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Combined Cyanoborylation, C—H Activation Strategy for Styrene Functionalization

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Abstract

A one-pot multicomponent, copper-catalyzed protocol for borylation/ortho-cyanation of styrene derivatives, followed by a Suzuki-Miyaura coupling, provides a platform to explore the factors that control selectivity between distal or proximal functionalization of arenes. Development of divergent nitrile-directed C—H functionalization (acetoxylation, pivalation and methoxylation) offers an effective approach to rapidly increasing synthetic complexity. Finally, development of a mild reductive decyanation allows a traceless method for accessing functionalized biaryl motifs.

Graphical Abstract

The ubiquity of simple alkenes and unactivated C—H bonds in common feedstocks and early-stage synthetic intermediates makes their regio- and site-selective derivatization an appealing strategy for a wide array of applications.^{1,2} As a result, efficient catalytic methods for alkene additions and C—H activation processes have transformed strategies in synthetic and medicinal chemistry. Starting from simple alkenes, a vast array of methods enable regioselective 1,2-additions to provide functionalized products.³ In some instances, transient alkyl metal intermediates generated in the processes undergo cascade sequences to enable

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Supporting Information

Experimental procedures, compound characterization, optimization tables, and copies of spectra are included (PDF). The Supporting Information is available free of charge on the ACS Publications website.

more highly functionalized products to be obtained. As an example, the previously developed cascade copper-catalyzed cyanoborylation of styrenes provides a net transformation that allows terminal borylation of the alkene and cyanation of the ortho position on the aromatic ring (Figure 1a).⁴⁻⁶ The newly installed BPin group can then serve as a handle for the installation of new aromatic functionality through Suzuki cross couplings, leading to arylation of the alkene terminal carbon in the process.

The nitrile functionality itself has proven to be a versatile directing group in C—H activation methods. For example, the linear characteristic of nitriles as ligands for transition metals has been widely utilized in directing group strategies for site-selective activation of aromatic C—H bonds. These approaches enable the *meta*- or *para*-selective functionalization of aromatic rings as well as site-selective derivatization of ring systems further removed from the nitrile directing group (Figure 1b).⁷⁻¹⁷ While this widely employed approach proceeds through end-on σ -coordination to the nitrogen of the nitrile group, side-on π -coordination has also been developed as a strategy for directed C—H functionalizations (Figure 1b).¹⁸⁻²⁰ While σ -coordination typically leads to remote functionalization, the π -coordination strategy typically leads to *ortho*-functionalization immediately proximal to the directing nitrile functional group. In this study, we describe the combination of the above methods, namely the cascade cyanoborylation of simple styrenes followed by the distal or proximal nitrile-directed functionalization of C—H bonds to allow the conversion of simple styrene building blocks into an array of functionalized intermediates (Figure 1c).

The detailed scope of the copper-catalyzed cyanoborylation of styrenes and related vinyl arenes was recently described through work independently developed by Buchwald⁴ and our lab,⁶ with mechanistic details elucidated through computational work from Liu.⁵ In order to explore the opportunity for cyano-directed C—H functionalizations, a small set of 1,2-diarylethanes were assembled, either through Suzuki couplings of the cyanoborylation products, or by using independent synthesis of simpler derivatives through traditional olefination/hydrogenation sequences, or other standard organic transformations. The model systems **3a-c**, derived from vinylarenes, can be accessed in two steps in good overall yield (Figure 2). Copper-catalyzed cyanoborylation followed by a C(sp²)-C(sp³) Suzuki cross coupling of an aryl bromide allows a variety of substituted benzonitriles to be accessed, as illustrated by the conversion of styrene, 4-methylstyrene, and 2-vinylnaphthylene to products **3a**, **3b**, and **3c**.⁶ This model scaffold not only represents substructures of natural products, and pharmaceuticals currently on the market,²¹ but the nitrile functionality is present in a number of these motifs, as it can render unique biological characteristics.²²⁻²⁶

With an efficient modular synthetic method in hand for the synthesis of substituted cyanobenzenes with an appended phenethyl group, we hypothesized that this template would be an ideal system for examining the directing capabilities of the nitrile group in late-stage functionalization across different arenes in a molecule. Selectively employing multiple transformations via a single, innate, directing group, especially one that is an inherently versatile handle in organic chemistry, is a highly attractive strategy for complex synthesis. Drawing inspiration from mono-protected amino acid (MPAA) promoted C—H functionalizations developed by Yu,^{7,11,27} selective C—H oxidation was observed at the

meta position on the distal arene, (**4**), when using Pd(OAc)₂, Ac-Gly-OH, PhI(OAc), and Ac₂O in HFIP at 90 °C for 18 hours (Table 1, entry 1).

Moving forward with optimization, we found that increasing catalyst and oxidant loading boosted yields significantly, leading to 78% of the *meta*-functionalized product (Table 1, entry 3). Although the yield of this transformation was synthetically useful, challenges associated with the separation of regioisomers prompted us to examine a variety of additives to increase selectivity for the distal *meta*-acetoxylation (Table 1). Silver salts were examined due to their ability to form hetero-bimetallic species that are poised for C—H functionalization.^{28,29} Previous studies have demonstrated that Lewis acids may lower the ring strain and energy barrier for formation of the necessary nitrile-coordinated macrocyclic transition state. Although selectivity benefited from the inclusion of silver acetate (AgOAc), the resulting yields were compromised (Table 1, entry 4). Lowering the loadings of AgOAc to 1.0 equiv restored the chemical yields and maintained selectivity, but lower loadings of AgOAc were less effective (Table 1, entries 6-7). Ultimately, silver trifluoroacetate (AgTFA) proved beneficial to the reaction and could be used in substoichiometric amounts to give good yield (77%) and high selectivity (15:2:1, *m:p:o*) (Table 1, entry 8). Previous template directed chemistry reports utilize MPAA ligands.³⁰ We found that a MPAA ligand (Ac-Gly-OH), was necessary for our method as well, improving both the reactivity and selectivity of the transformation (Table 1, entry 2). This class of ligands has been shown to simultaneously stabilize the palladium species, as well as, potentially aid in the C—H abstraction.³⁰ Finally, control studies showed that not only is the position of the nitrile (*ortho*-to the linker) important to the selectivity of the reaction, but also that substrates lacking the nitrile provide unselective and slower oxidation (Scheme S1, SI). Assessment of the general reaction selectivity on this model substrate **3a** then allowed for further investigation of the synthetic utility of the *meta*-acetoxylation in the context of other bibenzyls.

With optimized conditions in hand, the transformation was applied to a variety of different biaryl ethanes (Scheme 1). Selective distal *meta*-C—H acetoxylation was observed for substrates bearing electron-withdrawing and electron-donating substituents on both the distal and proximal aromatic rings (products **4b-4g**). Furthermore, we were able to extend the length of the carbon chain between the arenes (product **4i**), and maintain good yield and *meta*-selectivity. Several substrates with heteroatoms in the linker were also compatible in the reaction. Both an ether-type substrate, **4j** and, an amide-containing substrate **4k** gave *ortho*-acetoxylation. While the selectivity change for **4j** is potentially altered due to from increased linker-rigidity, the *ortho*-selectivity in **4k** likely results from the directing effects associated with carbonyl oxygen moieties. Additionally, a protected amine could be used in this tether to give *meta*-acetoxylation, albeit in low yield (product **4l**). These substrates showcase the nitrile's unique capability in directing acetoxylation in a variety of systems. The ability to include heteroatoms in the linker, and to increase linker length expands this chemistry to a broad array of substrates. Interestingly, when the amide orientation was reversed in substrate **3m**, no product formation was observed. Finally, an unprotected amine (**4n**), and quinoline substrate (**4m**) resulted in only recovered starting material, likely due to competitive catalyst binding to the basic nitrogen functionality.

Intrigued by the unique selectivity of the transformations, we hoped to expand this method to other distal C—H oxidative functionalization. Gratifyingly, by changing the identity of the hypervalent iodine reagent and switching to pivalic anhydride, we were able to achieve selective distal *meta*-C—H pivalation in 70% yield (**5**) (Scheme 2). This selective oxidation of the distal ring not only emphasizes the unique directing features of the nitrile group, but expands the scope of this reaction to include handles for further functionalization. To verify the source of the acetate (or pivalate) group, a competition experiment was carried out using $\text{PhI}(\text{OPiv})_2$ with Ac_2O and $\text{PhI}(\text{OAc})$ with Piv_2O . It was found that the anhydride employed in the reaction conditions determined the identity of the oxidation, irrespective of the oxidant used (Scheme S2, SI). This suggests that the hypervalent iodine may be undergoing a ligand-exchange event with the anhydride prior to oxidation of the palladium. Organic polyvalent iodine compounds are known to undergo and are often synthesized by ligand exchange processes.^{31,32}

With the procedures in hand for distal functionalization, we then examined an orthogonal method to direct proximal C—H acetoxylation through π -coordination of the nitrile.¹⁹ Examining various solvent/oxidant combinations illustrated that hydroxyl(tosyloxy)iodobenzene (HTIB) was effective in proximal oxidations. While additives and ligands played a beneficial role in the distal acetoxylation chemistry, these variations did not improve yields for this reaction. The use of hexafluoroisopropanol (HFIP) as cosolvent at room temperature provided *ortho*-methoxylation product **6** in 73% isolated yield (Scheme 2, optimization Table S2 in SI). Therefore, in using a common nitrile-containing starting material, regioselective oxygenation of C—H bonds proximal or distal to the nitrile could be observed by varying the oxidant and nucleophile.

While in some instances retaining the nitrile functionality is desired, reductive removal of the directing group allows for a greater range of synthetic applications. Additionally, nitriles serve as important precursors for amides, esters, amines, and ketones through a range of methods,¹⁹ and an array of catalytic methods including reductive decyanation,^{33,34} borylation,³⁵ silylation,³⁶ and cross-coupling at the *ipso*-carbon may be employed for product diversification.

Methods for reductive decyanation typically require forcing conditions, extended π -systems, precious metals, and stoichiometric quantities of strong Lewis acids, which are often highly pyrophoric and limit the functional group tolerance of these methods.³⁷⁻³⁹ Achieving a mild reductive decyanation would therefore improve the versatility of the oxidation protocols described above.

Motivated by our lab's previous experiences regarding reductive deoxygenation of silyloxyarenes⁴⁰, and other methods to functionalize inert electrophiles, we hypothesized that nickel-*N*-heterocyclic carbenes (Ni-NHCs) could be employed to conduct reductive decyanation. While current literature examples offer access to various decyanated substrates, via nickel-catalysis and other methods, limitations persist.^{33,34} During optimization, we found that an electron-rich nickel catalyst, in conjunction with $\text{Ti}(\text{O}-i\text{-Pr})_4$ utilized as both the Lewis acid and reducing hydride source, provided moderate yields of product **7** (Table S3, SI) derived from decyanation and pivalate deprotection. Further optimization revealed

that by switching the ligand from an NHC to tricyclohexylphosphine and increasing the amount of base, improved yields of the decyanated product were observed (Figure 3a). Finally, to test if the protecting group, or resulting phenol is impeding catalysis, a biphenyl variant (**9** and **11**) of this transformation was subjected to the reaction conditions. Both the pivalated substrate and biphenyl substrate performed comparably (Figure 3b, Table S4 in SI). Therefore, we surmise that the reduced yield in the biaryl ethane cases is due to the lack of an extended π - system making the cyano group more challenging to activate. Analogous to the bibenzyl (**5**) system, while deprotection of the pivalate group is observed (product **10**), reductive removal of the pivalate did not occur.

To further explore the orthogonality of transformations available to the cyano and pivalate functionalities, a series of catalytic manipulations were explored on substrate **5** (Figure 4). When subjecting pivalate **5** to the optimized proximal C—H methoxylation conditions, a second oxygenation can be achieved to give further functionalized aromatics (**13**). Next, a second distal oxygenation at the open *meta*-position was possible when re-subjecting **5** to the C—H acetoxylation procedure (**14**). These examples showcase how the divergent directing group ability of nitriles can be leveraged to conduct sequential, highly regioselective oxidations of unactivated arenes at both proximal and distal sites. Finally, we are able to further diversify **5** using Chatani's C—O amination conditions (**15**),⁴¹ and then remove the nitrile, to leave the functionalized product free of the nitrile functionality (**16**). These products showcase the selective C—H oxidation by a removable directing group. Thus, starting with simple vinyl arenes, cascade cyanoborylation, followed by a newly developed nitrile-directed C—H activation strategy, rapid access to diverse aromatic motifs can be conducted in a sequential and selective fashion.

In summary, a versatile method for the conversion of styrenes to functionalized 1,2-diarylethanes has been developed through the combination of copper-catalyzed cyanoborylation/cross-coupling paired with nitrile-directed C—H functionalization. Through use of the σ -binding mode for aryl nitriles, distal, *meta*-selective C—H functionalization was achieved in a highly regioselective manner. Furthermore, leveraging π -donation of aryl nitriles for proximal C—H functionalization allows *ortho*-methoxylation on the proximal arene. Lastly, a decyanation method was developed to enable the traceless removal of this directing group. Employing this sequence involving copper-catalyzed cyanoborylation and nitrile-directed C—H oxidation provides a versatile strategy where cyano installation through a key bond-forming event provides a rapid and traceless method for enabling the unique capability of nitrile-directed remote and proximal C-H functionalization methods.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Methods for alkene functionalization and C—H activation: (a) copper-catalyzed cyanoborylations of styrenes paired with Suzuki cross coupling (b) nitrile-directed C—H activations through σ - and π -coordination. (c) This work, using a combination of the above strategies.

Figure 2. Representative synthetic strategy for access to 1,2-diarylethylene derivatives. ^afrom reference 6.

(a) Bibenzyl Decyanation **(b) Biphenyl Decyanation** **Figure 3.**

Development of a mild reductive decyanation. (a) Original optimized system for model substrate **5**. (b) Optimization of decyanation on a biphenyl system to probe the role of the pivalate deprotection in the transformation.

Figure 4.

Exploration of newly developed methods: Further diversification of pivalate product.

(Isolated Yields. ^aYield of *meta* product: 33% of *para* acetoxy also isolated as a 66% yield mixture of the two isomers overall).

Scheme 1. Substrate Scope for Distal C—H Acetoxylation.^a

^aAll reactions carried out at 0.2 mmol scale, unless otherwise noted. Methods for accessing the requisite starting materials **3a-o** are provided in the supporting information. Isolated yields reflect compounds obtained as the meta isomer, unless otherwise noted. Analysis of byproducts and regioisomers is provided in the supporting information. ^bYield determined by GC-FID ^c1.0 mmol scale reaction: Isolated yield as a mixture of acetoxylation products 2.0:1.0 ratio *meta*: minor regioisomer. ^dProduct isolated as a mixture of 2.0:1.0 *meta*: minor regioisomers. ^eIsolated with trace minor isomer. ^fIsolated as unprotected amine, see SI. ^gIsolated as a 2.3:1.0 *meta*: minor regioisomer.

Scheme 2. Nitrile-Directed Remote C—H Pivalation and Proximal Methoxylation.

^aObtained with 7.0: 1.0 *meta*:minor regioisomer. Isolated yields are provided.

Table 1.

Optimization of Nitrile-Directed C—H Acetoxylation

entry	Pd(OAc) ₂ (mol %)	additive (equiv)	yield <i>meta</i> (%)	ratio (<i>m</i> : <i>p</i> : <i>o</i>)
1	10	-	48 ^{a,b}	-
2	10	-	51	9:2:1
3	20	-	78	12:4:1
4	20	AgOAc (3.0)	29	20:1:4
5	20	AgOAc (2.0)	36	11:1:1
6	20	AgOAc (1.0)	70	10:1:1
7	20	AgOAc (0.2)	55	7:1:1
8	20	AgTFA (0.2)	77(74 ^c)	15:2:1

Yields and regioselectivity ratios determined by GCMS and GC-FID.

^a Reaction carried out with 2.0 equivalents of PhI(OAc)₂.

^b Reaction carried out without Ac-Gly-OH ligand.

^c 1.0 mmol scale reaction: Isolated yield as a mixture of acetoxylation products 2.0:1.0 ratio *meta*: minor regioisomer.