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Authors: SUKDEV BAG, Ramasamy Jayarajan, Uttam Dutta, Rajdip Chowdhury, Rahul Mondal, and Debabrata Maiti

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Remote *meta*-C–H cyanation of arenes enabled by pyrimidine-based auxiliary

Sukdev Bag,[a] Ramasamy Jayarajan,[a][b] Uttam Dutta,[a] Rajdip Chowdhury,[a] Rahul Mondal,[a] and Debabrata Maiti*[a]

Abstract: An easily removable pyrimidine-based auxiliary has been employed for the remote *meta*-C–H cyanation of arenes. The scope of this Pd-catalyzed cyanation reaction using copper(I) cyanide as the cyanating agent has been demonstrated with benzylsilanes, benzylsulfonates, benzylphophonates, phenethylsulfonates and phenethyl ether derivatives. Present protocol was utilized for the synthesis of pharmaceutically valuable precursors.

A precise elimination of the electronic and steric bias in controlling the positional selectivity for chemical transformations has been successfully attained through a suitable employment of directing groups that affect functionalization in a highly regioselective fashion.[1] Recent time has seen an unexpected rise in the popularity of metal-catalyzed distal C–H bond functionalization.[2] In this regard, a judicious exhibition of *meta*- and *para*-selective C–H bond activation in aromatic arenes stand as worthy examples.[3] From the viewpoint of remote C–H functionalization; 1) judicious design of template, 2) choice of directing group (*i.e.*, weak *vs* strong coordination with metal), 3) proper selection of catalyst and coupling partners are recognized to be crucial factors. Importantly, the required effort would be high enough for those transformations where the reactions proceed through high energy macrocyclic pre-transition state and reductive elimination step.[3-5] Recently, the *meta*-C–H alkylation and alkenylation have been achieved with the aid of strong coordinating pyrimidine-based template.[5b] Although a handful of reports on distal C–H activation were prescient, extension of the strategy towards performing new functionalization has always continued to be an important goal.

Aromatic molecules containing nitrile groups are found to be integral constituents of dyes, agrochemicals, natural products, pharmaceuticals, and herbicides.[6, 7] Incorporation of a nitrile group by catalytic transformation suffers from its own limitations. One of the existing issues for cyanation reaction is the deactivation of the transition metal catalyst by formation of highly stable metal-cyano complex.[8] A defined concentration of dissolved cyanide ions can prevent the deactivation of transition metal catalyst.[9] Chelation-assisted C–H bond activation approach has emerged as a convenient and atom economical method by averting higher temperature and hazardous nitrile sources.[10] Regardless, appropriate selection of cyanide source is thought to be crucial for the directed C–H cyanation method.[11] Consequently, development of a methodology aimed to effectuate a selective incorporation of nitrile groups, not as part of the directing group anymore but now as the protagonist nucleophile, would be a worthy feat. Herein, we describe a highly selective *meta*-C–H cyanation reaction of arenes using copper(I) cyanide as the cyanating source.

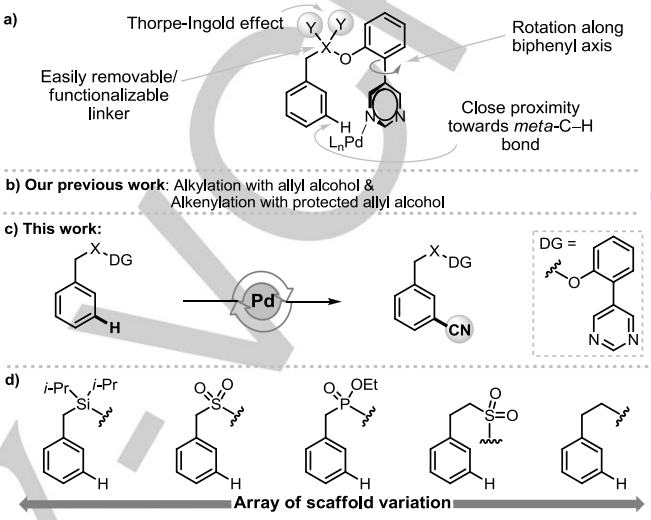
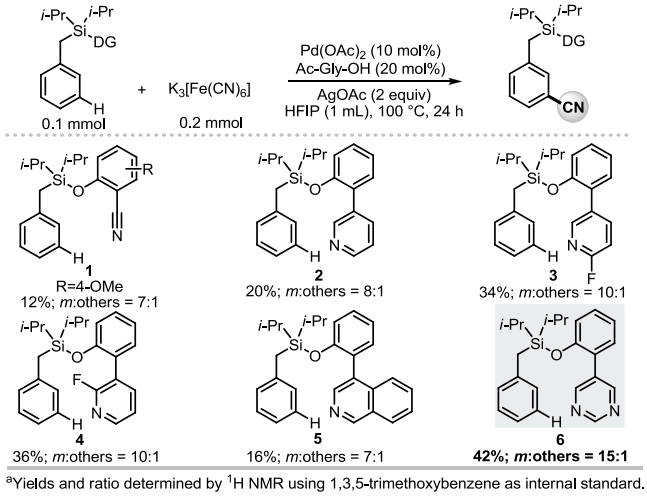


Figure 1. a) The key features of pyrimidine-based scaffold, b) Previous work with pyrimidine-DG, c) DG-assisted *meta*-C–H cyanation of arenes, d) Scaffold variation

As part of our foremost attempt, benzylsilane appended with 2-cyanophenol scaffold **1** was tested with potassium hexacyanoferrate(III) (Table 1).[12] Interestingly, the *meta*-cyanation product was obtained in 12% yield. However, weak coordinating ability, intolerance to harsh conditions, strenuous effort in proper placing and projection of nitrile group led us to explore alternative directing scaffold.

Table 1: Gradual evaluation of strong coordinating heterocycle-based DG[a]



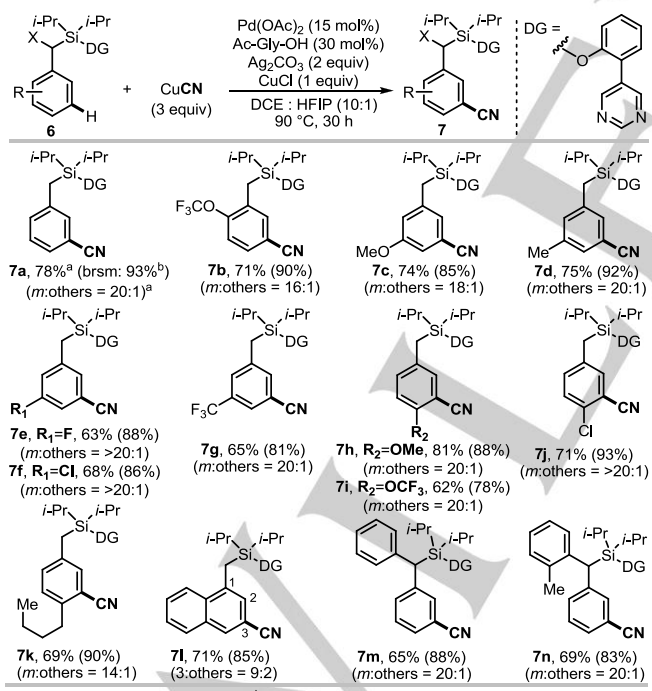
[a]Yields and ratio determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.

A substantial variation of the scaffolds showed that biphenyl pyridine-based template **2** predictively yields *meta*-cyanated product in comparatively good yield (Table 1). Notably, silyl bridged directing groups were effectively used owing to the easy installation/removal and modification features.[13] The two-geminal isopropyl groups in quaternary silyl center serve to bring the target *meta*-C–H bond towards the close proximity of metal

[a] S. Bag, Dr. R. Jayarajan, U. Dutta, R. Chowdhury, R. Mondal, Prof. Dr. D. Maiti
Department of Chemistry, Indian Institute of Technology Bombay
Powai, Mumbai-400 076 (India)
E-mail: dmaiti@chem.iitb.ac.in
[b] Dr. R. Jayarajan
Department of Biosciences and Bioengineering, IIT Bombay,
Mumbai-400 076 (India)

center (i.e., Thorpe–Ingold effect). Upon transmetalation of cyanide ion, palladium metal centre is expected to be more electron dense and therefore, the appropriate π-acidic ligand is required to stabilize the short-life intermediate.[4, 9] Accordingly, we have examined fluorinated pyridyl directing groups (as in **3** and **4**) and relatively improved yield than the parent pyridyl-based directing group was obtained. The lowering in yield and selectivity was observed when isoquinoline-based directing group (as in **5**) was employed. Interestingly, recently developed biphenyl pyrimidine-based directing group as in **6** provided most promising yield and *meta*-selectivity (42%; *m*:others = 15:1). Hydrogen-bonding interaction with pyrimidine and HFIP likely decreases the basicity of DG and synergistically increases π-acidity towards the palladium centre.[14]

In order to achieve the highest synthetic yield of *meta*-C–H cyanation product, we have first tested various cyanating reagents. We found that the usual organic cyanating reagents were completely inactive. Among various metal cyanides, copper(I) cyanide has remarkably increased the yield with exclusive *meta*-selectivity. As a bridging metal and oxidant silver carbonate along with copper(I) chloride ameliorate the yield significantly. The remarkable effect of solvent has also been observed when equivalent amount of HFIP was added to DCE. This combination drastically improved the yield (see the SI). Partial solubility of CuCN in HFIP/DCE likely helps to release the cyanide ions slowly which prevent the deactivation of Pd(II)-catalyst and subsequently facilitate the reductive elimination.



Scheme 1. *Meta*-cyanation of benzylsilane scaffolds.[12]

With the optimized reaction conditions in hand, we have probed the effect of aromatic substitutions in benzylsilane scaffold. We were delighted to find that the present reaction protocol provides selective *mono*-cyanation product (Scheme 1). The electron-rich (**7c**, **7d**, and **7h**), electron-poor (**7e**, **7f**, **7g**, and **7j**) and sterically-encumbered *para*-substituted subsrate such as 4-Bu (**7k**) were well tolerated. Selective mono-cyanation products have been detected in case of α,α-diphenyl scaffolds (**7m** and **7n**).

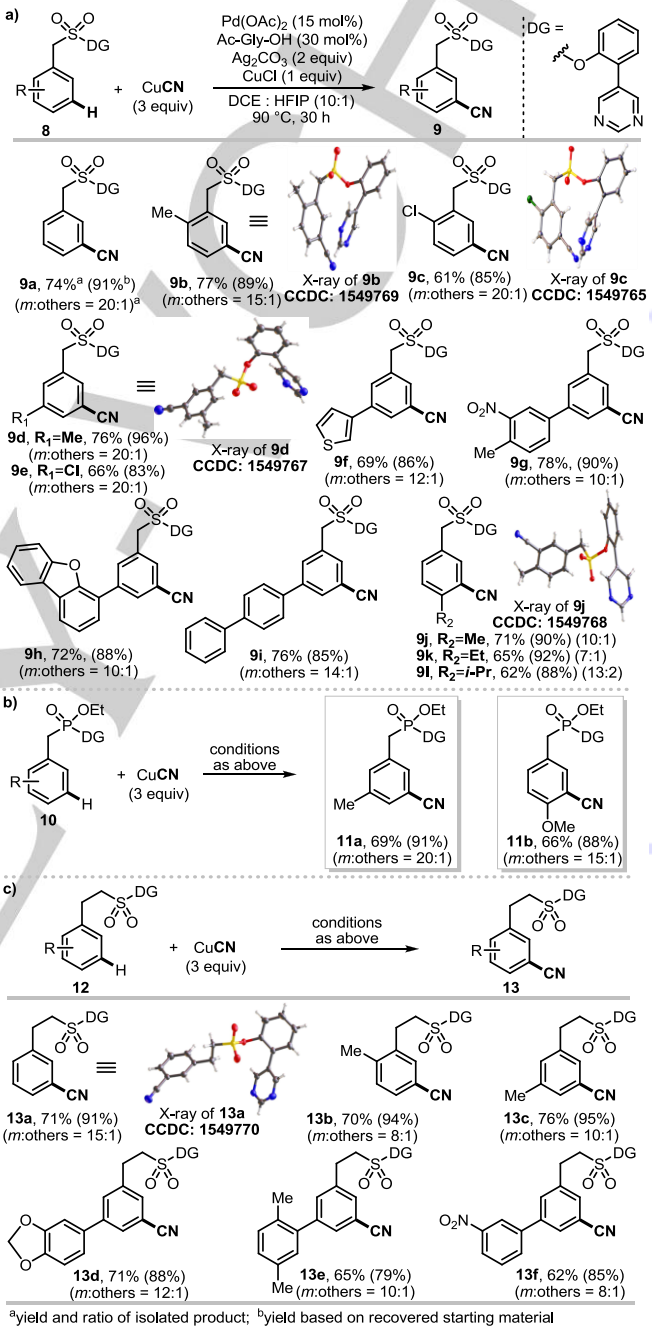
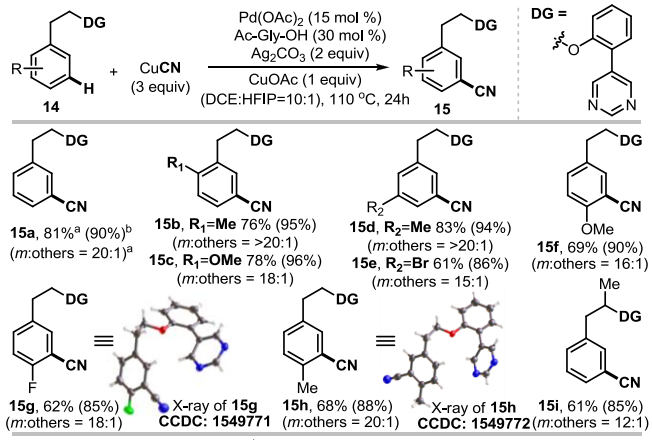


Figure 2. a) Scope with phenylmethanesulfonyl esters. b) *Meta*-cyanation of benzylphosphonates. c) Scope with phenethylsulfonyl esters.[12]

After successful implementation of cyanation in benzylsilane scaffolds, we have examined benzylsulfonyl ester motifs (Figure 2a). The compatibility of substituents on aromatic ring has been examined with electron donating (**9b** and **9d**), electron withdrawing (**9c** and **9e**) and sterically encumbered *para*-substituted benzylsulfonates (**9j**-**9l**). Interestingly, selective

meta-cyanation of 3-substituted (aryl/heteroaryl)-benzylsulfonyl derivatives has been achieved successfully (**9f**-**9i**). *Meta*-C–H cyanation has also been documented in benzylphosphonate derivatives (Figure 2b).



[a]yield and ratio of isolated product; [b]yield based on recovered starting material

Scheme 2. Scope with phenethyl ether derivatives.[12]

The scope of the reaction has been further investigated with the elongated backbone such as phenethylsulfonyl esters, which afforded the desired *meta*-cyano product in good yields (Figure 2c). To strengthen the backbone, we have also introduced simple ether linked phenethyl derivatives. The later provided synthetically useful yields under slightly modified conditions (Scheme 2).[12]

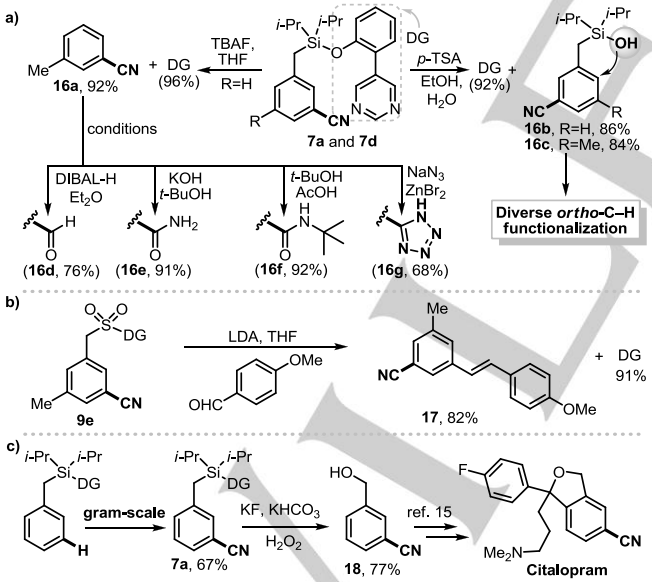


Figure 3. a) Post synthetic application of benzylsilane and conversion of cyano to useful functional groups. b) Removal of DG by Julia-type olefination. c) Synthetic route to citalopram.

Benzylsilane moiety is easily cleaved by fluoride source and produces *meta*-cyano toluene derivatives. The broad utility of nitrile group has been delineated by converting benzonitrile to corresponding benzaldehyde, benzamide, and tetrazole derivatives (Figure 3a).[10b] The benzylsulfonyl scaffold has been converted to the corresponding stilbene derivative resulting from reaction of 4-methoxy benzaldehyde by modified Julia-type olefination (Figure 3b). Direct *meta*-C–H cyanation of toluene derivatives and modifiable silyl linkage can lead to the preparation of antidepressant drug citalopram (Figure 3c).[15]

We have performed the systematic NMR studies by varying the amount of HFIP in presence of substrate **8d** in $CDCl_3$. The NMR studies revealed the hydrogen bonding between pyrimidine-DG (**8d**) and HFIP (see the SI).[12] To gain insight into the reaction mechanism, we carried out kinetic isotope effect (KIE) experiment (Figure 4a).[16] The average of three parallel experiments with **8a** and **8a-*d*$_5$** (k_H/k_D) provided 1.24 and intermolecular competition experiment, P_H/P_D is found to be 1.15 The ESI-MS studies of reaction mixture in absence of cyanide source suggested formation of macrocyclic palladacycle intermediate (see the SI).[12] Detailed mechanistic investigations and *in-silico* studies are underway in our laboratory.

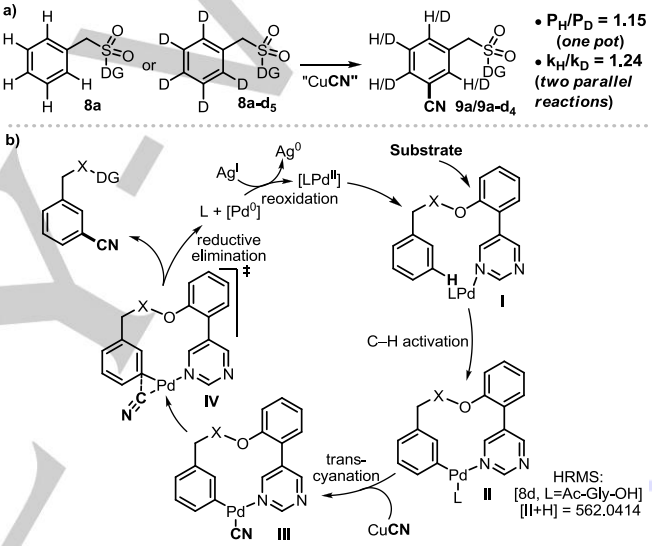


Figure 4. a) The experiment of primary kinetic isotope effect. b) Plausible mechanistic cycle

Probable catalytic cycle has been outlined in Figure 4b. The pyrimidine DG coordinates with mono-protected amino acid (MPAA)-ligated palladium catalyst (intermediate **I**) and the close proximity activates the *meta*-C–H bond (most probably *via* concerted metallation-deprotonation) to afford the macrocyclic transition state **II**. The ligand exchange of CN^- between copper(I) cyanide and cyclopalladated intermediate forms **III**. The reductive elimination from **III** *via* a complex transition state **IV** is presumed to provide the desired cyanation product.[4]

In summary, we have demonstrated a Pd(II)-catalyzed directing group assisted *meta*-C–H cyanation of arenes.[17] The directing group approach and the use of stoichiometric amount of copper(I) cyanide has greatly facilitated the access to selective formation of *meta*-cyano products, which are key building blocks for synthesis of complex natural products and drug molecules. A broad substrate scope presented by variation of synthetically useful linkers such as silyl, sulfonyl, phosphonates, ethers and electronically/sterically unbiased substituents has made the strategy attractive.

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Keywords: pyrimidine • *meta*-C–H activation • cyanation • copper(I) cyanide • palladium

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[12] See the Supporting Information for a detailed description.

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[17] A provisional patent application has been filed based on this work.

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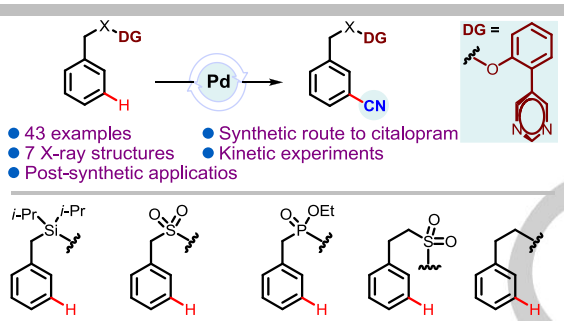
Table of Contents

COMMUNICATION

Pyrimidine-based directing group has been employed for *meta*-C–H cyanation of arenes using copper(I) cyanide as cyanating reagent. The broad substrate scope has been presented by varying different linkers such as silyl, sulfonyl, phosphonate, ether.



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