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Meta-Selective C−H Functionalization Using a Nitrile-Based Directing Group and Cleavable Si-Tether

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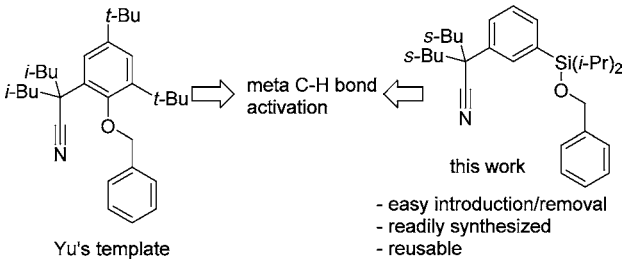
Supporting Information

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] or directing groups[1b−f] to differentiate C−H bonds. Among 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.

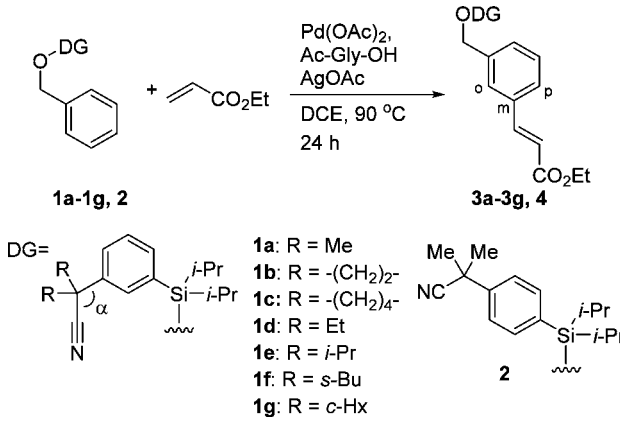
Herein we report a silicon-based directing/protecting group[6] for meta-selective C−H activation of aromatic rings (Scheme 1). The advantage of our methodology is that the directing group is easily incorporated onto alcohol-based substrates and removed under standard fluoride- or acid-catalyzed deprotection conditions. Moreover, the directing group is synthesized in three 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.

Scheme 1. Development of Silicon-Based Directing Group



As a first step toward 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 Supporting Information [SI]), 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 carbon-based directing group of Yu et al. 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

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 (5.0:1)
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 (1.7:1)

[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.

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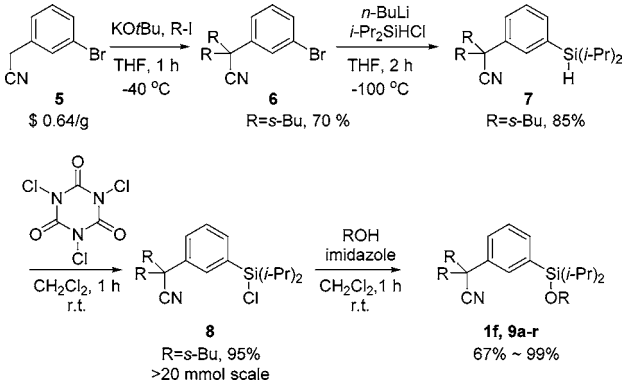
typical for a sterically driven C−H functionalization reaction (*o*:*m*:*p* = 22:43:35, Table 1, entry 2).[7] Furthermore, this reaction serves as a control reaction, verifying the necessity of having the nitrile properly positioned in the substrate for meta selectivity.

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 three steps from inexpensive starting materials and can be made in multigram quantities (Scheme 2). First, 2-(3-bromophenyl)-

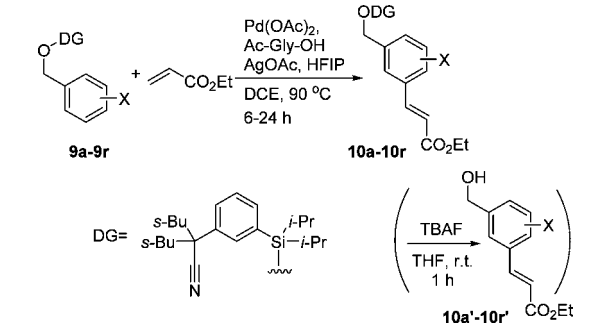
Scheme 2. Preparation of Directing Group and Installation

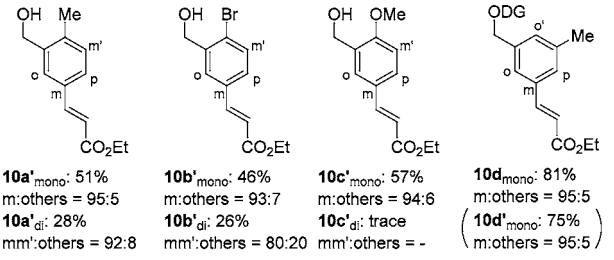


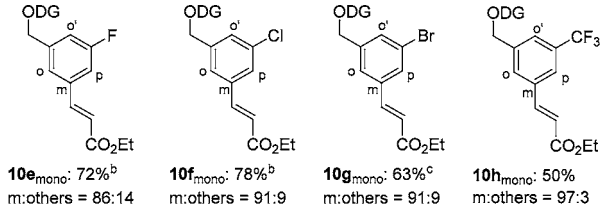
acetonitrile **5** was dialkylated using potassium *tert*-butoxide and *sec*-butyl iodide, followed by lithium−halogen exchange mediated silylation that produced intermediate silane **7** in good yield. Conversion to silyl chloride **8** was accomplished by trichloroisocyanuric acid in excellent yield.

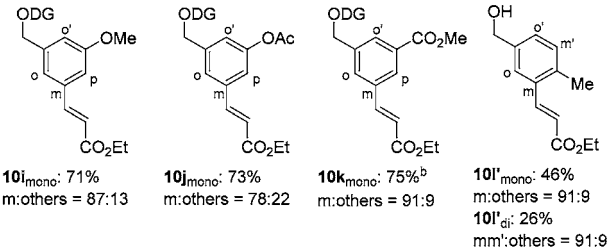
With the optimized conditions and template structure in hand, the substrate scope was investigated. Various benzyl alcohols with electron-withdrawing or -donating substituents were prepared from the corresponding alcohols and silyl chloride in one step (Scheme 2). Although we could not avoid formation of bis-substituted products for 2-substituted substrates (Table 2, **9a−9c**), high meta selectivity was observed regardless of the 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

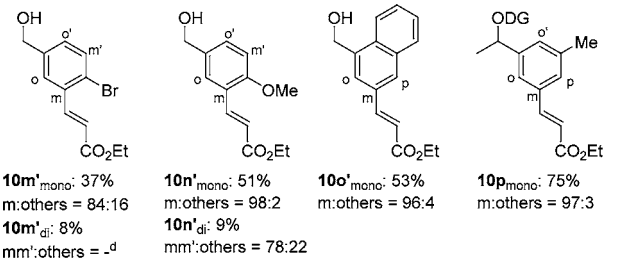
Table 2. Substrate Scope[a]

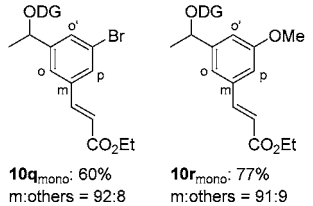












[a]Reaction conditions: 0.1 mmol substrate, 1.5 equiv ethylacrylate, 10 mol % $Pd(OAc)_2$, 20 mol % AcGly-OH, 3.0 equiv AgOAc, 5.0 equiv HFIP in 1 mL DCE, 90 °C, 24 h. Isomeric ratio was determined by ^1H NMR. [b]20 equiv HFIP was used. [c]10 equiv HFIP, 3.0 equiv acrylate were used. [d]Inseparable mixture with side product from metal−halogen exchange

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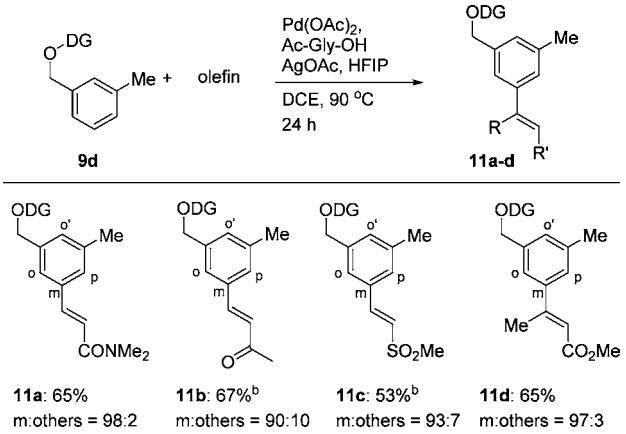
fluoride to bromide are well tolerated (**9e**–**9g**), resulting in good yields and selectivity. The presence of a strongly electron-withdrawing CF_3 group led to diminished yield (50%), but the highest selectivity (meta:others = 97:3, **10h**) was observed. C–H activation of **9i**, which contains 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**) (Table 3). 1,2-Disubstituted *trans*-methyl crotonate also proceeded well, affording a single stereoisomer **11d** as the major product.

Table 3. Reaction with Various Olefins[a]



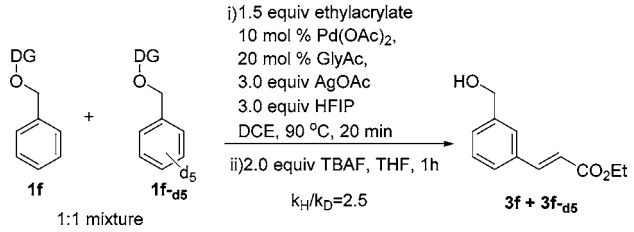
11a: 65% m:others = 98:2 | **11b**: 67%[b] m:others = 90:10 | **11c**: 53%[b] m:others = 93:7 | **11d**: 65% m:others = 97:3

[a]Reaction conditions: 0.1 mmol substrate, 1.5 equiv olefin, 10 mol % $Pd(OAc)_2$, 20 mol % AcGly-OH, 3.0 equiv AgOAc, 5.0 equiv HFIP in 1.0 mL DCE, 90 °C, 24 h. Isomeric ratio was determined by ^{1}H NMR. [b]10.0 equiv HFIP was used.

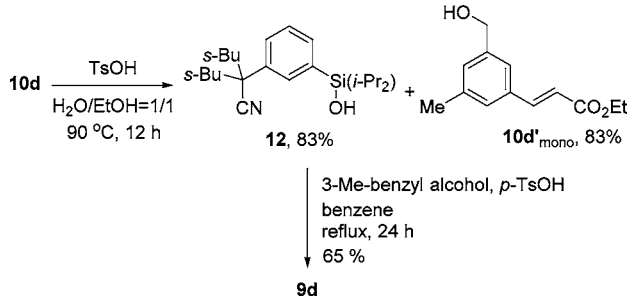
To probe the mechanism of the reaction an intermolecular competition experiment was performed. A kinetic isotope effect of 2.5 was estimated by NMR spectroscopic analysis after cleavage of the silicon-directing group (Scheme 3). This value suggests C–H bond activation is the rate-determining step, and 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 an 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 *p*-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.

Scheme 3. Kinetic Isotope Effect



Scheme 4. Template Regeneration



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.

■ ASSOCIATED CONTENT

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.

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Notes

The authors declare no competing financial interest.

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