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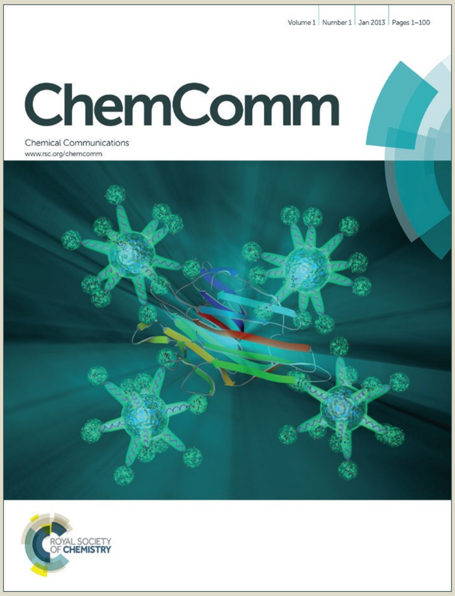

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From insertion to multicomponent coupling: temperature dependent reactions of arynes with aliphatic alcohols†

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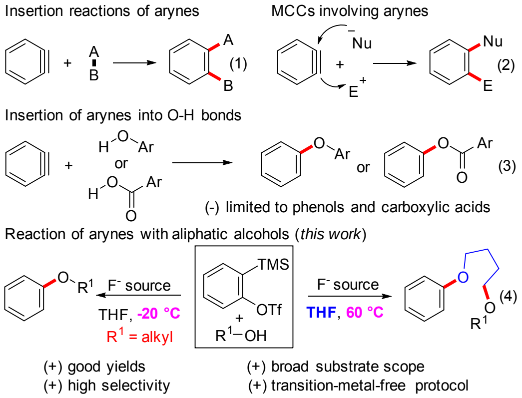
The temperature dependent selectivity switch in the reaction of arynes with aliphatic alcohols in THF has been reported. At -20 °C, arynes smoothly insert into the O-H bond of alcohols to form alkyl aryl ethers. Interestingly, at 60 °C, highly selective multicomponent coupling occurs with solvent THF acting as the nucleophilic trigger affording (4-(alkoxy)butoxy)arenes.

Arynes are a class of highly reactive intermediates that received widespread attention in the last three decades.[1] This renaissance of interest in aryne chemistry is primarily due to the development of mild protocols for their generation by the fluoride-induced 1,2-elimination of 2-(trimethylsilyl)aryl triflates.[2] Two of the important modes of aryne reactions include the insertion reactions[3] and multicomponent couplings (MCCs).[4] In insertion reactions, arynes are added to various element-element bonds to form various 1,2-disubstituted benzene derivatives (Scheme 1, eq 1).[5] The MCC results by the addition of nucleophiles (devoid of acidic protons) to arynes followed by the interception of the resulting aryl anion intermediate with electrophiles (eq 2).[6,7]

In 2004, Larock and co-workers reported the insertion of arynes into the O-H bond of phenols and carboxylic acids to form diaryl ethers and aryl esters (eq 3).[8] Intriguingly, the aryne insertion to aliphatic alcohols has been underexplored.[9] This will be interesting as the resultant alkyl aryl ethers are having potential application in medicine, crop protection, and fine organic chemicals.[10] Traditionally, alkyl aryl ethers are synthesized by the phenol alkylation using Williamson synthesis,[11] Cu-mediated Ullmann coupling,[12] and the use of Mitsunobu reaction.[13] Moreover, transition-metal-catalyzed *O*-arylation using aliphatic alcohols is a powerful strategy for the construction of alkyl aryl ethers.[14] In this context, synthesis of alkyl aryl ethers under transition-metal-free conditions have the economic and ecological advantage.[15] Herein, we report the transition-metal-free, and temperature dependent switchable reactions of arynes with aliphatic alcohols in THF for the synthesis of alkyl aryl ethers. At -20 °C, arynes undergo smooth insertion to O-H bond of alcohols to afford the alkyl aryl ethers in high selectivity.[16] However, when the reaction was performed at 60 °C, highly selective MCC occurs with THF acting as the nucleophilic trigger furnishing (4-(alkoxy)butoxy)arenes.[17,18]



Considering the importance of installing the alkoxy group directly to the aromatic ring, the present study commenced with treating 3-phenyl propanol **1a** with aryne generated from 2-(trimethylsilyl)aryl triflate **2a**.[2] When the reaction was performed using KF as the fluoride source (using [18] crown-6 as additive) at 30 °C, the *O*-arylated product **3a** was isolated in 12% yield and the MCC product **4a** was isolated in 44% yield with a selectivity of 20:80 (Table 1, entry 1).[19] When the reaction was carried out using tetrabutyl ammonium fluoride (TBAF), better selectivity for **3a** was observed while CsF returned almost similar results (entries 2, 3).[20] Interestingly, using KF at 0 °C, **3a** was formed in 59% yield with 82:18 selectivity (entry 4). Moreover, when the temperature was further reduced to -20 °C, **3a** was isolated in 75% yield and excellent selectivity of 95:5 (entry 5). Under similar conditions, TBAF and CsF furnished inferior results (entries 6, 7).

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Dedicated to Professor Tien-Yau Luh on the occasion of his 70th Birthday

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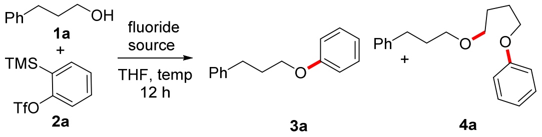
Gratifyingly, performing the reaction at 60 °C using KF, the selectivity was switched to MCC product **4a** (**3a: 4a** 13:87; 56% yield; entry 8). Using slight excess of **2a** and under dilution conditions, the selectivity for **4a** was improved to 9:91 and **4a** was isolated in 61% yield (entry 9).[21] The optimization studies revealed that low temperature prefers the insertion of arynes to O-H bond of **1a** where as high temperature shifts the selectivity towards the MCC product **4a** where THF is the nucleophilic trigger.

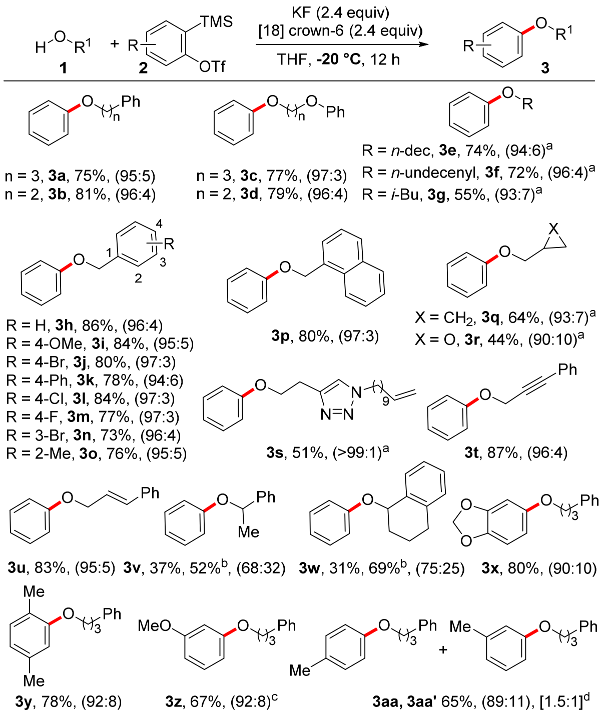
Table 1. Optimization of Reaction Conditions[a]



entry	fluoride source	temp (°C)	yield of **3a**[b]	yield of **4a**[b]	**3a:4a**[c]
1	KF/[18] crown-6	30	12	44	20:80
2	TBAF	30	25	<5	95:5
3[d]	CsF	30	11	43	19:81
4	KF/[18] crown-6	0	59	12	82:18
5	*KF/[18] crown-6*	*-20*	*75*	*<5*	*95:5*
6	TBAF	-20	41	<5	95:5
7[d]	CsF	-20	<5	11	27:73
8	KF/[18] crown-6	60	9	56	13:87
9[e]	*KF/[18] crown-6*	*60*	*<5*	*61*	*9:91*

[a] General conditions: **1a** (0.25 mmol), **2a** (0.30 mmol), KF (2.4 equiv), [18] crown-6 (2.4 equiv), THF (1.5 mL), for the indicated temperature and 12 h. [b] The yields of the isolated products are given. [c] Selectivity was determined using GC analysis of the crude reaction mixture. [d] Reaction performed using 1:1 CH_3CN:THF. [e] Using 1.5 equiv of **2a**, 3.0 equiv of KF and [18]-crown-6 and 2.0 mL of THF.

Having established a temperature dependent procedure for the selective aryne insertion to O-H bond of alcohols and THF triggered aryne MCCs, we then examined the scope of this reaction. First, we evaluated the scope of aryne insertion to O-H bond of alcohols (Scheme 1). A series of linear, *O*-tethered, and branched aliphatic alcohols underwent smooth aryne insertion at -20 °C affording the alkyl phenyl ethers in good yields and high selectivity (**3a-3g**). Moreover, a series of benzyl alcohols having electron-releasing or -withdrawing groups at the aryl moiety were well-tolerated to furnish the benzyl phenyl ethers in good yield and high selectivity (**3h-3p**). Additionally, cyclopropyl and epoxy substituted alcohols (**3q, 3r**), alcohol having a triazole functionality (**3s**) and alcohols with C-C triple bond and double bond (**3t, 3u**) worked well under the optimized conditions. Notably, secondary alcohols resulted in aryne inserted products in moderate yield and selectivity (**3v, 3w**). We also studied the variation of the aryne moiety. Symmetrical arynes generated from the corresponding precursors returned the desired products in good yield and selectivity (**3x, 3y**). Interestingly, the unsymmetrical 3-methoxy benzyne afforded a single regioisomer **3z** in 67% yield and 89:11 selectivity. Furthermore, the unsymmetrical 4-methyl benzyne afforded the regioisomeric mixture (in ratio 1.5:1) of *O*-arylated products **3aa** and **3aa'** in 65% yield, thereby further expanding the scope of this reaction.

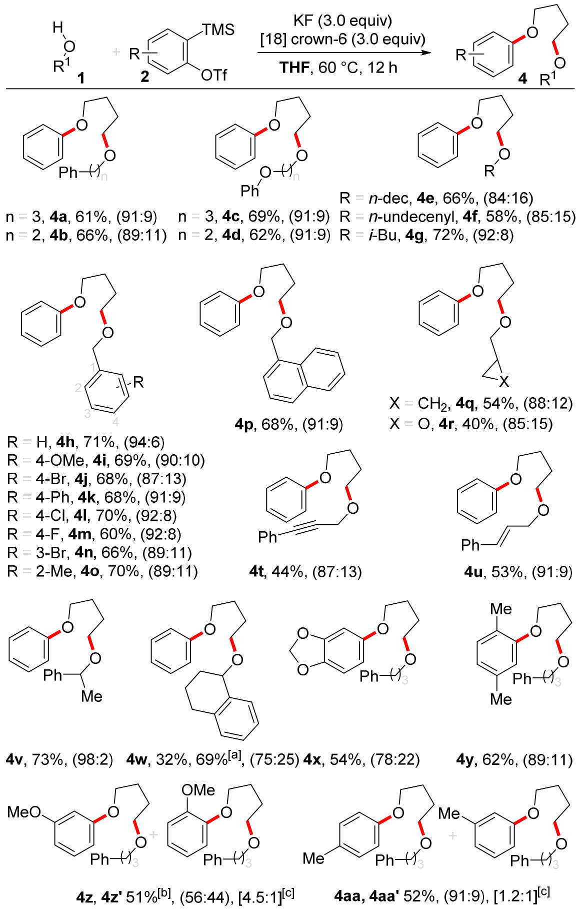


Scheme 1. Scope of the aryne insertion to O-H bond of alcohols. General conditions: **1** (0.5 mmol), **2** (0.6 mmol), KF (1.2 mmol), [18] crown-6 (1.2 mmol), THF (3.0 mL), -20 °C, 12 h. Yields of the isolated products are given. Selectivity ratio determined by GC analysis of crude reaction mixture is given in parentheses. [a] Reaction was run using 2.0 equiv of **2**, 4.0 equiv of KF and 4.0 equiv of [18]-crown-6. [b] Yield based on recovered **1**. [c] Reaction run on 0.25 mmol scale. [d] The regioisomer ratio determined by GC analysis.

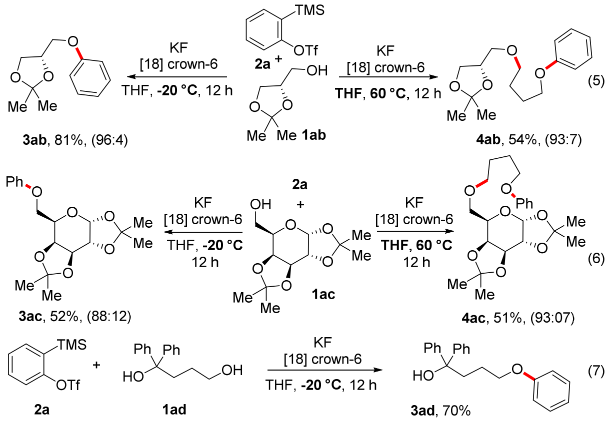
Next, we examined the substrate scope of this THF triggered aryne MCCs (Scheme 2). Almost all aliphatic alcohols (except the alcohol with the triazole group **1s**), where smooth aryne insertion was taking place at -20 °C underwent aryne MCCs initiated by THF at 60 °C affording the (4-(alkoxy)butoxy)arenes **4** in moderate to good yields and good selectivities. Interestingly, various linear and benzyl alcohols were well-tolerated under the present MCC conditions to furnish the desired alkyl aryl ethers (**4a-4p**). Notably, the epoxy methyl alcohol **1r** afforded the MCC product **4r** in 44% yield and in 85:15 selectivity. In this case, the product derived from the nucleophilic attack of epoxide oxygen was not observed. THF appears to be a competant nucleophilic trigger at 60 °C in the presence of phenyl propargyl alcohol or cinnamyl alcohol, and the corresponding propargyl and allyl ethers were isolated in moderate yields (**4t, 4u**). Delightfully, 1-phenylethanol underwent efficient aryne MCC affording the desired product **4v** in 73% yield and an excellent selectivity of 98:2. Finally, symmetrical arynes generated from their precursors afforded the target products in moderate to good yields (**4x, 4y**), and unsymmetrical arynes furnished regioisomeric mixture of products in moderate yields (**4z, 4aa**).

Interestingly, when the reaction of aryne was performed at -20 °C in THF using the enantiomerically pure acetal protected primary alcohol **1ab**, the *O*-arylated product **3ab** was isolated in 81% yield and 96:4 selectivity (eq 5). Moreover, when the reaction was carried out at 60 °C in THF, the corresponding MCC product **4ab** was obtained in 54% yield and 93:7

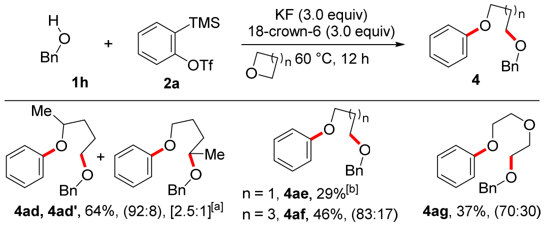
selectivity. It is noteworthy that the acetal protection was not affected under the reaction conditions. Similar results were obtained with acetal protected primary alcohol **1ac** (eq 6). In addition, the utility of diol **1ad** containing primary and tertiary alcohol moieties in the aryne reaction at -20 °C afforded the product **3ad** (70% yield) derived from the selective insertion to primary O-H group into aryne where as the tertiary alcohol moiety remained intact (eq 7).



Scheme 2. Scope of the aryne MCCs triggered by THF. General conditions: **1** (0.5 mmol), **2** (0.75 mmol), KF (1.5 mmol), [18] crown-6 (1.5 mmol), THF (4.0 mL), 60 °C, 12 h. Yields of the isolated products are given. Selectivity ratio determined by GC analysis of crude reaction mixture is given in parentheses. [a] Yield based on recovered **1**. [b] Reaction run on 0.25 mmol scale. [c] The regioisomer ratio determined by GC analysis.



Gratifyingly, this aryne MCC is not limited to THF as the nucleophilic trigger, but instead other cyclic ethers afforded the products in moderate yields (Scheme 3). The reaction of **1h** with aryne generated from **2a** in 2-methyl tetrahydrofuran afforded the regiosomeric mixture of MCC products **4ad** and **4ad'** in 64% yield and 2.5:1 regioselectivity. A high selectivity of 92:8 for MCC product was observed over the arylation product. Moreover, the reaction performed in oxetane, tetrahydropyran and 1,4-dioxane afforded the respective MCC products in moderate yields (**4ae-4ag**).



Scheme 3. Scope of the aryne MCCs with cyclic ethers. See the supporting information for details. Yields of the isolated products are given and selectivity ratio determined by GC analysis of crude reaction mixture is given in parentheses. [a] The regioisomer ratio determined by GC analysis. [b] NMR yield of the product given.

To get insight into the temperature dependence of the aryne reactions with aliphatic alcohols, we have carried out a series of experiments under varying temperature using benzyl alcohol **1h** and aryne generated from **2a**. It was found that as the temperature increases from -20 °C, the yield of O-H inserted product **3h** decreases where as the yield of MCC product **4h** increases.[22] The results are plotted in Figure 1. From Figure 1, it is clear that at ~25 °C, both **3h** and **4h** are formed in 1:1 ratio.

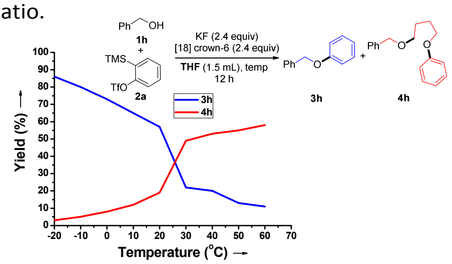


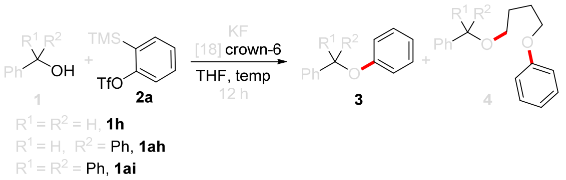
Figure 1. Variation of temperature on aryne reactions with benzyl alcohol

We also studied the reactivity of primary, secondary and tertiary alcohols with arynes (Table 2). Benzyl alcohol **1h** afforded 86% yield of insertion product **3h** at -20 °C (96:4 selectivity) where as 71% the MCC product **4h** (6:94 selectivity) was isolated at 60 °C (entries 1, 2). Interestingly, benzhydrol **1ah** afforded a 1:1 ratio of insertion product **3ah** and MCC product **4ah** at -20 °C. However, the selectivity was completely switched to **4ah** at 60 °C (entries 3, 4). Moreover, trityl alcohol **1ai** furnished only traces of insertion product **3ai** and 32% of MCC product **4ai** at -20 °C. At 60 °C, exclusive MCC product formation took place isolating **4ai** in 64% yield and 1:99 selectivity.[23] These studies clearly indicate that the ability of arynes to insert into O-H bond of alcohols are in the order primary>secondary>tertiary with arynes do not undergoing insertion to tertiary alcohols even at -20 °C.

In conclusion, we have developed a transition-metal-free temperature dependent switchable reactivity in the reaction of arynes with aliphatic alcohols.[24] At -20 °C, arynes insert into O-

H bond of alcohols to afford alkyl aryl ethers. However, at 60 °C, efficient aryne MCCs resulted where THF acts as the nucleophilic trigger.

Table 2. Comparative study of various alcohols



entry	R^1	R^2	temp (°C)	yield of **3** (%)[c]	yield of **4** (%)[c]	**3:4**[d]
1[a]	H	H	-20	86	<5	96:4
2[b]	H	H	60	<5	71	6:94
3[a]	Ph	H	-20	18	17	50:50
4[b]	Ph	H	60	<5	65	1:99
5[a]	Ph	Ph	-20	<5	32	1:99
6[b]	Ph	Ph	60	<5	64	1:99

[a] Conditions: **1** (0.5 mmol), **2a** (0.6 mmol), KF (2.4 equiv), [18] crown-6 (2.4 equiv), THF (3.0 mL), 12 h. [b] Conditions: **1** (0.5 mmol), **2a** (0.75 mmol), KF (3.0 equiv), [18] crown-6 (3.0 equiv), THF (4.0 mL), 12 h. [c] Isolated yields. [d] Selectivity was determined using GC analysis of the crude reaction mixture.

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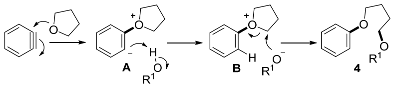
19 The MCC product **4** was formed by the nucleophilic addition of THF to aryne generating the zwitterion **A**, which deprotonates the alcohol to form the oxonium intermediate **B** followed by a nucleophilic attack of the generated alkoxide. The selective addition of THF to arynes at 60 °C in the presence of aliphatic alcohols is stricking.



20 Further studies to optimize the conditions for selective arylation reaction using CsF in CH_3CN alone did not improve the yield of **3a**. For details, see the Supporting information.

21 For details, see the Supporting information.

22 Notably, the conditions for the reactions above 30 °C are different from the procedure followed for the selective MCCs in Scheme 2 in order to make the temperature dependent study uniform.

23 *tert*-Butyl alcohol did not afford the insertion product at -20 °C. However, at 60 °C, exclusive MCC product formation took place in moderate yields.

24 For the details on computational chemistry studies on the mechanism, see the Supporting information.