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Meta-Selective C-H Functionalization using a Nitrile based Directing Group and Cleavable Si-Tether

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Abstract

A nitrile-based template that enables *meta*-selective C-H bond functionalization was developed. The template is applicable to a range of substituted arenes and tolerates a variety of functional groups. The directing group uses a silicon atom for attachment allowing for a facile introduction/deprotection strategy increasing the synthetic practicality of this template.

C-H functionalization is an area that has seen enormous growth over the past 30 years.[1] Given the ubiquity of C-H bonds in organic molecules, selectivity in C-H functionalization is a critical element to any successful methodology. The three main approaches to controlling selectivity have been to use either sterics,[2] inherent reactivity,[3] and directing groups[1b-f] to differentiate C-H bonds. Between these approaches, directing groups have been the most widely applied; however, this strategy has generally been limited to activating positions *ortho* to the directing functionality on aromatic rings. In a pioneering report, Yu and co-workers have demonstrated that *meta*-selective C-H activation[4] is possible using a directing group appended to both alcohol and acid substrates.[5] In this case the strain associated with forming the requisite metallocyclophane is alleviated by the application of a linear nitrile.

Herein we report a silicon based directing/protecting group[6] for *meta*-selective C-H activation of aromatic rings (Scheme 1). The advantage of our methodology is that the directing group is easily incorporated onto alcohol-based substrates and removed under standard fluoride or acid catalyzed deprotection conditions. Moreover, the directing group is synthesized in 3 steps from inexpensive reagents and is recyclable. The expansion of meta-selective C-H activation to alcohol-based substrates enriches the synthetic utility of these nitrile-based directing groups.

As a first step towards developing a practical directing group for *meta* selective C-H activation, we synthesized a series of silicon based directing groups and tested them in the oxidative C-H coupling to olefins. After preliminary optimization of the reaction conditions (see Supp. Info.), we found that placing the nitrile *meta* to the silicon atom results in a significant amount of *meta* functionalization of the aromatic ring (*o:m:p* = 7:81:12, Table 1, entry 1). It is worth noting that the relative position of the silicon tether and nitrile is different from the Yu group's carbon based directing group. We reasoned that the larger size of the silicon atom along with elongated Si-C and Si-O bonds may require greater separation between the directing nitrile and reacting aromatic group. The *para* isomer **2** provides the product in low yield and with selectivity that is typical for a sterically driven C-H

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Supporting Information. Starting material synthesis, characterization of compounds, and optimization data. This material is available free of charge via the Internet at http://pubs.acs.org.

functionalization reaction (*o:m:p* = 22:43:35, Table 1, entry 2).[7] Furthermore, this reaction serves as a control reaction, verifying the necessity of having the nitrile properly positioned in the substrate for *meta* selectivity.

With this initial success, we took advantage of the modular nature of the silicon-based directing group to further optimize the reaction. To improve the *meta* directing ability, we varied the groups adjacent to the nitrile in order to examine how compressing and expanding the bond angle (α) between the phenyl ring and nitrile affects the selectivity (Table 1). Changing the geminal methyl groups to a cyclopropane, which should expand α, affords comparable results to **1a** (Table 1, entry 3). A contraction of α by expanding ring size (**1c**) results in an increase in the *meta* selectivity. Switching to bulkier acyclic groups in order to further compress α improves the *meta* selectivity. This trend was observed from methyl (**1a)** to *sec*-butyl group (**1d-f,** Table 1, entries 5-7), which provided the maximum selectivity. More *ortho* product was obtained with cyclohexyl groups (**1g**, Table 1, entry 8) on the benzylic position, suggesting that optimum angle for meta selectivity had been exceeded. Although the reaction is highly *meta* selective with optimal substrate **1f**, the conversion of the reaction was found to be modest. Upon further optimization, higher conversion was achieved by the addition of 3.0 equiv of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) without any deterioration in selectivity (Table 1, entry 9).

The requisite silicon chloride **8** is synthesized in 3 steps from inexpensive starting materials, and can be made in multi-gram quantities (Scheme 2). First, 2-(3-bromophenyl)-acetonitrile **5** was dialkylated using potassium *tert*-butoxide and *sec*-butyl iodide, followed by lithium-halogen exchange mediated silylation produced intermediate silane **7** in good yield. Conversion to silyl chloride **8** was accomplished by trichloroisocyanuric acid in excellent yield.

With the optimized conditions and template structure in hand, the substrate scope was investigated. Various benzyl alcohols with electron withdrawing or donating substituents were prepared from the corresponding alcohols and silyl chloride in one step (Scheme 2). Although we could not avoid formation of bis-substituted products for 2-substituted substrates (Table 2, **9a**-**9c**), high *meta* selectivity was observed regardless of substrate's electronic nature. The result for 3-substituted substrates clearly shows this method is applicable to a wide variety of functional groups. Compound **9d** afforded the highest yield maintaining high selectivity. All the halogens from fluoride to bromide are well tolerated (**9e**-**9g**), resulting in good yields and selectivity. The presence of a strongly electron withdrawing CF_3 group led to diminished yield (50%) but the highest selectivity (*meta*:others=97:3, **10h**) was observed. C-H activation of **9i**, which contains a methoxy substitutent, results in inferior selectivity. Competition experiments with other *ortho*-directing groups present suggested that the directing ability of the nitrile group is superior to that of an ester (compound **9k**)[8] but not of an acetoxy group (compound **9j**).[9] *Meta* selectivity decreased slightly with 4-substituted compounds (**9l**-**9n**) due to steric hindrance. In the case of methoxy substitution, the electronic effect and directing group worked in concert to enhance *meta* selectivity (**10n**, *meta*:others=98:2). Interestingly, among the seven aromatic C-H bonds in 1-naphthyl methanol **9o**, the C-H bond at C-3 is activated and affords the product in 53% yield. We were also able to apply this method toward secondary α-methylbenzyl alcohol substrates with similar levels of selectivity and yield in the C-H activation step (**9p**-**r**).

Further investigation with various olefin partners revealed that electron deficient olefins bearing amide, ketone, and sulfone groups produced functionalized compounds with moderate yields and high selectivity (**11a-c**). 1,2-disubstituted *trans*-methyl crotonate also proceeded well affording a single stereoisomer **11d** as the major product.

To probe the mechanism of the reaction an intermolecular competition experiment was performed. A kinetic isotope effect of 2.5 was estimated by NMR spectroscopic analysis after cleavage of the silicon directing group (Scheme 3). This value suggests C-H bond activation is the rate determining step and a bent transition state is expected to be involved.[10]

An additional advantage of this chemistry is the potential to reuse the silicon directing group. The template was easily cleaved by tetrabutylammonium fluoride at room temperature within an hour after filtration of the silver and palladium precipitates without additional purification step (Table 2, compound **10d′**). Alternatively, when the purified C-H activation product is treated with wet ethanol in the presence of a catalytic amount of *para*-toluenesulfonic acid, the free benzyl alcohol **10d′** is obtained and the template is recovered as silanol **12** (Scheme 4). Silanol **12** can be used to prepare protected starting material **9d** in moderate yield.

In summary, we have developed an efficient *meta* directing group based on a silicon tether. Introduction of the template was performed using standard silicon protection conditions and *in-situ* cleavage was demonstrated as feasible. C-H activation was successful for all substitution patterns on the aromatic ring, and the template could be applied to primary and secondary alcohols with equal efficacy. Because of the reversible nature of the silicon oxygen bond, investigations are underway to develop conditions that will facilitate catalytic use of our template.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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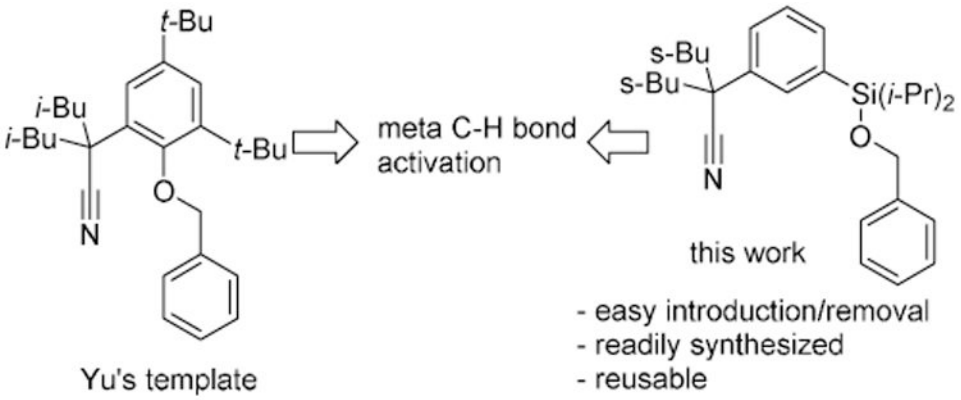
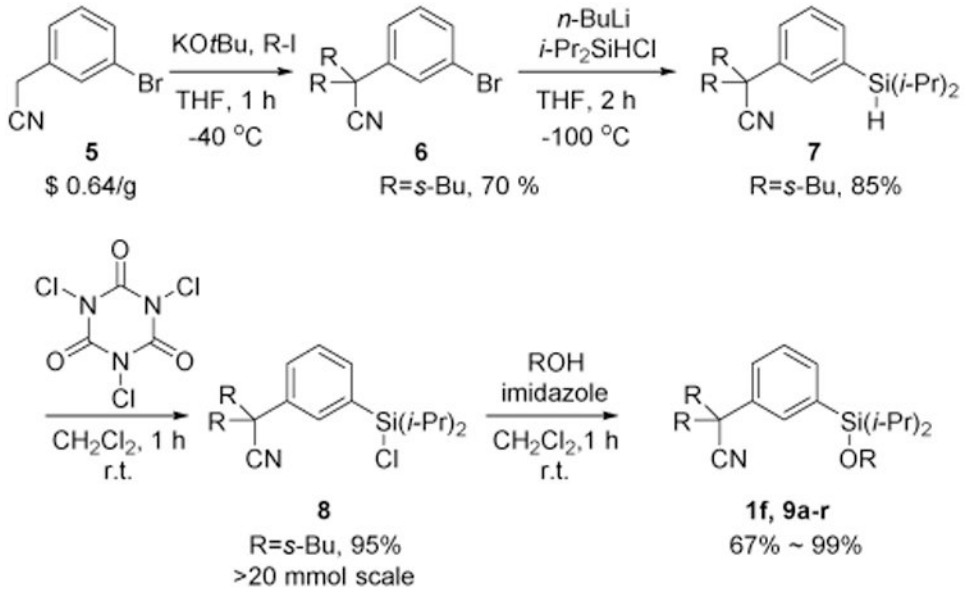
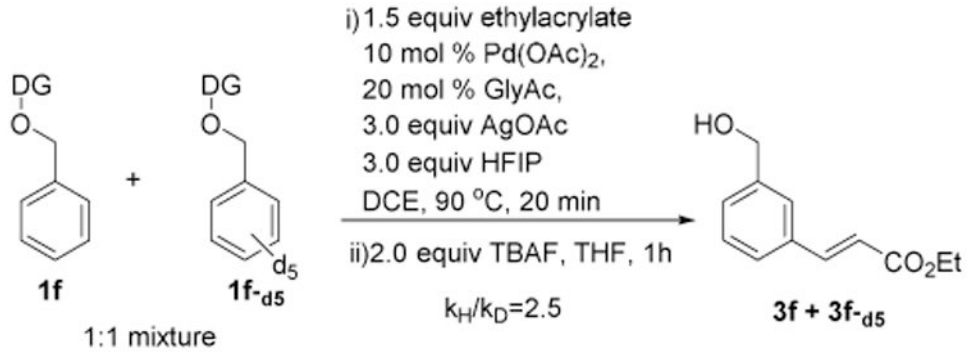


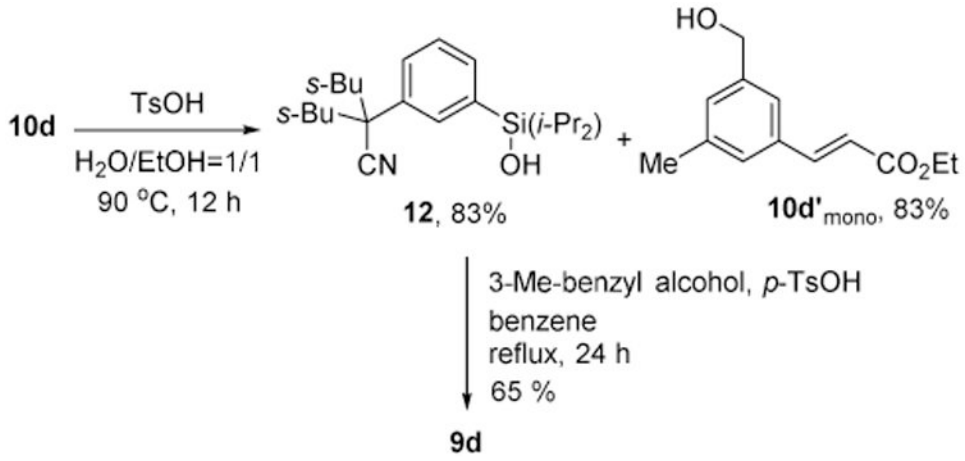
Scheme 1. Development of silicon based directing group



Scheme 2. Preparation of directing group and installation



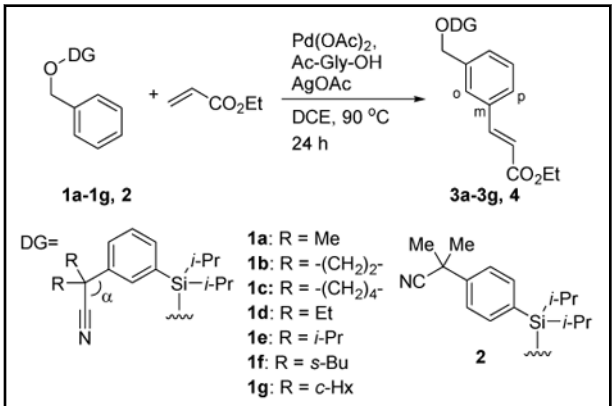
Scheme 3. Kinetic isotope effect



Scheme 4. Template regeneration

Table 1

Optimization of ligand structure[a]



entry	substrate	o:m:p[b]	product	yield [%] (mono/di)
1	**1a**	7:81:12	**3a**	43 (5.1:1)
2	**2**	22:43:35	**4**	8[c]
3	**1b**	6:81:13	**3b**	52 (4.8:1)
4	**1c**	5:86:9	**3c**	42 (5:1)
5	**1d**	6:88:6	**3d**	62 (3.4:1)
6	**1e**	4:90:6	**3e**	54 (2.6:1)
7	**1f**	4:92:4	**3f**	57 (3.6:1)
8	**1g**	6:90:4	**3g**	50 (5.3:1)
9[d]	**1f**	2:96:2	**3f**	84 (1.74:1)

[a] reaction conditions: 0.1 mmol substrate, 1.5 equiv ethylacrylate, 10 mol % $Pd(OAc)_2$, 20 mol % AcGly-OH, 2.0 equiv AgOAc in 1 mL DCE, 90°C, 24 h.

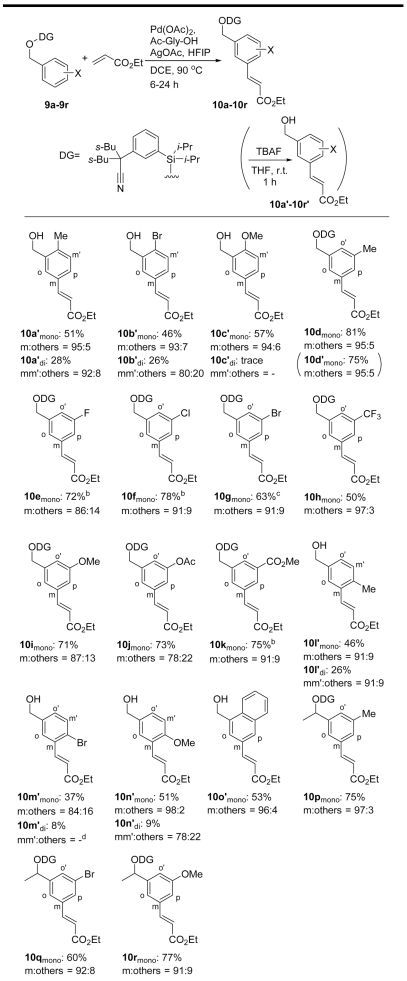
[b] Ratio was determined by ^1H NMR.

[c] NMR yield

[d] Reaction time was 6 h using 3.0 equiv. HFIP and 3.0 equiv AgOAc.

Table 2

Substrate Scope[a]



[a] reaction conditions: 0.1 mmol substrate, 1.5 equiv ethylacrylate, 10 mol % $Pd(OAc)_2$, 20 mol % AcGly-OH, 3.0 equiv AgOAc, 5.0 equiv HFIP in 1 mL DCE, 90 °C, 24 h. Isomeric ratio was determined by ^1H NMR.

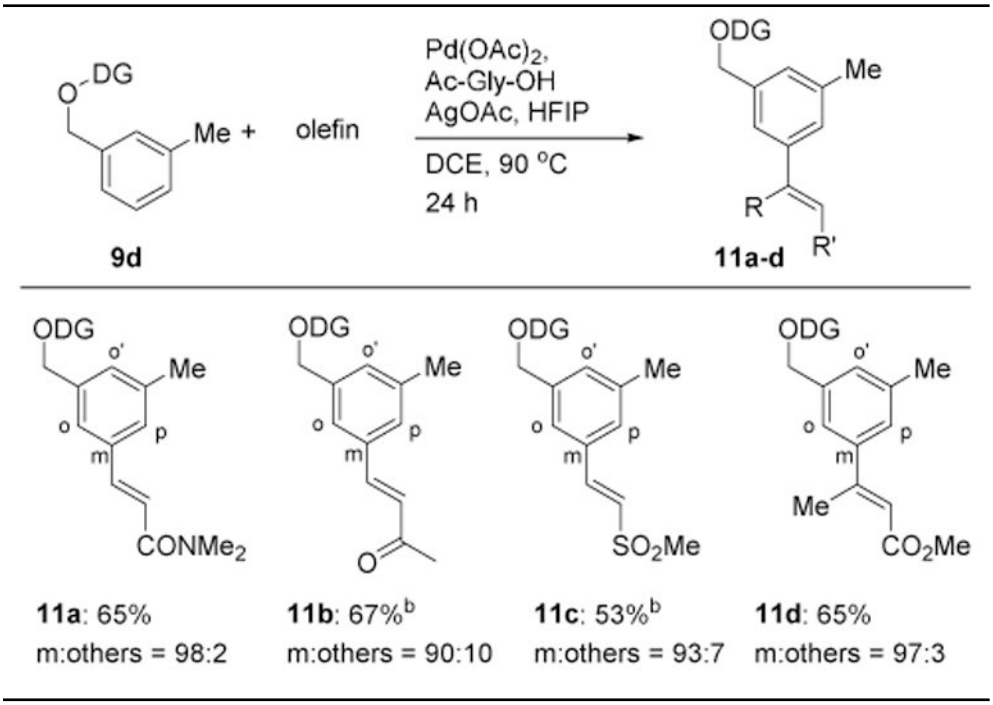
[b] 20.0 equiv HFIP were used.

[c] 10 equiv HFIP, 3.0 equiv acrylate were used.

[d] inseperable mixture with side product from metal-halogen exchange

Table 3

Reaction with various olefins[a]



[a] reaction conditions: 0.1 mmol substrate, 1.5 equiv ethylacrylate, 10 mol % $Pd(OAc)_2$, 20 mol % AcGly-OH, 2.0 equiv AgOAc, 5.0 equiv HFIP in 1.0 mL DCE, 90 °C, 24 h. Isomeric ratio was determined by ^1H NMR.

[b] 10 equiv HFIP was used.