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Sequential *meta*-C–H Olefination of Synthetically Versatile Benzyl Silanes: Effective Synthesis of *meta*-Olefinated Toluene, Benzaldehyde and Benzyl Alcohol†

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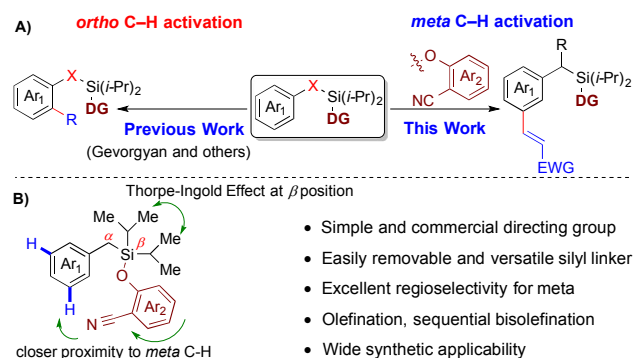
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Tremendous progress has been made towards *ortho*-selective C–H functionalization in the last three decades. Activation of distal C–H bonds and their functionalization remained fairly underdeveloped. Herein we report sequential *meta*-C–H functionalization by performing selective mono-olefination and bis-olefination with late stage modification of C–Si as well as Si–O bond. Temporary silyl connection was found to be advantageous due to its easy installation, easy removal and wide synthetic diversification.

Transition metal catalyzed functionalization of unactivated C–H single bond heralds the onset of a new era for the synthesis of complex molecular scaffolds, which being organic substances, display an undeniable presence of multiple C–H bonds.¹ Recent advances in the field of regioselective conversion of C–H bonds have widened scopes beyond the boundaries of classical catalytic cross-coupling reactions involving organohalides and the corresponding organometallic coupling partners. Moreover, a wise and prudential control of positional selectivity for C–H activation in a molecule containing multiple C–H bonds offers yet another outstanding challenge owing to its wide synthetic applications. An effective use of electronic bias² and steric crowding³ for regioselectively functionalizing C–H bonds in a molecule suffers from its own limitations, for it prevents functionalization of a less reactive C–H bond.⁴ However, in an attempt to override such an intrinsic bias, different strategies have been undertaken, viz. σ -chelation-directed C–H activation has been used as a potent technique for achieving *ortho*-selectivity.^{5,6} Although *ortho*-selective C–H functionalization has been established in great depth in the last three decades, selective functionalization of C–H bonds located farther away from the coordinating functional group, remains a noteworthy challenge,^{7–10} especially when their locations do not permit cyclometallation subjected to geometric strain. Similarly enough, *meta*-selective

functionalization, till now achieved primarily for disubstituted arenes using steric and electronic control,^{11,12} has emerged as a prolific area of scientific interest. Over last few years, alternate template based approach^{13,14} for position selective *meta*-C–H activation has been reported.¹⁵ During our recent studies for template assisted *meta*-C–H activation of benzyl sulfonic acid¹⁴ we were intrigued by the possibility to introduce a linker, which can be easily attached, easily removable and versatile towards different synthetic transformations.¹⁶ In pursuit of this objective,¹⁶ herein we report selective mono olefination and sequential bis-olefination at remote *meta* positions of benzyl silane by using nitrile based template with post synthetic diversification of silyl connection (Scheme 1).



Scheme 1. (A) *Ortho* and *meta*-C–H olefination of benzyl silane, (B) Advantages of benzyl silyl ether

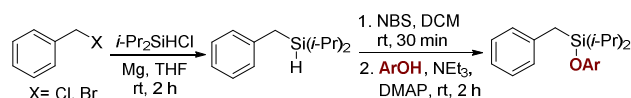
Initially this temporary silicon connection approach has been applied to restore superior regio- and stereoselectivity by switching intermolecular reactions to intramolecular reactions.¹⁷ Later, Gevorgyan group introduced this temporary silyl tethers for directed *ortho*-C–H activations followed by high degree of diversification of silyl moiety.^{18–20} We envisioned that employment of a silyl tethered directing group in place of sulfonyl linker might be beneficial for *meta*-C–H activation of an appended arene in two ways. Firstly, silyl

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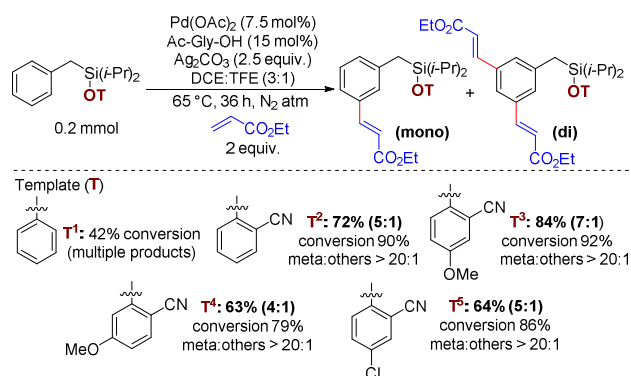
‡ T. P. and R. W. contributed equally.

tether can be removed easily.²¹ Secondly, silyl tether has advantage of wide applicability in different synthetic transformations.^{19,22,23} We hypothesized that use of a simple 2-hydroxybenzointrile ether of benzyl silanol may serve as an ideal choice for *meta*-C–H activation of benzyl scaffold through end on linear coordination of nitrile group (Schemes 1 and 2).



Scheme 2. Synthesis of directing template

To test the hypothesis, benzyl diisopropylsilyl ether of 2-hydroxybenzointrile was investigated with ethyl acrylate as a coupling partner. To our delight, desired *meta* olefinated product was observed in 72% yield with *meta* selectivity >20:1 (mono: di = 5:1).²⁴ Upon extensive optimization and careful control of electronic properties of cyanoarene derivatives, 2-hydroxy-5-methoxybenzointrile was found to be the best directing group producing 84% yield with *meta* selectivity >20:1 (Scheme 3, mono: di = 7:1).²⁴



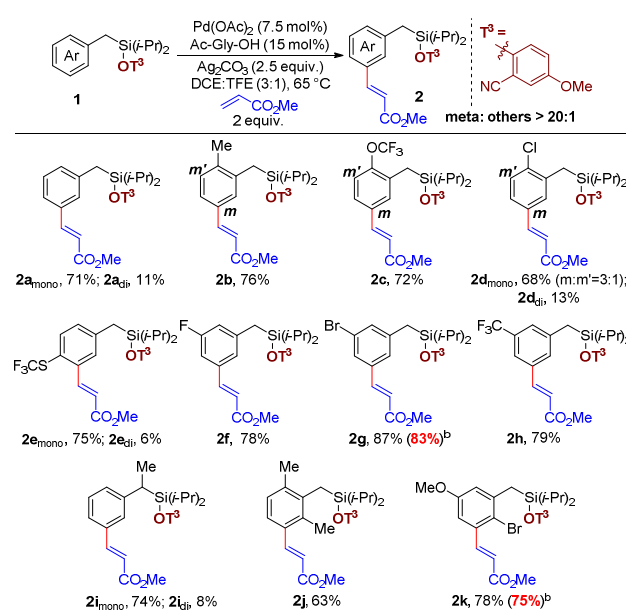
Scheme 3. Optimization of directing group

Initially, different benzyl derivatives were examined with methyl acrylate as the coupling partner in this optimized condition (Tables 1 and 2). The protocol was found to provide good to excellent yields irrespective of substituent position (*ortho*, *meta*, *para* or *alpha*). Diverse ranges of substitution like methyl, chloro, trifluoromethoxy, fluoro, bromo, trifluoromethyl, thiotrifluoromethyl, methoxy are well tolerated under the reaction condition (Table 1, entries 2a–2h). Interestingly, Heck coupling or protodehalogenation was not observed for halogenated arenes (entries 2d and 2g). Electronic (entries 2c–2e) as well as steric bias (entry 2j–2k) can be successfully overridden by this template-assisted approach.

Next, scope for olefin coupling partners was contemplated by varying wide range of electron deficient alkene. Vinylsulphonates (Table 2, entries 3a and 3c) and alkyl vinyl ketone (entry 3f) readily reacted to give the desired products. Acrylamide (entry 3d) and vinylphosphonate (entry 3e) provided good yields with in situ removal of template. Different 1,2-disubstituted acrylates can be employed successfully to give thermodynamically favorable *trans* isomer (Table 2, entries 3g and 3h). Notably, cyclic *tri*-substituted

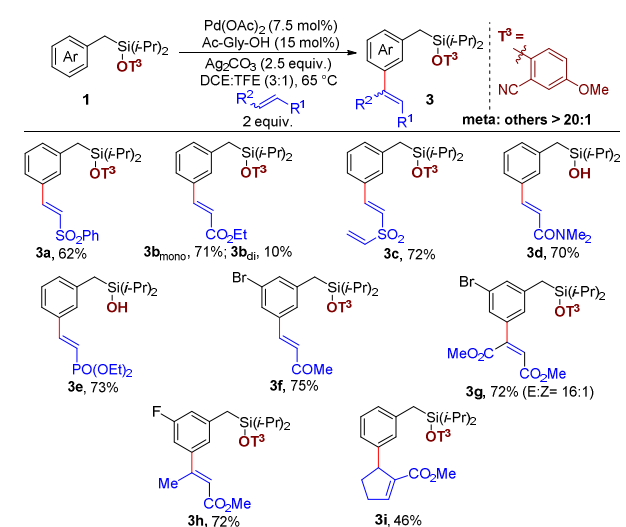
olefins provided moderate yields with expected allylic shift (entry 3i).²⁵ High regioselectivity for *meta* isomer (>20:1) was obtained in all of these cases irrespective of the position and nature of the substituents and olefins.

Table 1. Benzyl scope for *meta*-C–H olefination^{24,a}



^aAll reactions were carried out using 1 (0.2 mmol), methyl acrylate (0.4 mmol) in DCE/TFE (1.2/0.4 mL) for 24 h at 65 °C. ^b2 mmol scale.

Table 2. Olefin scope for *meta*-C–H olefination^{24,a}

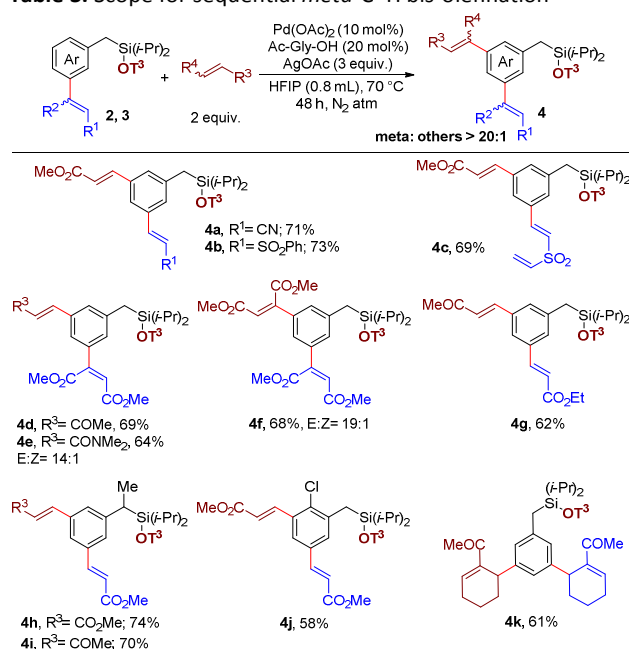


^aAll reactions were carried out using 1 (0.2 mmol), olefin (0.4 mmol) in DCE/TFE (1.2/0.4 mL) for 24 h at 65 °C.

During optimization and exploration of substrate scope for *meta*-mono olefination, we observed high reactivity of this catalytic system as in some cases diolefinated product was obtained in minor amount. Encouraged by such observations, an attempt was made for sequential bis-olefination,²⁶ since

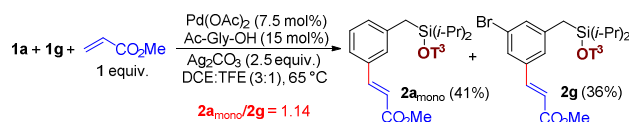
divinylbenzene derivatives are widely used as building blocks in materials research and synthetic chemistry.²⁷ Accordingly, mono-olefinated product was examined for further olefination at the remaining *meta* position (Table 3). We were pleased to find out that sequential bis-olefination indeed can be achieved in good yields under a modified reaction condition. Diverse set of olefins like acrylates (Table 3, entries **4a** and **4b**), α,β -unsaturated ketone (entries **4d**, **4i** and **4k**), acrylamide (entry **4e**), and disubstituted internal olefins (entry **4f**) were employed to provide moderate to good yields of bis-alkenylated products. Notably sterically demanding *ortho*-substituted chlorobenzyl silyl ether also furnished desired product (entry **4i**). Even bulky trisubstituted cyclic olefin can be incorporated sequentially at both the *meta* positions of benzyl silyl ether (entry **4k**).

Table 3. Scope for sequential *meta*-C–H bis-olefination^{24,a}



^aAll reactions were carried out using **2** or **3** (0.1 mmol), olefin (0.2 mmol) in HFIP (0.8 mL) for 48 h at 70 °C.

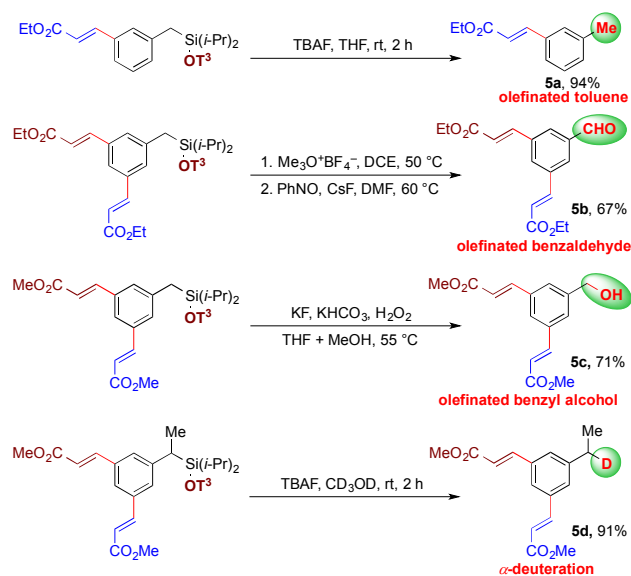
Next, to gain insight about the mode of action of this catalytic system, we performed intermolecular competition experiment between **1a** with two available *meta* positions and **1g** with only one site available for olefination. The product ratio clearly indicates that rate of reaction for both cases are similar (Scheme 4).



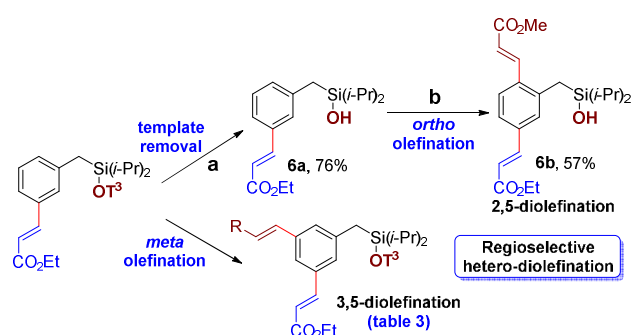
Scheme 4. Intermolecular competition experiment

This newly developed methodology with easily cleavable Si–O bond and a potentially modifiable C–Si bond could serve as a means to conduct a myriad of synthetic

diversifications.^{20,28} Importantly, silyl tether can be easily removed to provide olefinated toluene upon treatment of *n*-tetrabutyl ammonium fluoride (TBAF) in THF (Scheme 5, entry **5a**). *Meta* olefinated benzaldehyde can be achieved by modifying same benzylic C–Si bond using nitrosobenzene as oxidant (Scheme 5, entry **5b**). Alternatively Fleming–Tamao oxidation of this C–Si bond can deliver *meta* olefinated benzyl alcohol under mild condition (Scheme 5, entry **5c**).²⁹ Mono-deuterated toluene derivatives can be achieved selectively by simply changing the solvent from THF to methanol-d₄ at the time of silyl deprotection (Scheme 5, entry **5d**).



Scheme 5. Post-synthetic modifications of *meta*-C–H olefinated benzyl silyl ether.



Scheme 6. Sequential 2,5- and 3,5- hetero di-olefination of benzyl silane. [a] TsOH (10 mol%), EtOH/H₂O = 1/1, 90 °C, 12 h. [b] Pd(OAc)₂ (20 mol%), AgOAc (2 equiv.), KH₂PO₄ (2 equiv.), methyl acrylate (2 equiv.), CHCl₃, 100 °C, 16 h.

After *meta* olefination, cyanophenol template can be removed easily providing *meta* olefinated benzyl silanol **6a**. Subsequent *ortho* olefination²³ can be achieved on *meta*-olefinated benzyl silanol to give 2,5-diolefinated benzyl silanol (Scheme 6, entry **6b**). Notably, 3,5- hetero diolefinated benzyl silane has been synthesized successfully (Table 3). Therefore,

position selective 2,5- and 3,5-hetero diolefinated isomers can be achieved by applying required sequence judiciously.

In summary, selective and efficient *meta*-C–H olefination of benzyl silane derivatives has been achieved with simple and novel cyanophenol based directing scaffold. Sequential olefination techniques were also developed for synthesizing valuable 2,5- or 3,5-hetero divinylbenzene derivatives exclusively. *Meta*-olefinated toluene, benzaldehyde and benzyl alcohol were also prepared easily upon removal of silyl connection. Further synthetic applicability and detailed mechanistic investigations are currently underway.

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