3, entry 1). The desired alkylation went to completion within two hours (78% total yield) when the amount of the catalyst was increased to 40 mol% (entry 2).[21]

Similarly, treatment of 1,3-dimethoxybenzene with bromide **8** gave the alkylation products **29** and **30** in good combined yield (entry 3). In contrast, 1,2-dimethoxybenzene showed a comparatively low reactivity and, after two hours, product **31** was isolated as a single regioisomer in 47% yield (entry 4). On the other hand, 1,3,5-trimethoxybenzene exclusively gave the monoadduct **32** in 91% yield after two hours (entry 5).

Finally, we examined the reactions of a series of *N*,*N*-dimethylanilines with bromide **8**. *N*,*N*-Dimethylaniline itself reacted with an excess of bromide **8** to give product **33** in 23% yield (entry 6). The 3-methoxy analogue also showed normal reactivity, albeit with low regioselectivity, and all possible regioisomers **34**–**36** were obtained in good combined yield (entry 7).

In summary, we have developed a new and practical method for the organocatalytic benzylation of various π-excessive heteroaromatic and aromatic compounds by using chloride **5** or bromide **8** as reactive electrophiles and thiourea **1** as a catalyst. A Friedel–Crafts alkylation of this type might involve an S_N1-type mechanism with the formation of a carbocation intermediate from **5** or **8** by abstraction of a halide anion with the aid of the halophilic thiourea **1**.[22] We believe that this method might serve as part of a novel strategy for Friedel–Crafts alkylation reactions of aromatic compounds with thiourea-based organocatalysts. Further studies to extend the scope of this method are now in progress.

Acknowledgment

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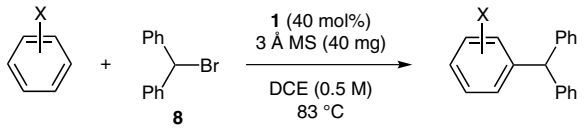
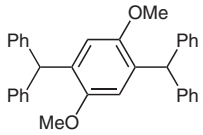
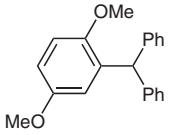
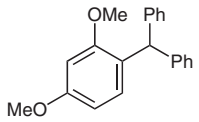
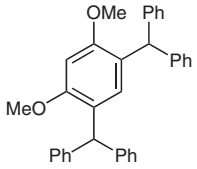
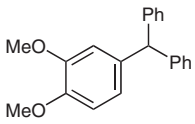
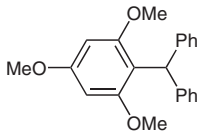
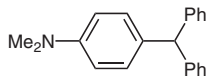
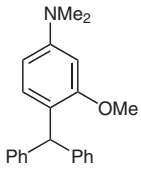
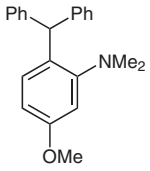
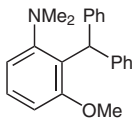
Table 3 Alkylation of π-Excessive Aromatic Compounds with 1,1′-(Bromomethylene)dibenzene



Entry[a]	Product(s)	Time (h)	Yield[b] (%)
1[c]	 **27**  **28**	6	34 + 17
2		2	42 + 36
3	 **29**  **30**	2	51 + 28
4	 **31**	2	47[d]
5	 **32**	2	91
6	 **33**	2	23[e]
7	 **34**  **35**  **36**	2	33 + 18 + 11

[a] Unless otherwise noted, all reactions were performed at 0.5 M with 1.0 equiv of the nucleophile and 3 Å MS (40 mg/1.0 mmol) in refluxing DCE, and quenched after consumption of bromide **8**.
[b] Isolated yield based on reacted starting aromatics.
[c] 10 mol% of catalyst **1** and 10 mg of 3 Å MS were used.
[d] Unidentified complex byproducts were formed.
[e] Unreacted *N*,*N*-dimethylaniline was recovered.

sity for performing the elemental analyses. This work was supported in part by a Grant-in-Aid for Scientific Research on Innovative Areas ‘Advanced Molecular Transformations by Organocatalysts’ from the MEXT (Japan) (No. 24105523).

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(10) As expected, the use of TrOH in place of TrCl was ineffective in this transformation.
(11) **2-Tritylfuran (6) and 2,5-Ditritylfuran (7); Typical Procedure (Table 1, Entry 4)**
Catalyst **1** (50.0 mg) and powdered activated 3 Å MS (10 mg) were added to a colorless solution of Ph_3CCl (**5**, 279 mg, 1.0 mmol) and freshly distilled furan (340 mg, 5.0 mmol) in dry CH_2Cl_2 (2.0 mL), and the mixture was stirred for 4 h at r.t. At the end of the reaction, the solution became reddish purple. The mixture was concentrated and the residue was purified by column chromatography [silica gel, hexane–Et_2O (50:1 to 10:1)] to give **6** and **7**.
2-Tritylfuran (6)
Colorless needles; yield: 186 mg, (60%); mp 201–202 °C (hexane–Et_2O); R_f = 0.24 (hexane). FTIR (KBr): 1595, 1490, 1442 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 6.04 (dd, *J* = 2.0, 1.0 Hz, 1 H), 6.32 (dd, *J* = 2.0, 1.5 Hz, 1 H), 7.06–7.11 (m, 6 H), 7.22–7.28 (m, 9 H), 7.45 (br s, 1 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 60.84, 109.78, 111.31, 126.58 (×3), 127.60 (×6), 130.20 (×6), 142.25, 145.14 (×3), 159.28. Anal. Calcd for $C_{23}H_{18}O$: C, 89.00; H, 5.85. Found: C, 89.15; H, 5.47.
2,5-Ditritylfuran (7)
Colorless needles; yield: 108 mg (39%); mp >280 °C (sublimed, $CHCl_3$); R_f = 0.15 (hexane). FTIR (KBr): 1594, 1492, 1444 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 5.96 (s, 2 H), 6.98–7.05 (m, 12 H), 7.15–7.25 (m, 18 H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 60.92 (×2), 110.92 (×2), 126.35 (×6), 127.52 (×12), 130.27 (×12), 144.85 (×6), 159.51 (×2). Anal. Calcd for $C_{42}H_{32}O·H_2O$: C, 88.39; H, 6.00. Found: C, 88.58; H, 5.75.
(12) (a) The use of molecular sieves as acid scavengers is well established; see: *Encyclopedia of Reagents for Organic Synthesis*; Vol. 9; Paquette, L. A.; Crich, D.; Fuchs, P. L.; Molander, G. A., Eds.; Wiley: Chichester, **2009**, 2nd ed., 7162–7165. (b) Unfortunately, the same reaction in the presence of a tertiary amine base such as Et_3N as an acid scavenger gave a rather complex mixture of products, and the yields were not determined.
(13) When the same reaction was conducted by adding 10 mol% of TBACl, the reaction was completely suppressed, indicating the important contribution of the common-ion effect.
(14) Judging from this result, there is some possibility that 3 Å MS not only acted as an acid scavenger, but also an accelerator.
(15) Judging from the result shown in entry 9 of Table 1, we were obliged to conclude that diphenylthiourea **3** acted as a catalyst poison in this system..
(16) We did not check the recyclability of catalyst **1**. However, after the reaction was complete, in most cases **1** could be clearly detected by TLC and should be recoverable.
(17) In a control experiment (Table 2, entry 1), only a trace amount of products was formed in the absence of catalyst **1** (36 h in refluxing DCE).
(18) Unfortunately, the product distribution did not change when the reaction was performed in the presence of a radical inhibitor such as hydroquinone (6 h in refluxing DCE): **14** (44%), **15** (17%), and Ph_3CH (20%). This product distribution is similar to that obtained the presence of a radical initiator such as AIBN: **14** (45%), **15** (8%), and Ph_3CH(26%). Importantly, the formation of furanylmethyl radicals has only been noted under conditions of photo-irradiation. See, for example: Cantrell, T. S.; Allen, A. C.; Ziffer, H. *J. Org. Chem.* **1989**, *54*, 140.
(19) All attempts to perform the tritylation of 1,4-dimethoxy-benzene in the presence of catalyst **1** failed for reasons that are not yet clear.
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(21) In a control experiment (Table 3, entry 2), the reaction was significantly retarded in the absence of catalyst **1** (6 h in refluxing DCE), and gave 25% of **27** along with 7% of **28.**
(22) We cannot exclude the possibility that an S_N2-type mechanism might also operate in reactions with **8** as the electrophile. At present, we have no clear idea of the halophilic strength (Br versus Cl) of catalyst **1.**

