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Perspective

Achieving Site-Selectivity for C−H Activation Processes Based on Distance and Geometry: A Carpenter's Approach

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ABSTRACT: The ability to differentiate between highly similar C−H bonds in a given molecule remains a fundamental challenge in organic chemistry. In particular, the lack of sufficient steric and electronic differences between C−H bonds located distal to functional groups has prevented the development of site-selective catalysts with broad scope. An emerging approach to circumvent this obstacle is to utilize the *distance* between a target C−H bond and a coordinating functional group, along with the *geometry* of the cyclic transition state in directed C−H activation, as core molecular recognition parameters to differentiate between multiple C−H bonds. In this Perspective, we discuss the advent and recent advances of this concept. We cover a wide range of transition-metal-catalyzed, template-directed remote C−H activation reactions of alcohols, carboxylic acids, sulfonates, phosphonates, and amines. Additionally, we review eminent examples which take advantage of non-covalent interactions to achieve regiocontrol. Continued advancement of this distance- and geometry-based differentiation approach for regioselective remote C−H functionalization reactions may lead to the ultimate realization of molecular editing: the freedom to modify organic molecules at any site, in any order.

1. INTRODUCTION

1.1. Regioselectivity: An Enduring Challenge in Synthesis. Over the past 50 years, chemists have transformed the synthesis of molecules by developing a wide range of chemical tools to forge strategic bonds at will and ease. Despite these tremendous advances, achieving "selectivity" still remains a fundamental challenge that underscores chemical reactivity old and new. This challenge can be divided into three specific subcategories: (A) chemoselectivity, the selective transformation of one functional group in the presence of others; (B) site-/regioselectivity, the positionally selective transformation of identical functional groups; and (C) stereoselectivity, the differentiation of identical functional groups affixed to the same carbon atom. While chemoselectivity can be realized through masking reactive functional groups, or more elegantly, through judicious reagent choices, the problem escalates in complexity when faced with achieving regioselectivity (and even more so with stereoselectivity): *In a molecule containing several identical functional groups, how does one selectively transform a single functional group with high specificity, spatial precision and efficacy?* A solution toward achieving regioselectivity often entails the exploitation of inherent stereoelectronic differences between similar functionalities. A canonical example of this approach is the regioselective epoxidation of non-conjugated dienes with *m*CPBA. Here, the selective epoxidation of vinyl ethers is achieved as they are more electron-rich compared with simple olefins, which themselves are more reactive than olefins conjugated to electron-withdrawing groups (Figure 1A).[1]

In many cases, the stereoelectronic differences between reactive functional groups are negligible, rendering the previous approach untenable. In these instances, directing groups can be employed to bring the reactive component of the reagent within proximity of a single target functional group. In essence, directed reactions operate by lowering the entropic barriers for the reactivity of one functional group relative to another through substrate−reagent pre-assembly. This reduces the free energy of reactivity, and therefore favors the reaction for the proximate functionality. An elegant example of this approach is the Sharpless asymmetric epoxidation, which exhibits excellent regioselectivity (as well as stereoselectivity) for olefins bearing allylic alcohols over other olefins (Figure 1B).[2] In this reaction, the allylic alcohol directs the active titanium catalyst to the proximal olefin, enabling regioselective oxidation in the presence of a distal, yet electronically similar, olefin. This result sharply contrasts that of the corresponding epoxidation with *m*CPBA, which instead produces a mixture of oxidized products. Arguably, nature exemplifies the power of this directive approach, where a cumulative set of interactions between the functionalities present in the substrate and the active site imbues nature's enzymes with their exquisite selectivity.[3] Taking inspiration from nature, Miller et al. demonstrated that the tunable regio- and enantioselective mono-epoxidation of polyenes containing stereoelectronically similar olefins could be achieved using low-molecular-weight

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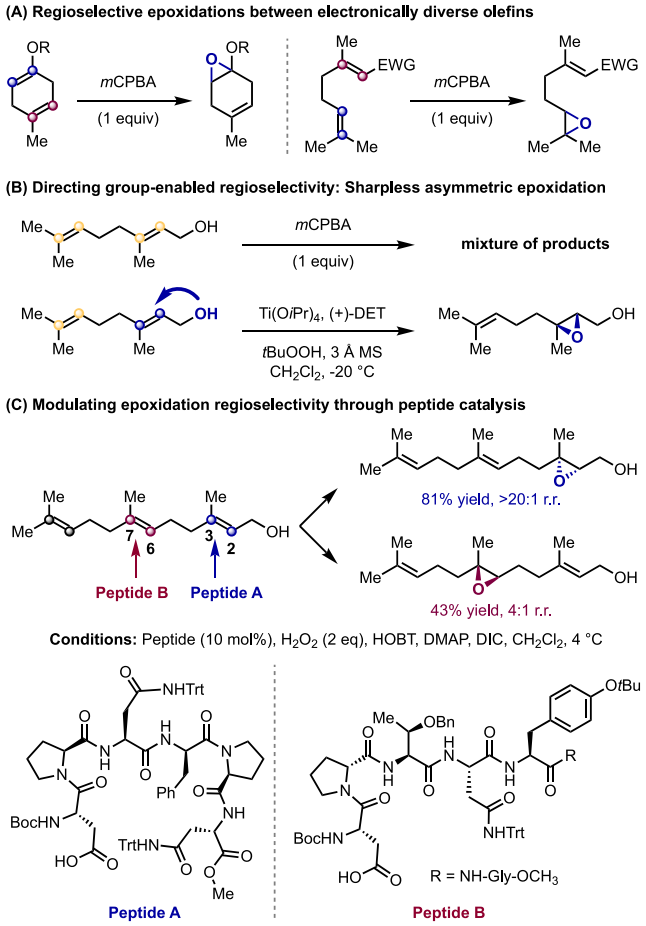

Figure 1. Classical approaches for achieving regioselectivity.

peptide catalysts (Figure 1C).[4a] Here, the differential choice of peptide catalyst allows for the corresponding differential regioselective, and in some cases enantioselective, epoxidation of the polyene substrate.[4b]

1.2. Central Challenges of Transition-Metal-Catalyzed Site-Selective C−H Functionalization Processes.

The use of native functionalities as directing groups has enabled the development of valuable variants of canonical transforms, allowing reactions such as regioselective hydrogenation,[5] carbometalation,[6] and various oxidation[7] and reduction[8] processes to become established in the chemical vernacular. Beyond the conventional modes of chemical reactivity, the directing group strategy has been particularly pivotal for the advancement of the relatively nascent field of transition metal-catalyzed C−H functionalization (i.e., the conversion of a C−H bond to a C−X bond).[9] As a synthetic strategy, C−H functionalization represents a potentially transformative paradigm given the ubiquity of the C−H bond in organic compounds, where skeletal complexity and/or functional group diversity can be rapidly and divergently generated from simple starting materials in a modular manner.[10−14] Owing to the ubiquity of the C−H bond, however, achieving regioselectivity for a C−H functionalization process represents a far more formidable challenge when compared with canonical synthetic transforms. In a typical chemoselective reaction, a reagent may only have to differentiate between a small number of similar functional groups (as exemplified in Figure 1) to achieve regioselectivity. In the case of C−H functionalization, each C−H bond in the molecule represents a functional group, which needs to be differentiated against another to allow for its precise functionalization. This notion underpins the first key challenge to be addressed in the field: *In a molecule with multiple C−H bonds that are of indistinguishable steric and electronic properties, how can one selectively transform a single C−H bond without targeting another?*

Moreover, functional groups distal to directing groups are inherently entropically disfavored from directive processes relative to proximate groups. This is rendered more problematic in the case of transition metal-catalyzed C−H functionalization reactions, where conventional directing groups enthalpically and entropically favor the activation of proximate C−H bonds to yield conformationally rigid five-, six-, and occasionally seven-membered cyclometalated intermediates. This property is particularly deleterious toward accessing distal C−H bonds, which obligatorily requires the transition metal−directing group complex to forge a larger macrocyclic pretransition state, leading to a cyclometalated intermediate that is disfavored both enthalpically, and entropically *vis-à-vis* its more proximal neighbor.[15] These attributes lead to the second key challenge in the field: *How can a C−H bond that is distal from a directing functionality be selectively transformed in the presence of proximate C−H bonds?* Finally, these already formidable challenges are further exacerbated by the often minute, and therefore insufficiently distinguishable, stereoelectronic differences between multiple C−H bonds distally positioned from a given functional group. Assuming that an energetically disfavored cyclometalated intermediate arising from distal C−H activation was indeed possible to access, a third key challenge still remains: *How can one distinguish between adjacent C−H bonds that are both remote to a given directing group, and only selectively functionalize one of the two?* Achieving chemical discrimination between the *ortho-*, *meta-*, and *para*-C−H bonds in an aromatic ring, or the *α-*, *β-*, and *γ*-C−H bonds in an aliphatic system, is a challenging endeavor analogous to visually differentiating between similar cultivars of apples from afar (Figure 2A).

These challenges were recognized by early practitioners in the field, who targeted the problem by taking inspiration from the directive elements present in enzymatic processes to enable the site-selective functionalization of remote C−H bonds. In a seminal work, Breslow et al. reported the first example of a remote methylene C−H functionalization process through directed radical C−H abstraction, followed by elimination and ozonolysis to achieve a net remote C−H oxidation, notionally directed by an acetophenone motif through a macrocyclic hydrogen atom transfer process (Figure 2B).[16] Subsequently, Crabtree et al. elegantly demonstrated the possibility of harnessing molecular recognition of substrate functionalities to achieve a manganese-catalyzed remote C−H oxidation of ibuprofen (Figure 2C).[17,18] In this work, the carboxylic acid on the substrate selectively binds to the carboxyl functionality on the ligand, orienting the manganese catalyst over the target C−H bond for oxidation. These pioneering examples, while elegant in design and exquisite in execution, were highly limited in their scope and applicability. Thus, for C−H functionalization to realize its potential as a transformative strategy in organic synthesis, a critical examination of the parameters that dictate regioselectivity was necessary to enable the development of site-selective functionalization of proximal and, in particular, remote C−H bonds.

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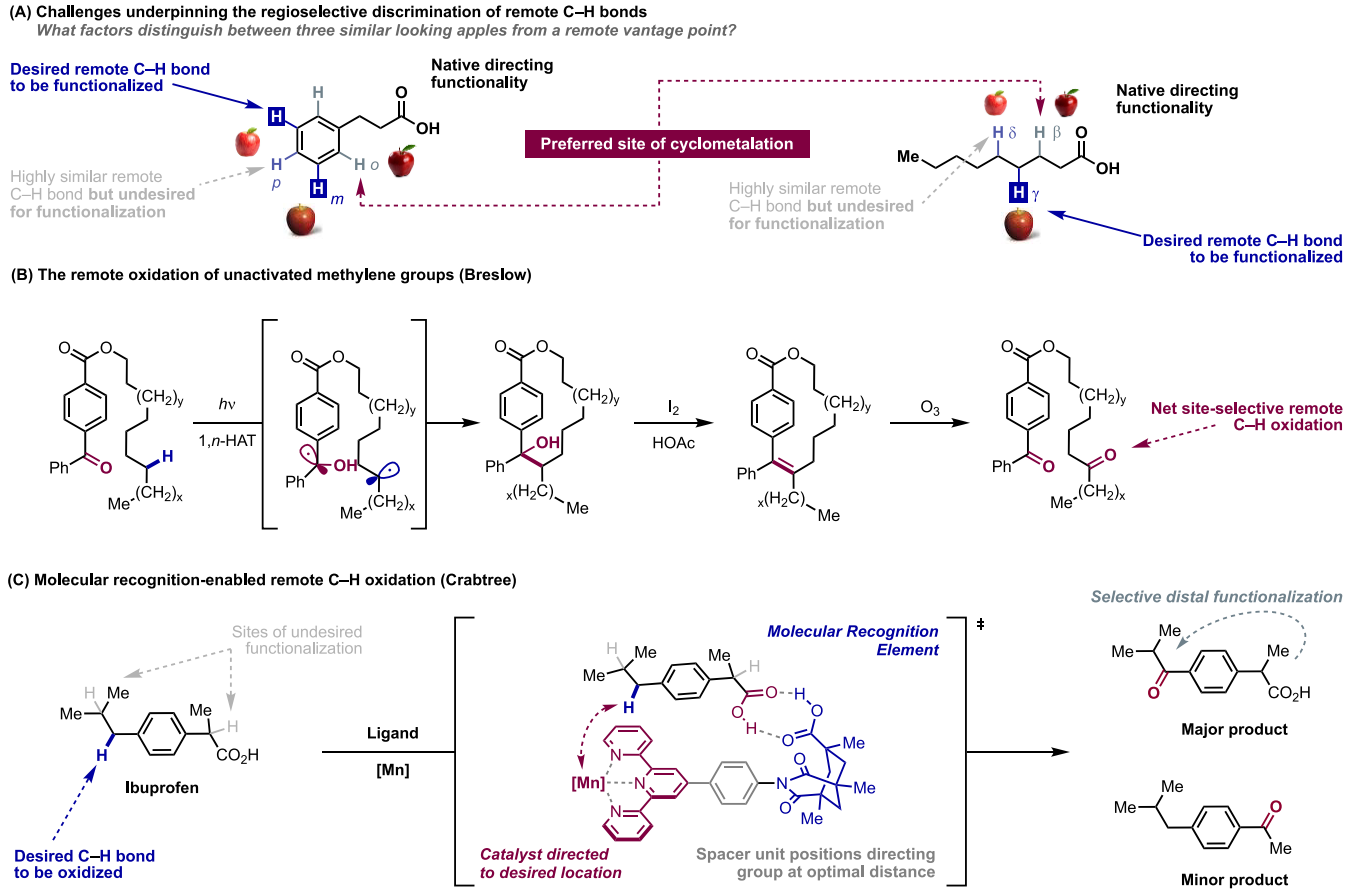

Figure 2. Central challenges in regioselective remote C−H activation, and early pioneering work in this field.

1.3. Interplay between "Distance" and "Geometry" as Crucial Parameters to Achieve Remote Site-Selectivity.

Our research group has had a long-standing interest in targeting the three aforementioned challenges underlying the field of C−H functionalization. To demonstrate that a site-selective remote C−H functionalization was indeed possible in the presence of proximal C−H bonds, our initial forays centered on realizing the selective *meta*-functionalization of hydrocinnamic acid through palladium catalysis. The judicious choice of substrate poses two distinct challenges: first, the inherent directivity imposed by the carboxyl group was posited to favor *ortho* activation; second, the absence of strongly electron-donating or -withdrawing substituents rendered *all* target C−H bonds electronically similar and unbiased. Thus, we needed to overcome the inherent substrate selectivity, while additionally proposing new design parameters to selectively target one of the many stereoelectronically alike C−H bonds distal to a directing functionality. To quantify the extent of the hurdle prohibiting the *meta*-C−H activation process relative to the more proximal *ortho* neighbor for hydrocinnamic acid, we investigated the relative energies of the respective cyclometalated intermediates via density functional theory as an indicator for the energy barrier needed to be overcome to facilitate such a transformation (Figure 2A).[19] Unsurprisingly, the eight-membered palladacycle arising from *meta*-C−H activation was disfavored relative to the corresponding seven-membered *ortho*-palladacycle by 32.1 kcal/mol (Figure 3).

The insurmountable energetic penalty for a direct *meta*-C−H activation of hydrocinnamic acid clearly indicates that the native substrate is not poised to direct a palladium catalyst to

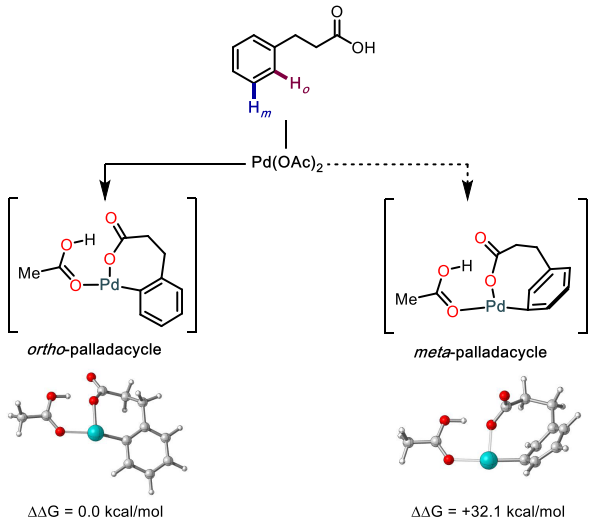

Figure 3. Free energy comparison between an *ortho*- and a *meta*-palladacycle arising from the cyclopalladation of hydrocinnamic acid.

the *meta* position without extrinsic aid. Recognizing that the two major factors disfavoring the formation of the *meta*-palladacycle were the macrocyclic strain imposed by the tight cyclophane-like structure, *i.e., the distance of the directing group to the target bond*, as well as the unfavorable spatial positioning of the directing group, *i.e., the geometry of the directing group relative to the target bond*, we turned toward incorporating and optimizing *distance* and *geometry* as our two key parameters for template design. This led to the incorporation of a molecular

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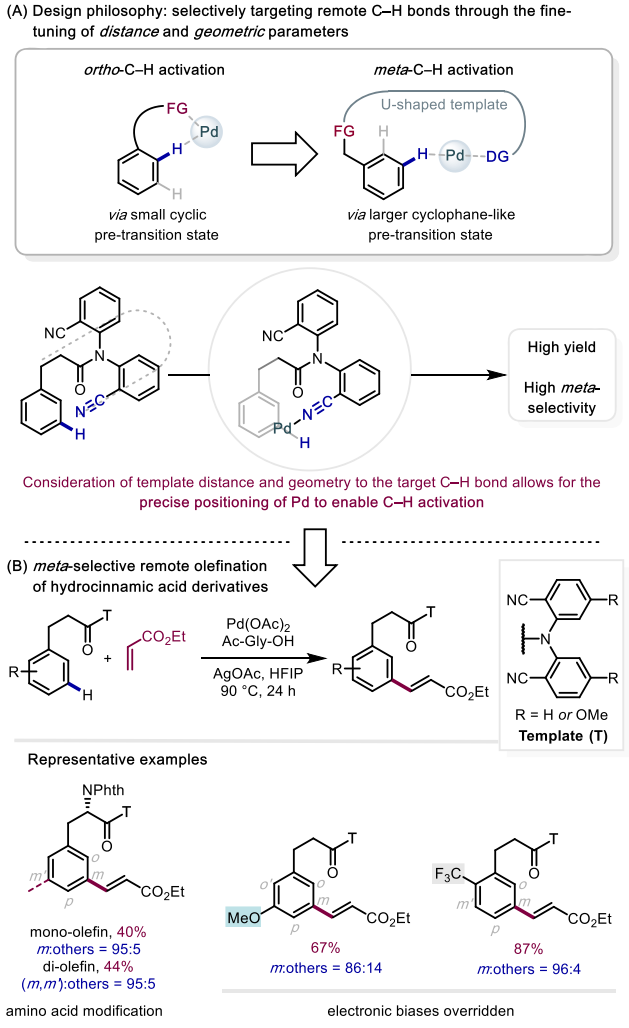
U-turn motif arising from an amide derivative of hydrocinnamic acid bearing a rigid, linear atomic arrangement, i.e., a nitrile functionality, as the directing group.[20]

We hypothesized that the careful combination of distance and geometric features would preferentially position the palladium catalyst proximal to the *meta* position. Due to the rigidity of the linear nitrile group, we speculated that deviations from the favored template conformation would impose increased strain. In particular, the rigid, linear nitrile functionality would severely disfavor the generation of a smaller palladacycle, and thus disfavoring the formation of a competing *ortho*-palladacycle (Scheme 1A). Additionally, the incorporation of a weakly coordinating nitrile functionality was thought to further allay any developing ring strain in the *meta*-palladacycle through the catalyst's facile dissociation from the directing group, in a "catch-and-release"-like manner. Through extensive design, our group successfully realized this strategy for the selective remote functionalization of *meta*-C−H bonds in arenes in 2012.[21] In this report, a wide range of hydrocinnamic acids bearing covalently attached, weakly coordinating nitrile templates were olefinated selectively at the *meta* position, and in certain instances the directing ability of the templates was able to *override* the electronic preference of other aryl substituents (Scheme 1B). Akin to a carpenter reliant on a tape measure and carpenter's square to make exact incisions, this finding demonstrates that the judicious incorporation of *distance* and *geometry* as key design parameters can allow for precise tuning of the resulting macrocyclic cyclophane (or macrocyclophane)-like pre-transition state, ultimately overriding the innate proximal directivity in metal-catalyzed C−H activation processes.

Scheme 1. Incorporating "Distance" and "Geometry" as Key Design Parameters Leads to the Highly Selective *Meta*-Olefination of Hydrocinnamic Acid



Since this report, the applicability of our approach has been demonstrated in a wide number of transition metal-catalyzed remote C−H activation processes across a diverse range of substrates. In this perspective, we focus on the development of remote *meta*-C−H activation reactions of arenes as our primary case study, particularly emphasizing the importance of tuning the distance and geometric relationship of the directing group relative to the target bond in order to favor the formation of the desired macrocyclophane-type pre-transition states. Additionally, we highlight recent advances which expand on these principles through novel substrate-catalyst interactions as a means for macrocyclophane assembly. These examples all serve to exhibit the power and generality of our approach as the guiding philosophy to precisely control site-selectivity in remote C−H bond functionalization processes. Finally, we briefly discuss preliminary and promising forays toward applying geometric considerations as the overarching design principle for the site-selective functionalization of C(sp^3)−H bonds. Overall, this Perspective serves to demonstrate the importance of carefully considering spatial and geometric factors in the design of directing functionalities to achieve one of the most challenging regioselective transformations in the chemical repertoire: the selective functionalization of remote C−H bonds.

2. TEMPLATE-ASSISTED *Meta*-C−H FUNCTIONALIZATION VIA C−H ACTIVATION FROM A VARIETY OF FUNCTIONAL HANDLES

The execution of the remote *meta*-C−H olefination of hydrocinnamic acid provides a compelling proof-of-concept that the inherent substrate-directed *ortho* cyclometalation process can be overturned for carboxylic acid derivatives. By itself, however, this is a niche transformation that needs broadening in scope for it to become a truly versatile strategy. In this section, an overview of recent developments for remote *meta*-C−H activation enabled by covalently attached templates will be presented. Particular attention will be drawn to how tuning distance and geometric parameters relative to the target bond leads to the fine-tuning of the macrocyclophane pre-transition state, allowing for the selective functionalization from a wide range of functional handles.

2.1. Template-Enabled Remote C−H Activation of Alcohols. Building on the aforementioned principles, we applied the corresponding design logic to effect the first remote *meta*-C−H functionalization of alcohol-containing substrates. To do so, we constructed a template for benzyl alcohols by incorporating a rigid U-turn motif with a weakly binding nitrile functionality, with the aim to position the directing functionality within close proximity to the *meta*-C−H bond. In this case, however, derivatives of the alcohol substrate suffered from increased conformational flexibility when compared with the more rigid carboxylic acid derivatives, resulting in a greater entropic penalty for the organization into the requisite macrocyclophane pre-transition state. To over-

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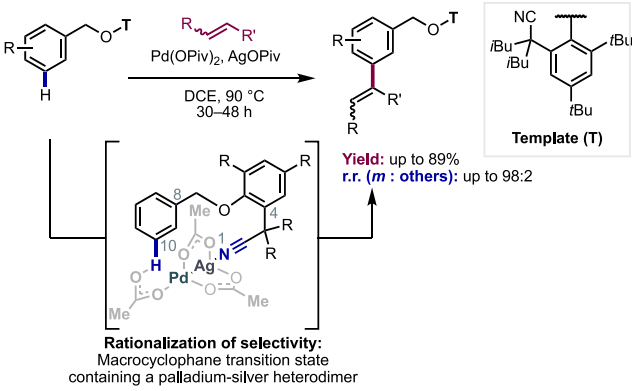
come this obstacle, the Thorpe-Ingold effect was leveraged through the incorporation of bulky *tert*-butyl groups, allowing for a highly efficient and selective *meta*-C−H olefination on a wide variety of arene substrates and olefin coupling partners (Scheme 2). It is worth noting that the di-*tert*-butyl

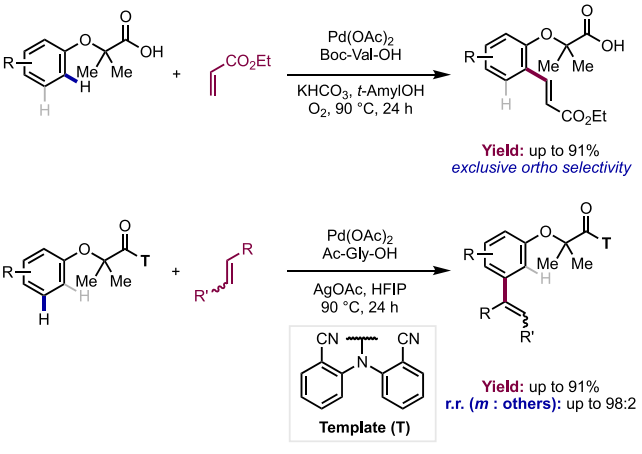
Scheme 2. Template-Mediated Remote *Meta*-C−H Olefination of Benzyl Alcohols



substitution was essential for activity; the replacement with dimethyl groups led to complete loss of activity. Further computational studies revealed the underlying mechanism for this reaction's excellent *meta*-selectivity, which was attributed to a palladium(II)−silver(I) heterodimeric pre-transition state complex. This study posits that the nitrile group coordinates to the silver, and coordination between silver and palladium positions the palladium catalyst adjacent to the *meta* position of the arene.[15]

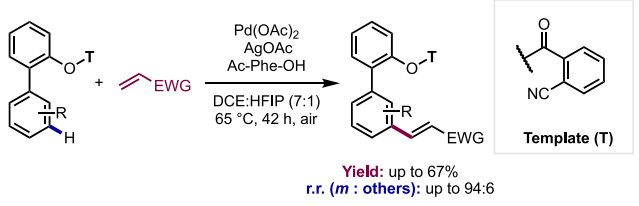
Up until this point, the substrates employed for such remote *meta*-C−H functionalization reactions were electronically unbiased. We then considered the possibility of leveraging this template to override the inherent directive *and* electronic preferences of the substrate. For this, we looked toward executing the *meta*-functionalization of phenol derivatives through applying an analogous U-shaped template (Scheme 3).[22] Because C−H activation tends to favor electronically rich positions of aromatic rings, the *meta* position of phenol derivatives represents a particularly challenging target. To

Scheme 3. Modulating Site-Selectivity through Template Attachment Demonstrated by the Tunable *Ortho*- or *Meta*-C−H Olefination of Phenolic Substrates



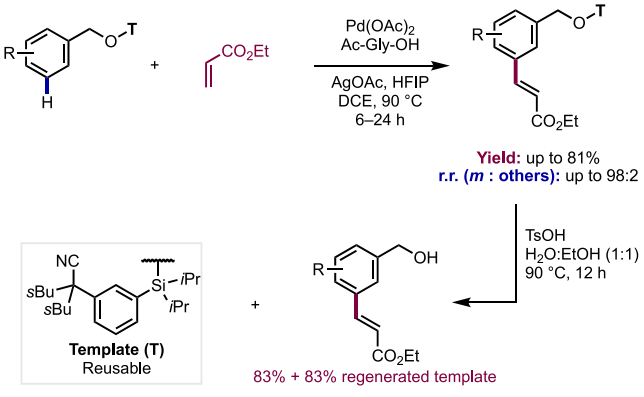
accommodate the shorter distance between the native functional group and the target bond in question, we increased the distance between the native functional group and the U-turn motif possessing the nitrile directing group. Gratifyingly, through the alkylation of phenol with a substituted carboxamide derivative, a highly selective *meta*-olefination was observed with a range of phenol derivatives. We also demonstrate the crucial importance of the nitrile template for *meta*-selectivity, with its hydrolysis to the corresponding carboxylic acid resulting in exclusive *ortho*-selectivity in the olefination reaction. These results demonstrate that innate reactivity patterns influenced by electronic effects can be overridden with an appropriately designed template guided by distance and geometry, and can allow chemists to build a modular portfolio of reactivity by simply employing the appropriate template. This design element has also been successfully applied by Maiti et al., where a *meta*-selective olefination of biaryl phenols has been realized through an ester-linked nitrile template (Scheme 4).[23]

Scheme 4. Template-Enabled *Meta*-C−H Olefination of Biaryl Phenols



In 2014, Tan et al. developed an innovative silicon-based nitrile template for the *meta*-selective C−H olefination of benzyl alcohols (Scheme 5),[24] where the template anchors

Scheme 5. Silyl Ether-Anchored Nitrile Template as Applied to the Remote *Meta*-Olefination of Benzyl Alcohols



onto the alcohol through a silyl ether linkage. In an analogous manner, a tertiary nitrile directing group was employed, presumably conferring conformational rigidity through the Thorpe−Ingold effect. Notably, the template's facile introduction, removal, and regeneration showcases its synthetic practicality. Following this work, the sequential *meta*-selective mono- and diolefination of benzyl silanes as surrogates for a wide range of functionalities was reported by Maiti et al. (Scheme 6).[25] As a versatile synthetic handle in its own right, Maiti et al. demonstrated a wide range of silane trans-

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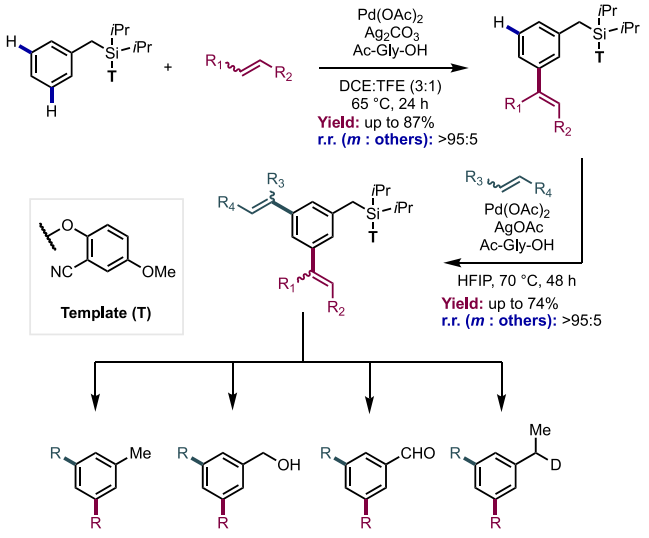
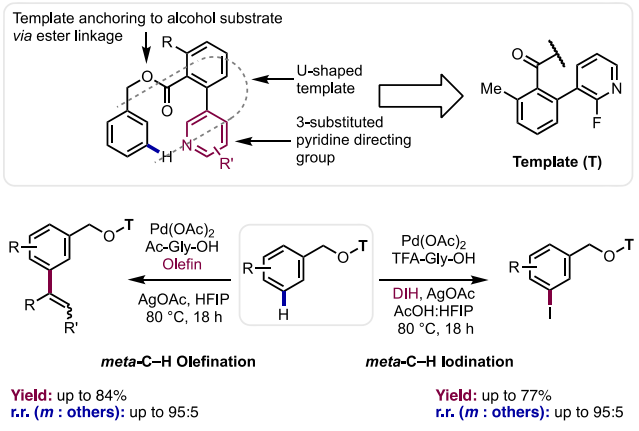
Scheme 6. Template-Directed Remote *Meta*-C−H Olefination of Benzyl Silanes



formations to afford *meta*-substituted derivatives of benzyl alcohol, benzaldehyde, and toluene products.

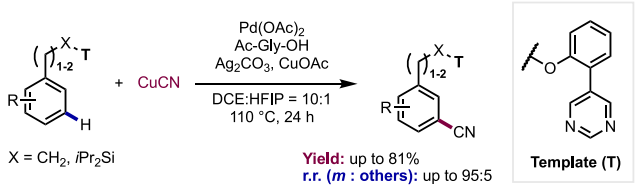
The U-shaped template design, nitrile-enabled weak coordination, as well as the crucial consideration of distance and geometric parameters has led to the broad discovery of novel remote, site-selective C−H olefination transformations. At the same time however, the weakly coordinating nitrile functionality also constrained our ability to realize a broader range of C−H functionalization transformations, particularly with substrates that can outcompete against the weak coordination of the nitrile functionality. Recognizing the paramount importance of the geometry brought upon by the linear nitrile motif, we wondered whether other more strongly coordinative motifs could be employed for catalyst coordination in an analogous geometric manner, leading to a more tightly associated macrocyclophane pre-transition state. This was investigated by using the pyridyl group as a strong σ-donor, leading to a novel reaction platform that enabled the selective *meta*-C−H olefination and, for the first time, *meta*-C−H iodination of benzyl and phenethyl alcohols (Scheme 7).[26] Subsequent to our disclosure, Maiti et al. reported a pyrimidine template for the *meta*-C−H cyanation of a variety of substrates,

Scheme 7. *Meta*-C−H Functionalizations Facilitated by a Pyridine-Containing Directing Group



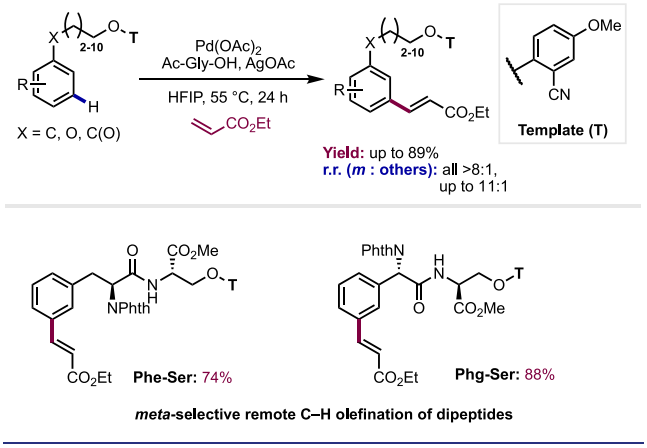
again harnessing the strong σ-coordinative ability of heteroaryl motifs to overcome the deleterious reagent−catalyst coordination (Scheme 8).[27]

Scheme 8. *Meta*-C−H Cyanation of Arenes Enabled by a Pyrimidine Template



So far, these examples have showcased the power and versatility of template-enabled remote *meta*-C−H transformations of alcohol substrates, enabled through the incorporation of distance and geometric parameters for template design. A long-standing challenge that remains is the remote modification of arenes where the template is positionally anchored *beyond* an ethyl linker. As alluded to previously, the success of our initial reports partially relied on reducing the entropic penalty required for macrocyclophane pre-organization; without rigidifying units, this problem ostensibly amplifies with the incremental addition of each rotatable bond. In 2017, Jin et al. reported a seemingly counterintuitive, but elegant, solution to this problem, achieving a selective *meta*-C−H olefination of arenes from distal alcohols tethered with a simple arylnitrile template (Scheme 9).[28] In this report, substrates bearing various linker

Scheme 9. Achieving Selectivity in a Range of Distally Directed *Meta*-C−H Olefination Reactions for Substrates Containing Flexible Alkyl Tethers



lengths all afforded the *meta*-functionalized product selectively, with the most extreme example involving a C_{10} linker, invoking a 19-membered macrocyclophane pre-transition state. Building on our proposed selectivity model involving a nitrile−silver−palladium heteromeric complex, computational studies rationalized the observed *meta* selectivity over *ortho* and *para* positions, which found that the silver−nitrile bond angle was determinant for selectivity with smaller linker lengths, with both *ortho* and *para* functionalization requiring deviations from the optimal linear geometry of the Ag(I) complexes. With longer linkers, the primary determining factor switches to minimizing torsion-induced steric interactions, with both *ortho*

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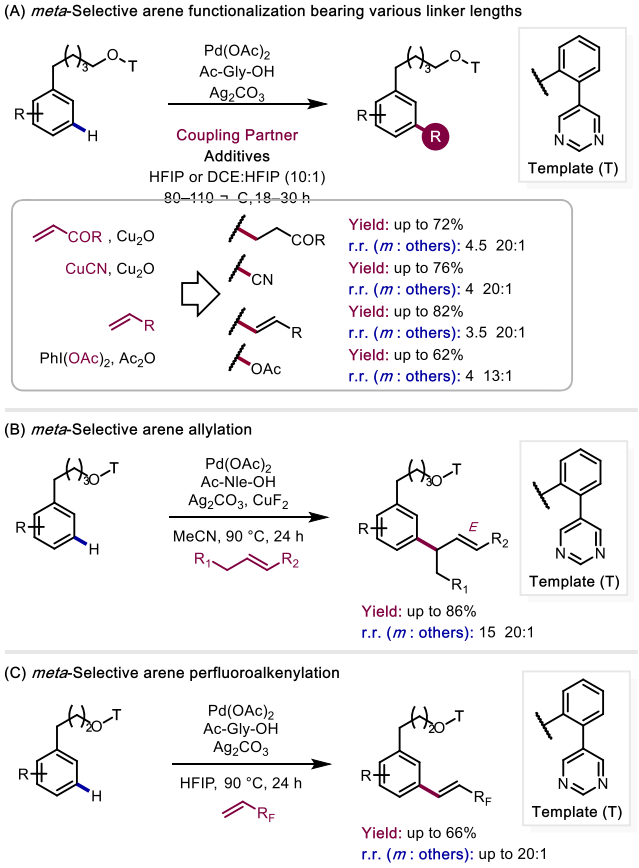
and *para* positions incurring more disfavored *gauche* interactions than the corresponding *meta* transition state. These subtle conformational factors represent an advancement on top of the established distance and geometric parameters that can be exploited in the design of effective site-selective arene functionalization reactions. Indeed, Jin et al. demonstrated the utility of this transformation through the *meta*-selective functionalization of phenylalanine−serine and phenylglycine−serine dipeptides, in both cases directed by template attachment at the serine hydroxyl residue.

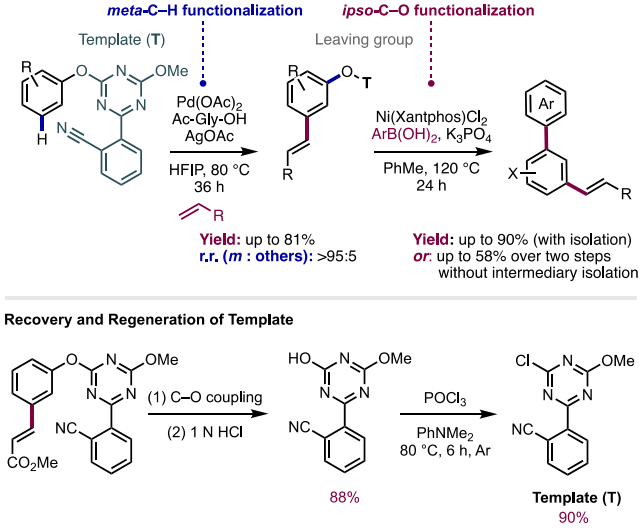
In the following year, Maiti et al. built on this finding, and reported the utilization of a pyrimidine-based template tethered to a remote alcohol to promote the *meta*-C−H activation of arenes containing long alkyl chains (Scheme 10A).[29] Diverse functionalization reactions including alkylation, cyanation, olefination, and acetoxylation were reported. Very recently, Maiti et al. further extended the applications of this pyrimidine template to the *meta*-C−H allylation of arenes utilizing unactivated acyclic internal olefins (Scheme 10B).[30] With the same template, Maiti et al. also developed the perfluoroalkenylation of arenes with pendant alcohols valuable for the construction of useful fluorine-containing motifs (Scheme 10C).[31]

Scheme 10. *Meta*-C−H Functionalization of Arenes across Different Linker Lengths, Enabled by a Pyrimidine Template



could selectively deliver a palladium catalyst to the *meta* position, and subsequently serve as a leaving group for nickel-catalyzed *ipso*-C−O arylation (Scheme 11).[32] This ambitious sequence was enabled through a triazine-benzonitrile template that was facile in its preparation, installation, removal, and recovery, which efficiently delivered the *meta*-olefinated product. Beyond this, we found that the subsequent *ipso*-C−O arylation could be carried out in tandem without intermediary purification. Cumulatively, the significant advances charted for the remote C−H activation of arenes reflects on the paramount role both distance and geometry (between the functional group in question and the target C−H bond) play in developing a selective and modular remote C−H functionalization process for arenes.

Scheme 11. Sequential Functionalization of *Meta*-C−H and *Ipso*-C−O Bonds for Phenolic Substrates



2.2. Template-Enabled Remote C−H Activation of Carboxylic Acids, Sulfonates, and Phosphonates. Aside from alcohols, carboxylic acids, sulfonates, and phosphonates represent ubiquitous structural motifs commonly present in medicinal agents. Additionally, the versatility of these functionalities renders them particularly valuable as functional precursors for the construction of complex molecules. These attributes make the direct derivatization of these compounds by selective C−H functionalization particularly attractive for their synthesis and modification. Noting that carboxylic acids, sulfonates, and phosphonates can generate equivalent linkages (e.g., esters and amides) with a suitable template functional handles, a general strategy could be conjectured that incorporates distance and geometric design parameters to enable a highly selective remote C−H functionalization. This section will outline the recent advances of template-directed remote *meta*-C−H bond functionalization of carboxylic acid, sulfonate, and phosphonate derivatives, paying particular attention to how distance and geometry have served as guiding factors for the design of effective and broadly applicable templates.

The favorable results obtained from the *meta*-selective olefination of hydrocinnamic acid substrates led to our later report, where we achieved the *meta*-C−H arylation and methylation of hydrocinnamic and benzoic acid substrates, utilizing organoborons as coupling partners (Scheme 12A).[33]

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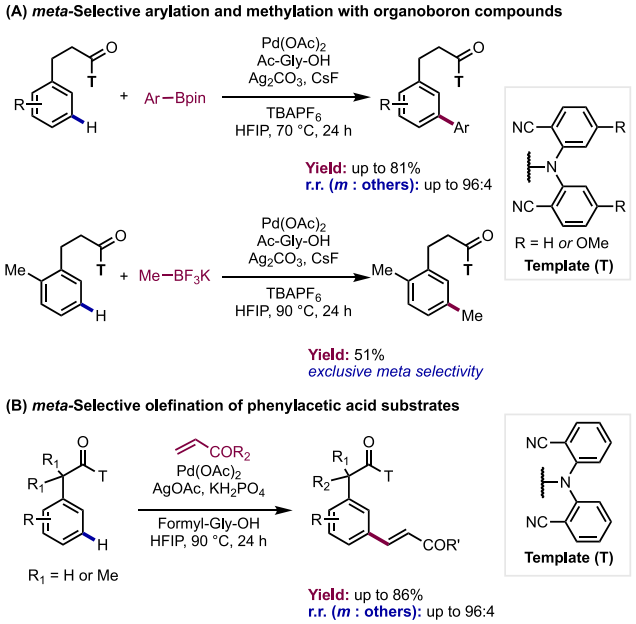
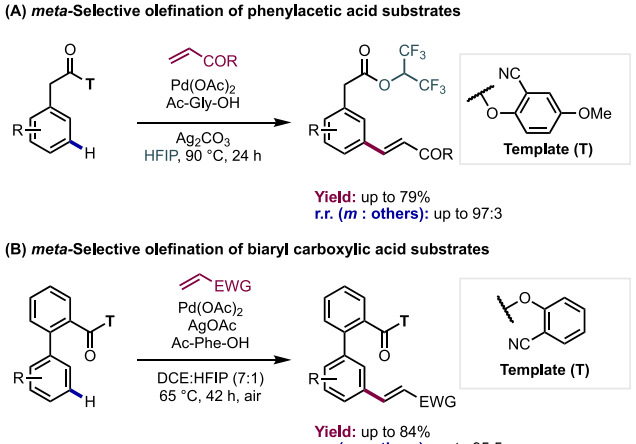
Scheme 12. *meta*-Selective Cross-Coupling of and Olefination of Acid Derivatives Enabled by a Nitrile Template



The success of this transformation was enabled through the use of *N*-acetylglycine as a key ligand. Using the same template and a key *N*-formylglycine ligand, these conditions could also be applied to the remote *meta*-selective olefination of a wide variety of phenylacetic acid substrates previously inaccessible (Scheme 12B).[34] Similarly, Maiti et al. employed an ester-tethered hydroxybenzonitrile template to effect a *meta*-C−H olefination of phenylacetic acid derivatives, which under the reaction conditions, undergo transesterification with HFIP to cleave the template *in situ* (Scheme 13A).[35] As an extension of

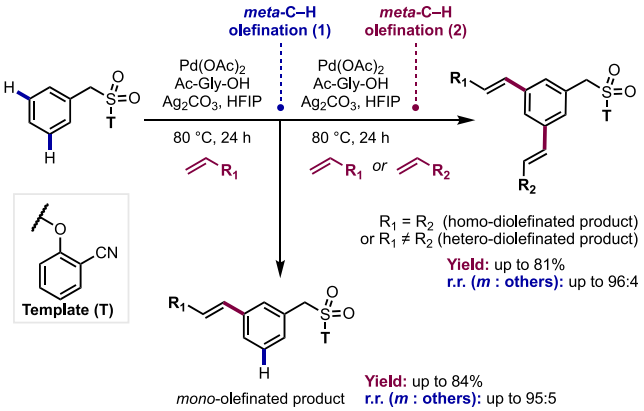
Scheme 13. *Meta*-Olefination of Phenylacetic Acid and Biphenyl Carboxylic Acid Derivatives



their previous report on the *meta*-functionalization of biarylphenol motifs, Maiti et al. subsequently reported the use of an ester-tethered benzonitrile template in a selective remote *meta*-C−H olefination of biaryl carboxylic acids (Scheme 13B).[23]

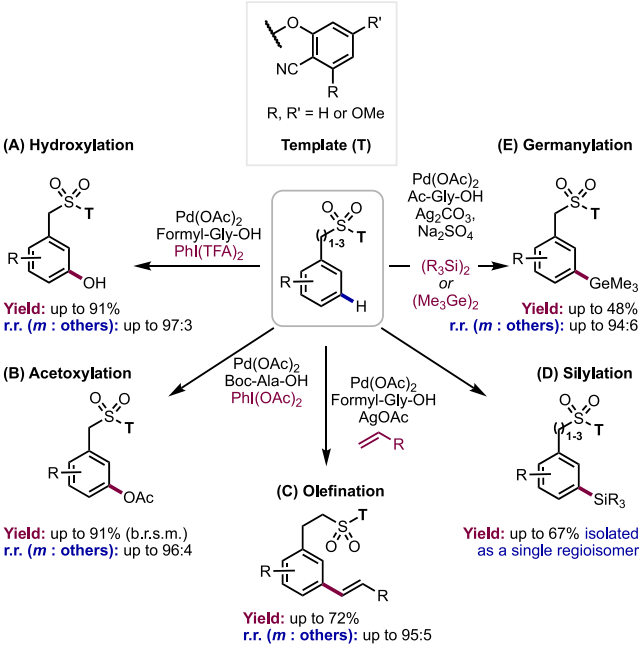
In 2015, Maiti et al. investigated the use of sulfonic acids as template anchors to effect remote *meta*-olefination of alkyl-tethered arylsulfonic acids bound to the commercially available 2-cyanophenol templates (Scheme 14).[36] By tuning the

Scheme 14. Divergent *Meta*-Selective C−H Mono- or Diolefination of Sulfonate-Containing Substrates



reaction conditions, a variety of mono-, di-, and heterodiolefinated products could be generated for the first time. Maiti et al. further expanded the applications of this nitrile template to enable the *meta*-hydroxylation and acetoxylation of phenylmethanesulfonic acid derivatives (Scheme 15A,B),[37] as well as

Scheme 15. Accessing a Variety of *Meta*-Substituents from the Selective C−H Functionalization of Sulfonate-Containing Substrates



meta-olefination,[38] *meta*-silylation, and *meta*-germanylation reactions[39] of arylsulfonates (Scheme 15C−E). A similar template could be employed for the remote *meta*-C−H functionalization of phosphonate-containing substrates, where in 2016, Maiti et al. reported the selective *meta*-C−H olefination, acetoxylation as well as hydroxylation reactions of benzylphosphonate derivatives (Scheme 16).[40]

Building on our findings from replacing the nitrile group with a stronger σ-donating *N*-heteroaryl motif (see Scheme 7),

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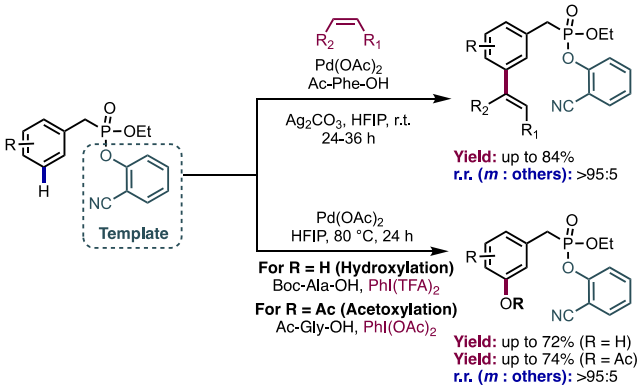
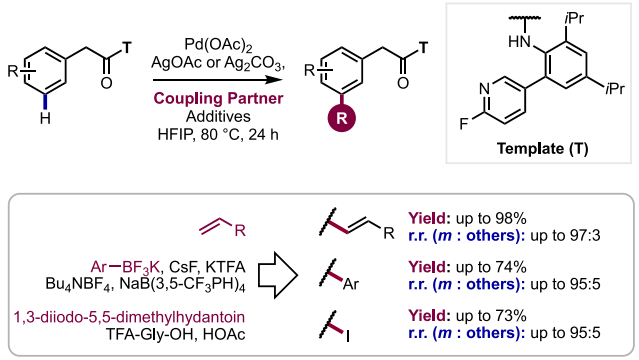
Scheme 16. Template-Mediated Remote *Meta*-C−H Functionalization of Phosphonate-Containing Substrates



we generated carboxyl-anchored 2-fluoropyridyl-containing templates to enable the remote *meta*-functionalization with more challenging reagents (Scheme 17).[41] This principle

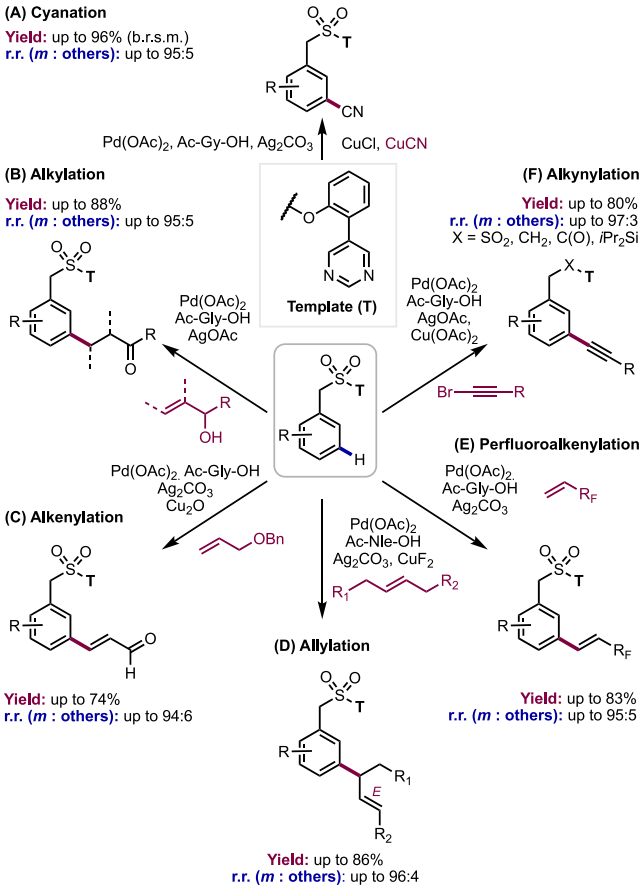
Scheme 17. *Meta*-Selective Remote Olefination, Arylation, and Iodination of Phenylacetic Acid Substrates Enabled by a 2-Fluoropyridine-Containing Template



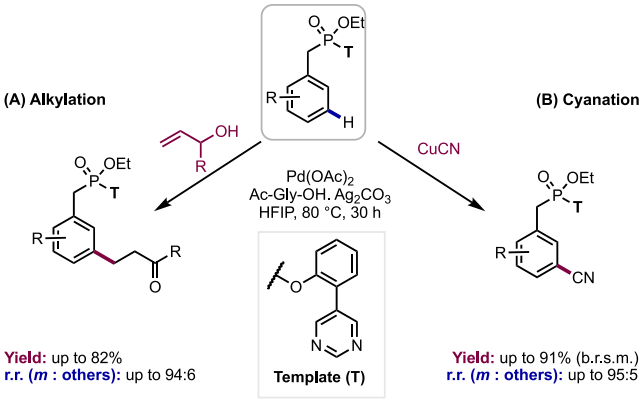
allowed us to broaden the competency of coupling partners, and we were able to achieve *meta*-selective arylation and iodination of carboxylic acid substrates for the first time. Likewise, Maiti et al. extended the scope of *meta*-functionalization of sulfonate derivatives by employing an arylpyrimidine template. This enabled a variety of *meta*-cyanation (Scheme 18A),[27] alkylation (Scheme 18B), alkenylation (Scheme 18C),[42] allylation (Scheme 18D),[30] perfluoroalkenylation (Scheme 18E),[31] and alkynylation (Scheme 18F)[43] transformations, and can be recapitulated with the corresponding benzylphosphonate substrates (Scheme 19A,B).[27,42] The application of this arylpyrimidine template was successful in realizing a *meta*-selective C−H alkynylation reaction with alkynyl bromides (Scheme 18F). In this example, template attachment onto a wide variety of functional groups and pharmaceutical agents was successful in generating the *meta*-alkynylated product.[43]

In conjunction with carefully tuning distance and geometric parameters, a further exposition for the utility of strongly directing motifs lies in effecting the *meta*-selective C−H deuteration reaction, a transformation difficult to access *via* traditional means. To this end, we were able to effect a *meta*-selective C−H deuteration enabled by a pyridyl template for a wide range of ester-linked substrates (Scheme 20A).[44] Similarly, Maiti et al. extended the application of their

Scheme 18. A Pyrimidine-Containing Template Allows for the Cyanation, Alkylation, Alkenylation, Allylation, Perfluoroalkenylation, and Alkynylation of Sulfonate-Bearing Arenes



Scheme 19. *Meta*-C−H Alkylation and Cyanation of Phosphonate-Containing Substrates Mediated by a Pyrimidine-Containing Template



pyrimidine template to report a *meta*-selective C−H deuteration of phenylacetic acids, sulfonates, and common pharmaceutical substrates (Scheme 20B).[45]

Extending beyond monocyclic *N*-heteroaryl directing groups, Maiti et al. recently disclosed the application of an 8-nitroquinoline-based template for the *meta*-olefination and acetoxylation of benzenemethanesulfonates (Scheme 21).[46] The proximally positioned nitro moiety was hypothesized to assist in the spatial positioning of the palladium catalyst, and

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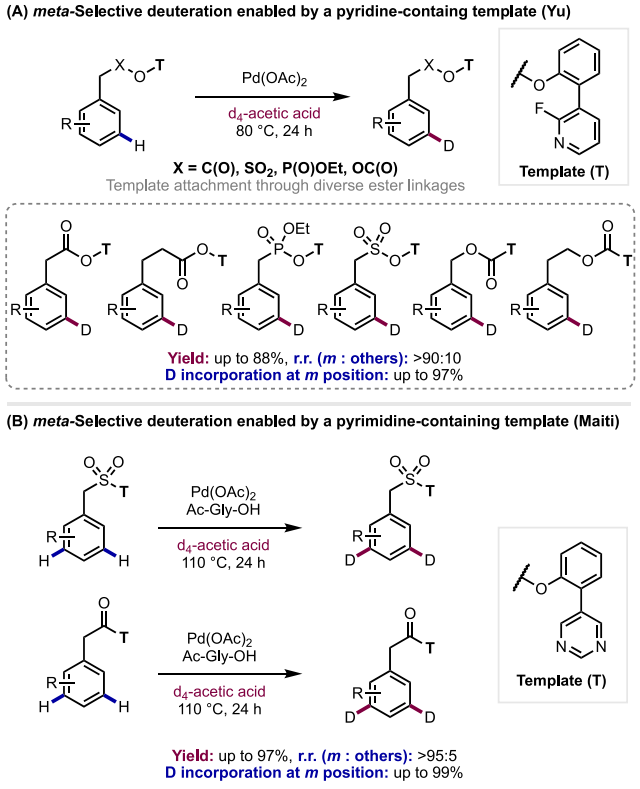
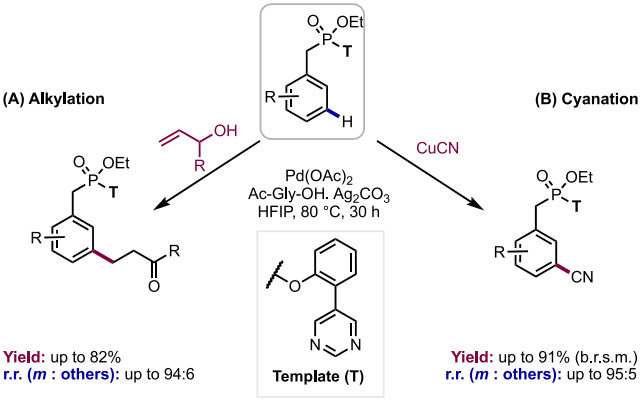
Scheme 20. *Meta*-Deuteration of Arenes Bearing Diverse Ester-Linkable Functionalities Enabled through a Pyridine- or Pyrimidine-Containing Template



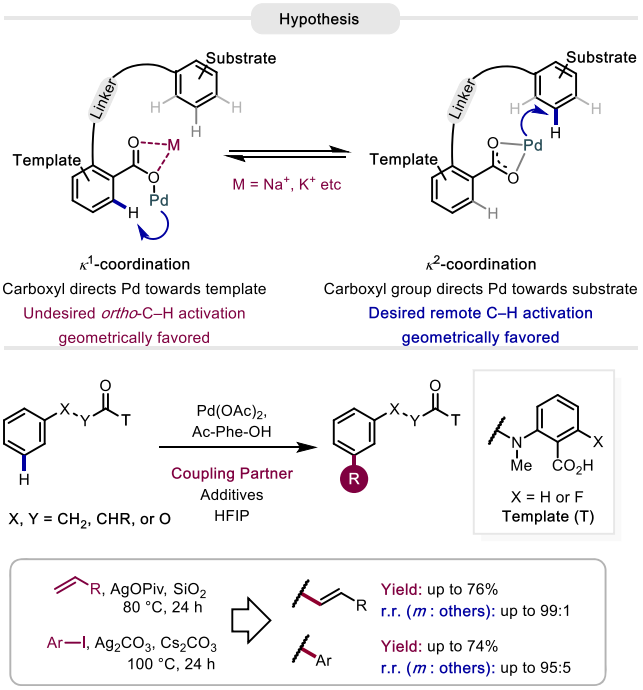
Scheme 21. *Meta*-Functionalization of Arenes Enabled by an 8-Nitroquinoline-Based Template



was thought to stabilize the palladacyclic intermediate required for *meta*-functionalization, a hypothesis that was reinforced through *ab initio* studies and mass spectrometric analysis.

Departing from the established directivity from *N*-based directing groups, Li et al. recently reported the first example of carboxyl-group-directed *meta*-C−H arylation and olefination reactions (Scheme 22).[47] Central to their design was the suppression of the κ^1 coordination mode promoted by inorganic salts, which would instead favor the undesired *ortho*-C−H activation pathway. With the κ^2 coordination mode, the active palladium catalyst would be directed to the target *meta*-C−H bond and generate the desired macrocyclophane pre-transition state. Through tuning the template

Scheme 22. *Meta*-Olefination and Arylation Enabled by a Carboxyl-Containing Template



substituents, this approach was successfully applied to effect the *meta*-C−H olefination and arylation processes.

These aforementioned examples illustrate the broad applicability of U-shaped templates for the remote functionalization of carboxylic acid, sulfonate, and phosphonate substrates. An elusive, yet valuable, transformation is the direct *meta*-functionalization of benzoic acid substrates, relying on a templated approach to overturn the inherent *ortho*-selectivity of the cyclometalation process.[48a] Additionally, three substrate-imposed challenges will have to be overcome for the development of a suitable *meta*-selective process: first, the electron-poor nature of benzoic acids renders the C−H activation process more difficult compared with electronically richer aromatic rings; second, the reduced number of bonds between the functional group and the target C−H bond in question (four compared with five or six for phenylacetic acid) shrinks the size of the macrocyclophane intermediate; third, benzoic acids possess a greater number of contiguous sp^2 centers compared with phenylacetic acid, rendering the substrate far more rigid compared with the corresponding phenylacetic acid analog (Scheme 23). These challenges necessitated a careful assessment of how best to incorporate the U-turn motif at the right distance and geometry to reduce the incurred strain for macrocyclophane assembly.

Perhaps owing to these challenges, the first report of a *meta*-selective functionalization of benzoic acids was not reported until 2016, where Li et al. disclosed a palladium-catalyzed *meta*-C−H olefination and acetoxylation of benzoic acid derivatives assisted by an amide-linked nitrile-based template (Scheme 24A).[48b] Concurrently, our laboratory established the *meta*-C−H olefination of benzoic acid derivatives (Scheme 24B),[48c] where computational studies suggested that selectivity was attributed to the formation of a macrocyclic palladium−silver heterodimer stabilized by the mono-*N*-protected amino acid ligand *N*-acetylglycine. In both examples, two design features were crucial for the success of the transformation: first,

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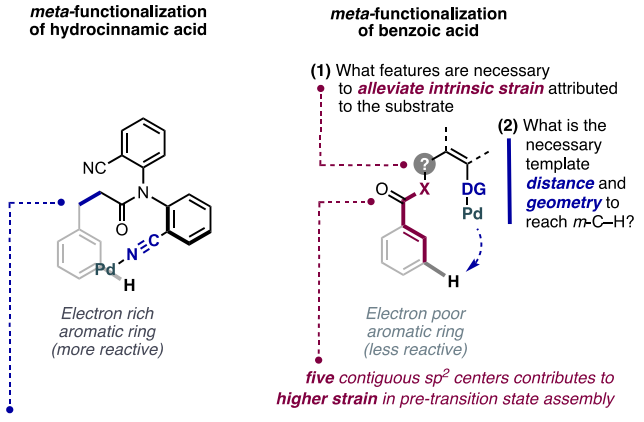
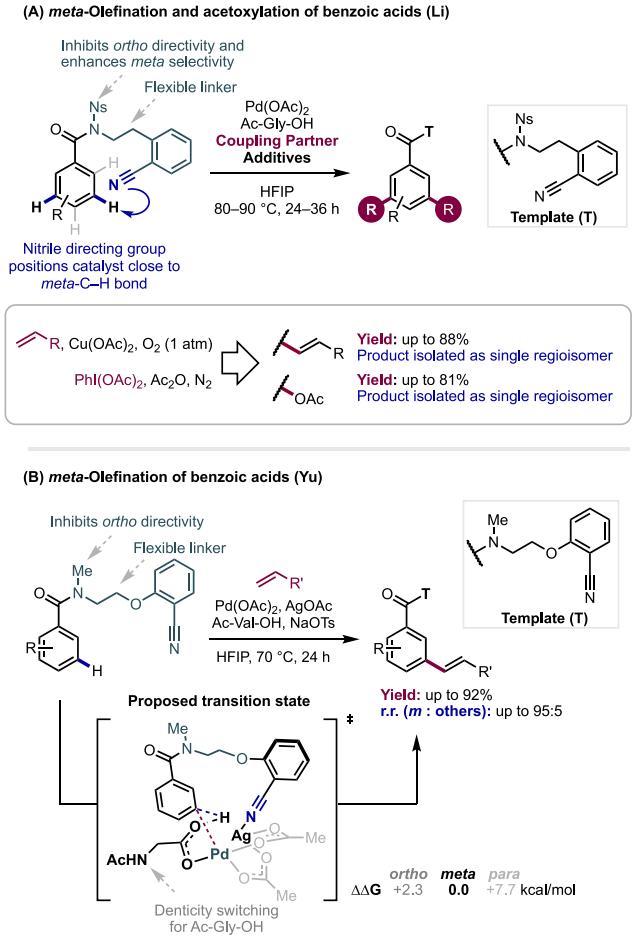
Scheme 23. Challenges Surrounding the *Meta*-C−H Functionalization of Benzoic Acids Relative to Other Aryl Carboxylic Acid Substrates



Scheme 24. Enabling the *Meta*-C−H Functionalization of Benzoic Acids through a Nitrile Directing Group with a Flexible Tether

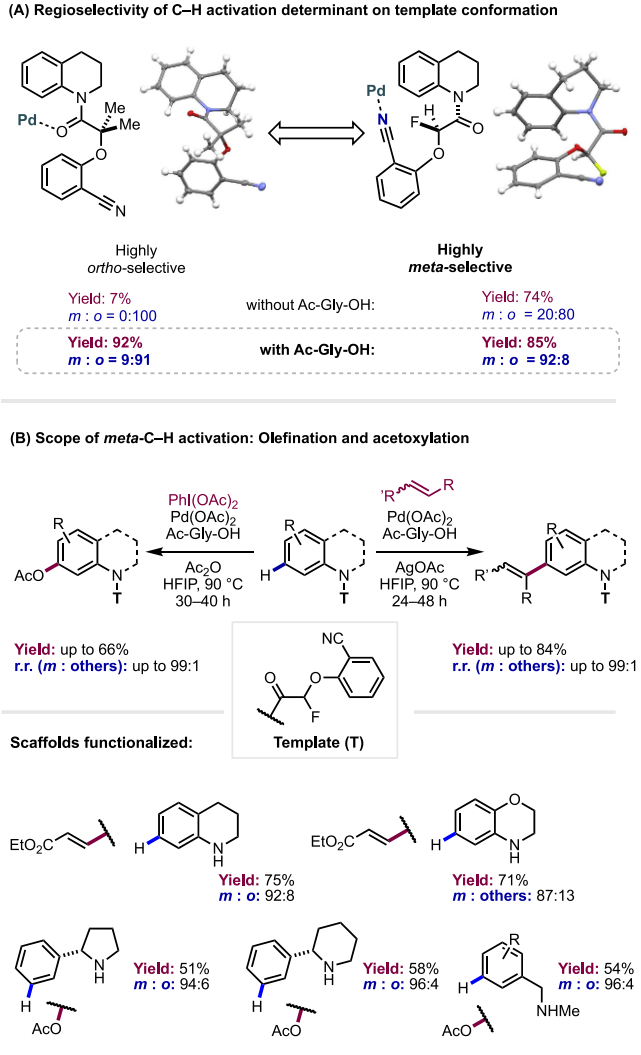


the *N*-substitution immediately adjacent to the carboxyl functionality was crucial to suppress the *ortho* directivity of this moiety. Additionally, the incorporation of an optimally spaced flexible linker before the U-shaped directing group geometry was necessary to the success of the transformation, as it alleviates the strain imparted by the macrocyclophane pre-transition state.

2.3. Template-Enabled Remote C−H Activation of Amine Substrates. As one of the most common functionalities present in both bioactive natural products and pharmaceutical agents, the flexible late-stage derivatization of amine-containing substrates represents a valuable transformation for practitioners of organic chemistry. However, despite significant progress in template-enabled C−H activation processes, executing the corresponding remote C−H functionalization for amine derivatives remain sparse and underexploited by this strategy. This section covers recent advances in template-mediated remote C−H functionalization of amine substrates, paying particular attention to how careful consideration of distance parameters and template geometry has enabled their successful realization.

In 2014, we first reported the conformation-induced *meta*-C−H olefination and acetoxylation of anilines and benzylic amines (Scheme 25).[49] This work focused on the rational design of new nitrile-based templates to enable functionalization of the previously inaccessible tetrahydroquinoline C7, or *meta*-C−H bond. This objective was exceptionally challenging due to the highly strained tricyclic cyclophane intermediate

Scheme 25. Conformation-Induced *Meta*-C−H Activation of Amines



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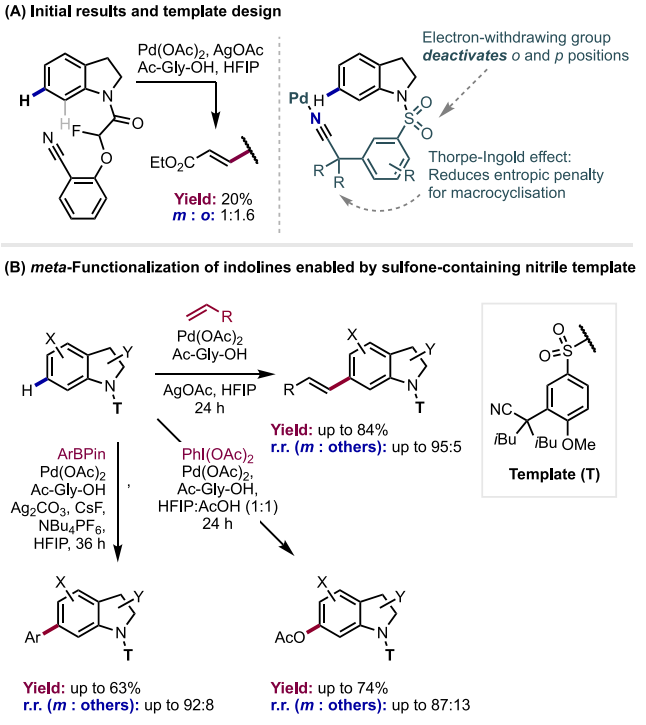
that would be generated upon C−H activation. Here, geometric factors were instrumental for the success of this transformation. We found the nature of the substituents adjacent to the amide carbonyl functionality in the template to be particularly determinant for the template conformation, and therefore for the regioselectivity obtained. X-ray analysis revealed that the *gem*-dimethyl substitution resulted in the amide carbonyl group aligning in the optimal geometry for *ortho* C−H activation (Scheme 25A). Interestingly, introducing a single fluorine atom at the same α-position of the amide carbonyl resulted in the complete reversal of the orientation of the amide carbonyl group, allowing the nitrile to be positioned in the optimal geometry to promote *meta*-C−H activation. Notably, templates that do not contain α-substitution, as well as truncated templates where the aryl U-turn motif was directly appended to the α-position, all afforded poor selectivity. These results not only demonstrate the crucial importance of the optimal distance required between the functional handle and directing group of choice, but also highlight the subtle, yet pivotal role substituents can play in determining the overall template conformation. Further reaction optimization was obtained through utilizing *N*-acetylglycine as a ligand, improving both the selectivity and yield for this transformation. This observation was rationalized in part by the ligand's ability to increase both electron density and steric congestion at the palladium center. Owing to the more electron-rich and sterically hindered nature of the *ortho* C8 C−H bond, these attributes cumulatively promoted the desired *meta*-regioselectivity over the undesired *ortho*-C−H bond. Our in-depth spatial and conformational understanding of this template has enabled the selective remote C−H olefination and/or acetoxylation reactions of a broad range of cyclic amine-containing substrates (Scheme 25B).

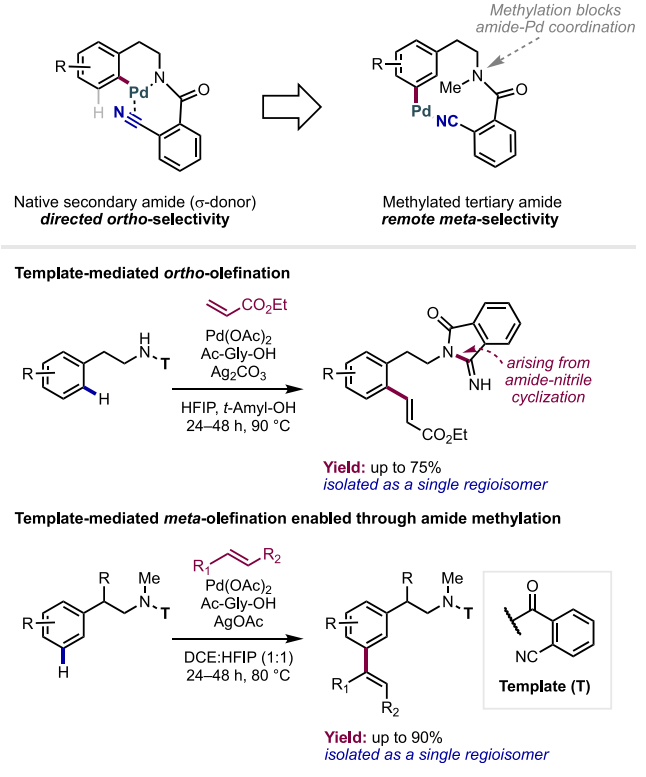
Our initial report established the viability of employing distance and geometric parameters to enable the site-selective remote functionalization of amine functional groups. Building from our previous report, we then developed a platform for the selective *meta*-C−H olefination, arylation, and acetoxylation of indoline scaffolds by employing a new U-shaped nitrile-based template (Scheme 26).[50] Our initial attempts toward effecting such a transformation began with our previously developed templates, which afforded poor site-selectivity for the transformation (Scheme 26A). This discrepancy between the selectivity observed for indolines and tetrahydroquinolines was attributed to the increased electron-donating ability of the indoline nitrogen, which enhances the reactivity of the *ortho* and *para* C−H bonds, as well as the marginally altered geometry of the nitrogen atom, which positions substituents away from the aromatic ring and decreases steric hindrance around the *ortho*-C−H bond. Based on these hypotheses, our template design strategy focused on increasing the electron-withdrawing nature of the nitrogen linkage, as well as biasing the geometry of the template through leveraging the Thorpe-Ingold effect. This was successfully realized through a sulfonamide-linked nitrile template bearing a geminal di-isobutyl motif, which allowed for the selective *meta*-olefination, arylation, and acetoxylation of native and complex indoline analogs in good yields and excellent selectivity (Scheme 26B).

In 2015, Li et al. reported a modular approach toward achieving a regiodivergent *ortho*- and *meta*-C−H olefination of phenylethylamines utilizing an amide-tethered 2-cyanobenzoyl template (Scheme 27).[51] During the course of this study, Li et al. discovered the unanticipated cyclization of the amide tether

Scheme 26. *Meta*-C−H Olefination and Acetoxylation of Indolines Mediated by a Sulfonamide-Tethered Nitrile Template



Scheme 27. *Ortho*- and *Meta*-C−H Olefination of Phenylethylamines Enabled by an Amide-Anchored Nitrile Template



to the *ortho*-C−H bond, which could be intercepted to generate the *ortho*-olefinated product. This observation led to the realization that the amide linker itself was an active

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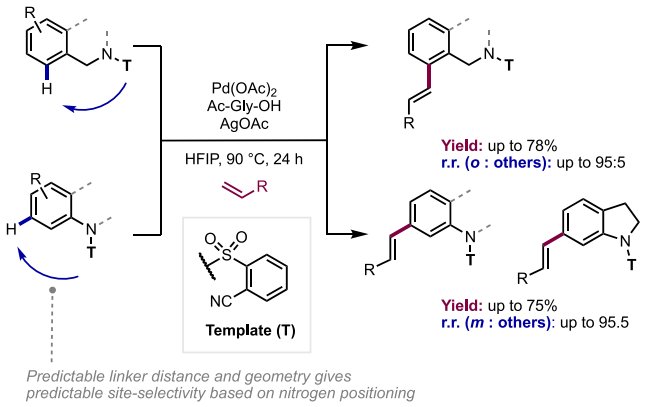
directing group, perhaps with π-coordinative assistance from the proximal nitrile moiety. Through amide methylation, Li et al. confirmed this hypothesis through a switch in regioselectivity, obtaining the product arising from the nitrile-directed *meta*-olefination process. This protocol was successfully utilized to generate a series of trisubstituted arenes *via* sequential *ortho*- and *meta*-C−H olefination, demonstrating the utility of this approach for the direct and modular synthesis of substituted arenes.

Taking the key lessons learned from previous studies, we sought to develop a unified approach for the remote C−H functionalization of amine-containing substrates. This led to the development of an *ortho*-sulfonylbenzonitrile template, which is able to furnish the remote C−H olefination of six different *N*-heterocycles (Scheme 28).[52] Importantly, this

Scheme 28. A Single Sulfonamide-Tethered Nitrile Template Enables the Divergent Olefination of Various *N*-Heterocycles

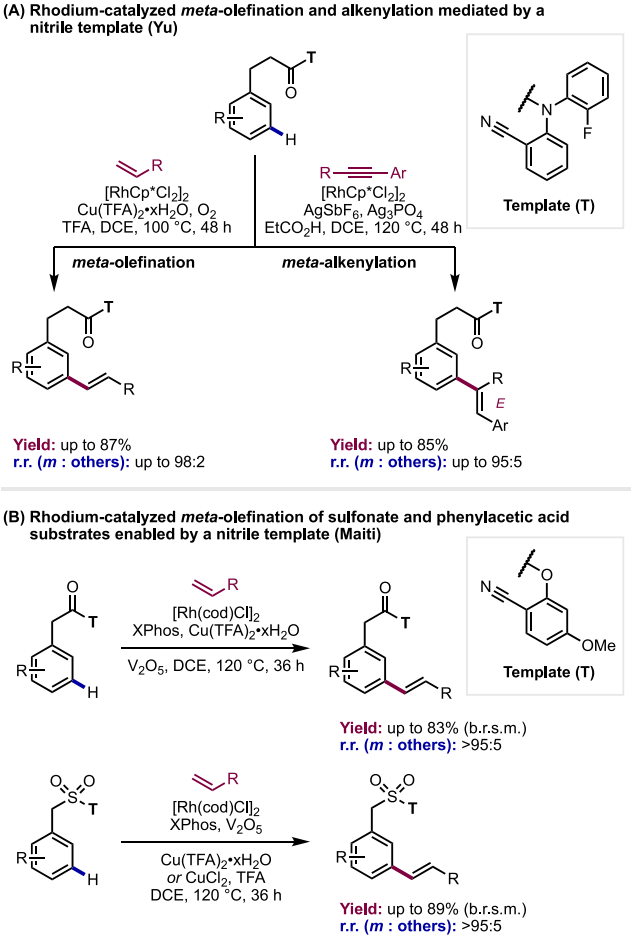


template was able to generate predictable and reliable site-selectivity depending on the positioning of the nitrogen atom, generating a wide variety of *ortho*- and *meta*-olefinated products for a diverse range of *N*-heterocycles without further template optimization. The generality of this transformation was attributed to the shorter template linker and electronics modulation through the sulfonamide linkage. Our understanding of distance and overall geometry for this class of template allows a balance to be struck, and enabled *ortho*-activation in the case of a more distal *N*-heteroatom, as well as *meta*-activation for more proximal *N*-heteroatom positioning in the heterocycle. This example represents the first time where a smaller, more rigid macrocyclophane-type pre-transition state was successfully employed for a remote C−H activation process, and is notable for enabling the challenging direct C6 functionalization of indole-containing scaffolds.

3. TEMPLATE-ENABLED RH(III)-CATALYZED REMOTE C−H BOND ACTIVATION

To this point, we have demonstrated that a templated strategy is broadly applicable for enabling a range of site-selective remote functionalization process *catalyzed by palladium*. This "template algorithm" could potentially be generalized across a wide range of transition metal-catalyzed C−H activation processes. Despite this, however, the feasibility of this strategy has not been widely demonstrated across other metals, perhaps owing to the multivariate tuning required to optimize ligand binding kinetics, coordination geometries, and redox properties for other metals. To tackle this challenge, we developed a rhodium(III)-catalyzed *meta*-C−H alkenylation reaction for carboxylic acid, indoline, and aniline derivatives using a modified mono-nitrile template (Scheme 29A).[53] The

Scheme 29. Rh(III)-Catalyzed *Meta*-C−H Functionalizations Enabled by a Template-Mediated Strategy



selectivity of this transformation was rationalized to proceed via a 12-membered macrorhodacyclic intermediate, and allowed a broad range of substrates to undergo a range of selective *meta*-olefination processes.[54a] The applicability of this strategy for other metals was also demonstrated by a report published by Maiti et al., where a range of rhodium-catalyzed *meta*-selective olefinations were realized for a variety of sulfonate- and phenylacetic-bearing substrates mediated by a cyanophenol-type template (Scheme 29B).[54b]

4. BEYOND REMOTE *META*-FUNCTIONALIZATION: COVALENTLY ATTACHED TEMPLATE-ASSISTED *PARA*-C−H ACTIVATION

Since our initial report in 2012, our distance- and geometry-guided template design philosophy has proven successful in enabling a wide variety of *meta*-selective remote C−H functionalizations. These guiding design features have the potential to be generalized to allow for the direct access to *para*-functionalized products. This is a non-trivial challenge, as the altered distance and geometry of the *para*-C−H bond relative to the native functional group demands the develop-

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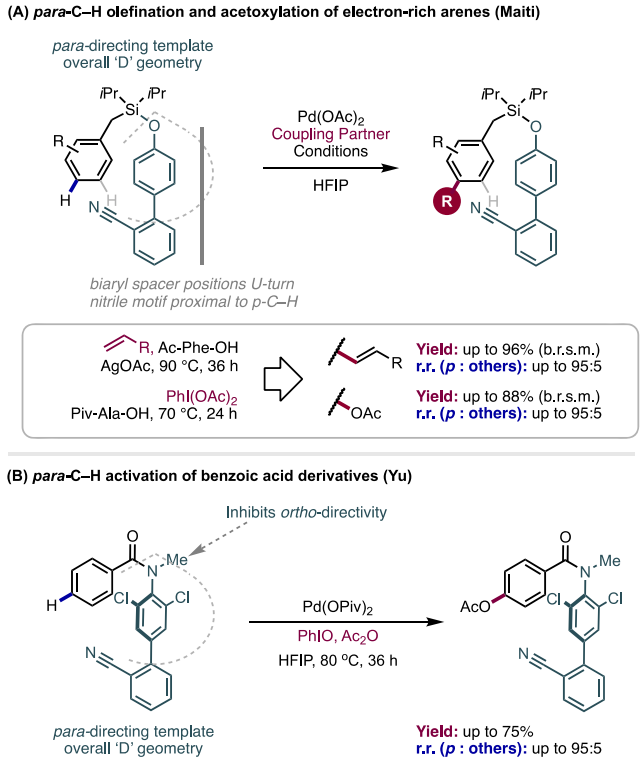
ment of a new set of templates to enable its selective functionalization. In 2015, Maiti et al. reported a template-enabled *para*-C−H functionalization of phenolic substrates (Scheme 30A).[55a] This previously elusive transformation was

Scheme 30. Development of a Template-Mediated Strategy to Enable *Para*-Selective C−H Functionalization



enabled by an recyclable silyl ether-linked *para*-substituted biaryl template, forming a D-shaped assembly that positions the nitrile group over the *para*-C−H bond. Aided by the inherent electronics of phenolic substrates, which deactivates the *meta* position relative to the *para*-C−H bond, this transformation enabled the direct olefination and acetoxylation of phenols.

Building on this promising proof-of-concept, we sought to apply our design principle to develop a *para*-selective functionalization of electron-deficient arenes. This approach would definitively demonstrate that *para*-selectivity could be achieved solely through template directivity, without any biases imposed by electronic effects inherent to the substrate. In 2019, our laboratory reported a nitrile-based template that enabled the *para*-C−H acetoxylation of electron-deficient benzoic acid derivatives (Scheme 30B).[55b] The success of this transformation was dependent on a methylated amide-linkage to discourage the undesired *ortho* activation, as well as a *para*-substituted biaryl skeleton that similarly positions the nitrile group at an optimal position for accessing the desired *para*-C−H bond.

5. BEYOND COVALENT ATTACHMENTS: COORDINATIVE AND NON-COVALENT INTERACTIONS IN ENABLING THE REMOTE C−H ACTIVATION OF ARENES

The preceding sections chronicled the development of a diverse set of remote C−H functionalization transformations uniformly enabled by carefully designed templates covalently anchored to a native functional group. While highly effective, one drawback of this strategy pertains to its synthetic inefficiency; to execute the desired transformation, one has to attach and remove the template in two operations. This inefficiency can render these transformations impractical to the wider community. Therefore, an ongoing pursuit is the development of effective *non-covalently*-bound templates capable accessing the macrocyclophane transition state required for C−H activation. If successful, this concept could pave the way for developing templates *that can be used catalytically* to effect the desired C−H functionalization transformation.[56] This section will briefly survey the nascent development in the field of remote C−H functionalizations enabled by non-covalently bound templates, and will highlight recent advances in substrate-template assembly through metal coordination, hydrogen-bonding, and ionic interactions. Again, attention will be paid toward how design features incorporating template distance and geometry to the target C−H bond are leveraged to realize each highlighted transformation.

5.1. Remote C−H Activation Mediated by Coordinative Template Attachment. In many cases, the lack of a suitable functional group for the facile template attachment renders our covalent templated strategy intractable. This limitation is particularly relevant for substrates bearing heteroarene scaffolds, which are incompatible with covalent template attachment, but are ubiquitous motifs in medicinal chemistry and often comprise the core pharmacophore of a bioactive compound. Therefore, a strategy for the direct site-selective functionalization of these scaffolds represents a valuable addition to the synthetic literature.

To target this problem, we first looked toward effecting the remote functionalization of 3-phenylpyridine motifs. Noting that the Lewis basic *N*-heteroatoms are competent binders to metals, we envisaged a template that could be anchored via metal coordination (Scheme 31A), which, if successful, could allow a template to recruit an active catalyst and conduct C−H activation at a desired remote C−H bond. In this study, we found that a catalytic, bifunctional template was successful in achieving selective *meta*-C−H functionalization of 3-phenylpyridine (Scheme 31B). In this design, the backbone disulfonamide serves as an X,X-type bidentate ligand, which coordinates to a palladium(II) center and subsequently anchors two equivalents of the pyridyl substrate through L-type coordination. Importantly, the template bears a 3-substituted pyridine motif designed to recruit the active palladium catalyst at the optimal distance and geometry relative to the target C−H bond. This template design allowed for the selective *meta*-olefination of 3-phenylpyridine with a variety of olefins, successfully demonstrating that such a strategy was viable for remote functionalization.[56] It is worth noting here that the strong and typically deleterious pyridine−palladium coordination (a major catalyst poisoning pathway) was productively harnessed to anchor the template in place with the substrate, leading to the exquisite selectivity observed for this reaction.

With this promising result, we next explored the remote site-selective functionalization of quinoline substrates. In a similar manner, we intended to anchor the template with the quinoline substrate through palladium coordination, where the bifunctional nature of the template could recruit the active catalyst near the target remote C−H bond of choice. By designing a template containing an X,L,X-tridentate scaffold,

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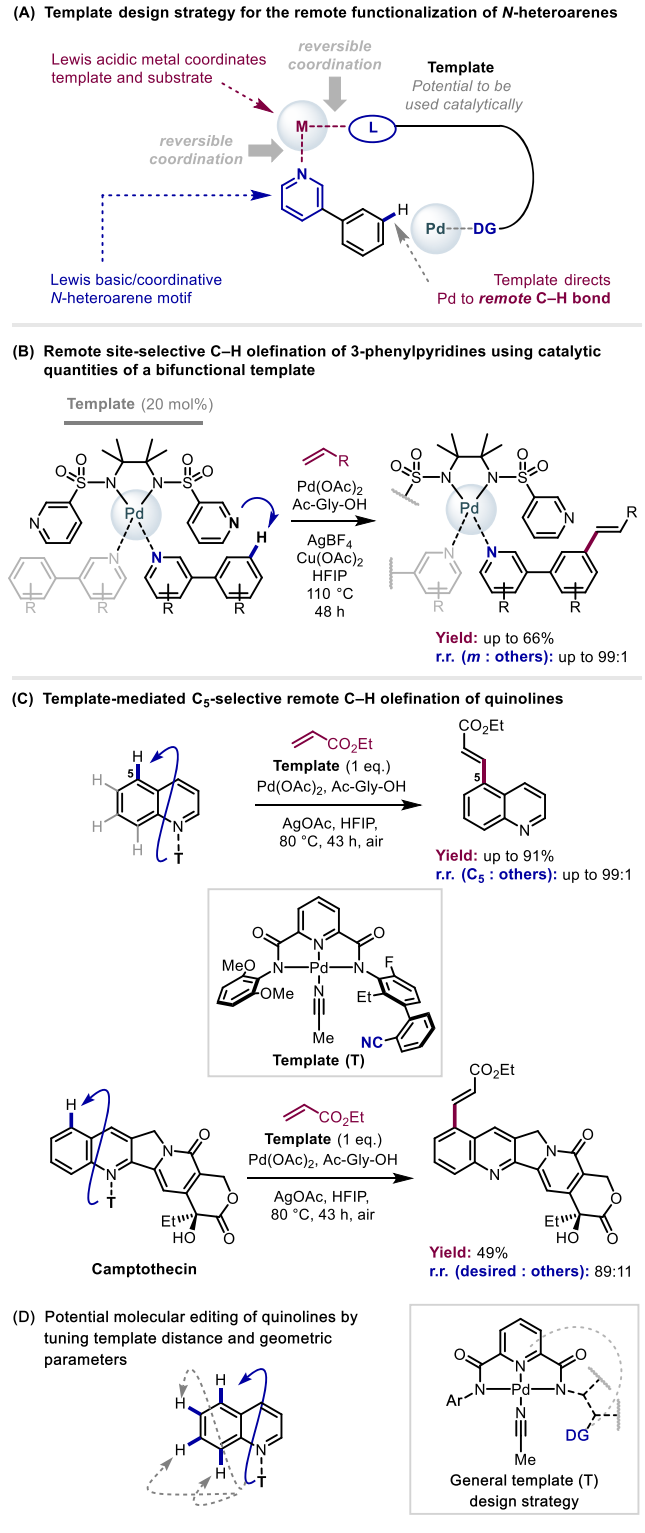
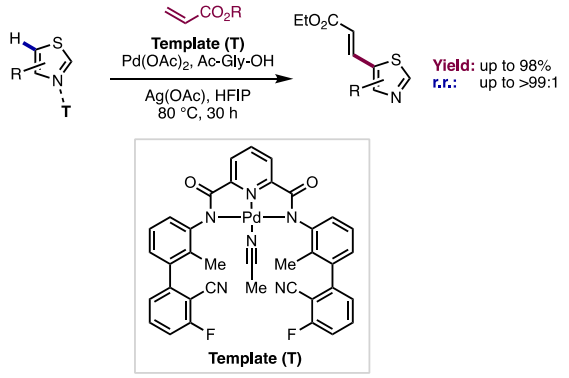
Scheme 31. Employing a Bifunctional Template Strategy for the Remote Functionalization of *N*-Heteroarenes, and Its Application to the Remote Functionalization of 3-Phenylpyridine and Quinoline Substrates



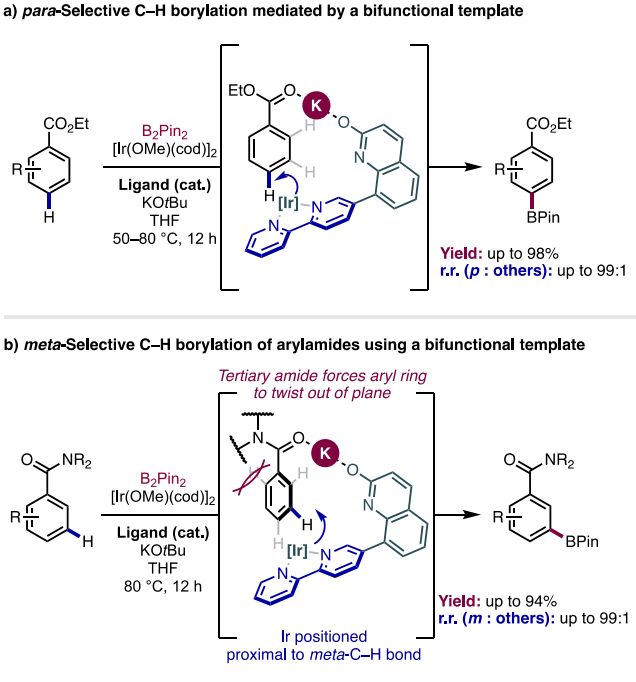
we generated a conformationally robust scaffold that could strongly bind to palladium and recruit the quinoline substrate. Careful optimization of the substituents on the scaffold backbone allowed us to fine-tune both the distance to the target C−H bond, as well as its geometry to best enable site-selective C−H activation (Scheme 31C). In doing so, we were able to achieve a C5-selective distal olefination for quinoline, benzoxazole, and benzothiazole substrates, as well as the selective late-stage olefination of the anticancer agent camptothecin. We envisage that this strategy could allow us to systematically functionalize other remote positions, where current research is focused on tuning distance and geometric parameters to allow for the selective C6, C7, and C8 functionalization of the quinoline scaffold (Scheme 31D). Subsequent to this report, Maiti et al. applied this template architecture to successfully enable the palladium-catalyzed site-selective olefination of thiazole and other related small heterocycles (Scheme 32).[57]

Scheme 32. Site-Selective C−H Olefination of Small Heterocycles via a Bifunctional Template Strategy



In a separate report, Chattopadhyay et al. demonstrated the feasibility of a *para*-selective C−H borylation of arylesters, uniquely mediated by an L-shaped template anchored through potassium coordination (Scheme 33A). Here, the template consists of a 2-hydroxyquinoline motif that is deprotonated

Scheme 33. Remote C−H Borylation Mediated by a Bifunctional Template Anchored through Potassium Coordination



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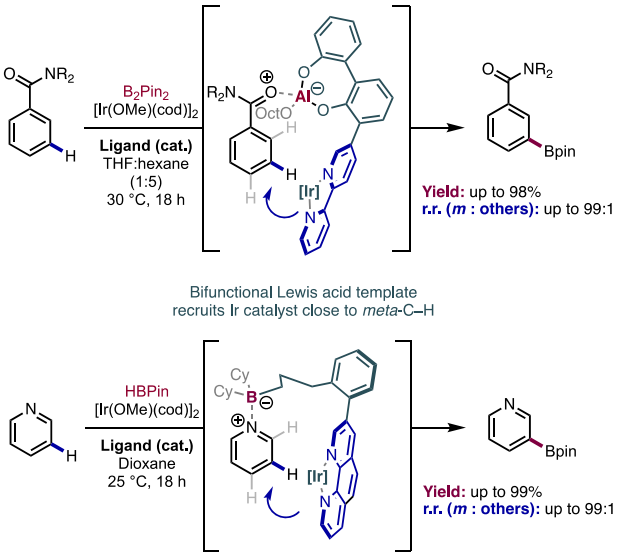
under the reaction conditions, connected to the bipyridyl-directing motif where it directs the active iridium catalyst proximate to the *para* C−H bond. Crucial to the success of this reaction was the presence of the potassium cation; it was experimentally shown that sequestration or replacement of the potassium cation with smaller homologs (e.g., lithium or sodium) deleteriously impacted the selectivity. In addition, Chattopadhyay et al. demonstrated that this strategy was viable for a range of remote functionalization of (hetero)arenes, with its regioselectivity principally dictated by the position of the ester-containing aromatic systems. Interestingly, applying the same template to aromatic amide substrates afforded almost exclusive *meta*-selectivity, posited to arise from arene distortion from the carbonyl plane, rendering the *meta* C−H bond closer to the active catalyst (Scheme 33B).[58b] The general principle of utilizing a Lewis acid to anchor two Lewis basic motifs present in both the substrate and template was applied by Nakao et al. in a *meta*-selective C−H borylation of benzamides and pyridines (Scheme 34).[59] Here, an L-shaped template

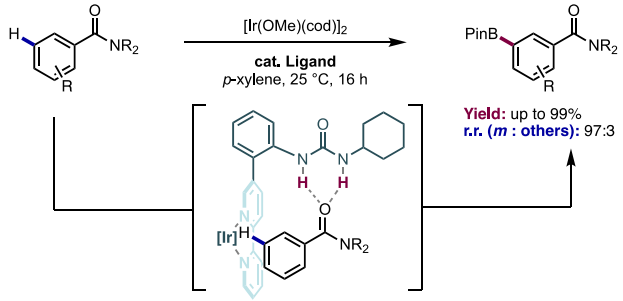
Scheme 34. *Meta*-Selective C−H Borylation Mediated by Substrate−Lewis Acid Interaction



architecture was employed, featuring a Lewis acidic motif aimed for substrate recruitment (e.g., Al chelated to a biphenol moiety, or a borane-containing motif) tethered to a bipyridyl region which recruits the iridium catalyst near the desired C−H to be borylated. The successful execution in these case studies provides compelling evidence that non-covalent interactions can be a powerful technique for the remote functionalization of aromatic motifs.

5.2. Remote C−H Activation Mediated by Hydrogen-Bonding and Ion-Pairing Interactions. Beyond metal coordination, two emergent classes of non-covalent interaction leveraged to enable template-directed remote C−H functionalization include hydrogen-bonding and ion-pairing interactions. These processes are promising in their ability to harness the innate acid/base properties of native functionalities, such as carboxylic acids and amines, and to use them as reversible anchors for template coordination. An elegant example of remote C−H functionalization enabled by hydrogen-bonding interaction has been demonstrated by Kanai et al., where a *meta*-selective C−H borylation of a variety of phenylamide substrates was achieved (Scheme 35).[60] An L-shaped template was employed for this transformation, consisting of a urea

Scheme 35. Hydrogen-Bonding Interactions Mediated by a Bifunctional Urea Template Enables a *Meta*-Selective Iridium-Catalyzed C−H Borylation of Benzamides



recognition motif for substrate anchoring, tethered to a bipyridyl motif that recruits the active iridium catalyst. Although the intrinsic reactivity of the substrate theoretically does not require directing motifs for its selectivity, the macrocyclic template assembly significantly enhanced the *meta*-selectivity of this C−H borylation process.[60]

In 2016, Phipps et al. demonstrated that ion-pairing interactions could be harnessed to dictate site-selectivity in remote C−H activation reactions. In this report, a range of aniline derivatives, aromatic heterocycles, and phenylalkyl ammonium salts bearing various linker lengths could undergo borylation with good yields and excellent regioselectivity (Scheme 36A).[61] The selectivity was enabled through the ionic interaction between a cationic ammonium substrate paired with an anionic sulfonate-tethered bipyridyl ligand, able to recruit the required iridium catalyst proximal to the target *meta* C−H bond. This pioneering account paved the way for further exposition of this strategy, including the site-selective *meta*-C−H borylation of phosphonium salts (Scheme 36B).[62] In a recent example, Phipps et al. demonstrated the power of harnessing a combination of hydrogen-bonding and ion-pairing interactions,[63a] achieving a regio- and enantioselective C−H borylation for benzhydrylamide and phosphonamide substrates (Scheme 36C).[63b] This process was enabled both by an anionic sulfonate ligand, which was posited to form a key hydrogen bond contact with the amidic substrate, and its tethered bipyridyl motif which recruits the catalyst near the target C−H bond. Outside this, the ion-paired quinine-derived countercation then provides the stereochemical environment to allow the sulfonate-tethered iridium catalyst to distinguish between the two prochiral *meta*-C−H bonds.

6. BEYOND ARYL C−H FUNCTIONALIZATIONS: HARNESSING DISTANCE AND GEOMETRIC CONSIDERATIONS FOR REMOTE C(SP^3)−H FUNCTIONALIZATIONS

So far, we have illustrated a wide range of remote arene C−H functionalization processes enabled by template anchoring. It remains to be demonstrated that this strategy can be cross-applied to corresponding aliphatic C−H bonds; a venture more challenging owing to the higher basicity of the target bond, the absence of accessible filled/unfilled orbitals available for metal pre-coordination, as well as the propensity for alkyl-palladium intermediates to undergo undesired *β*-hydride elimination pathways.[64] We approached this problem by

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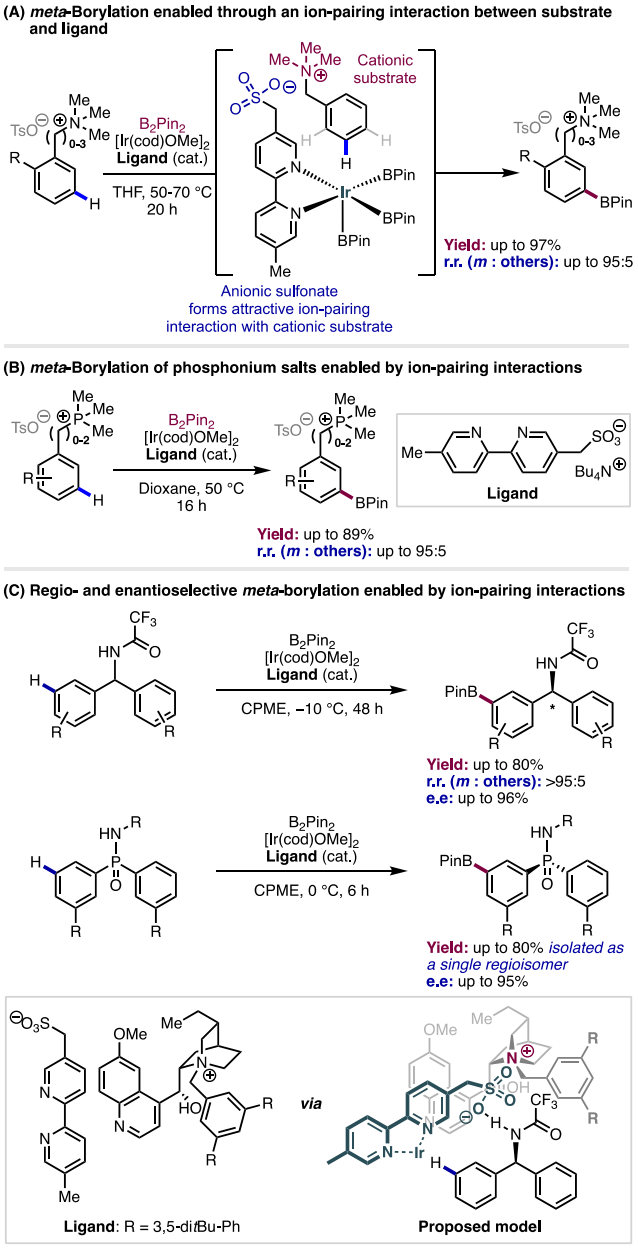
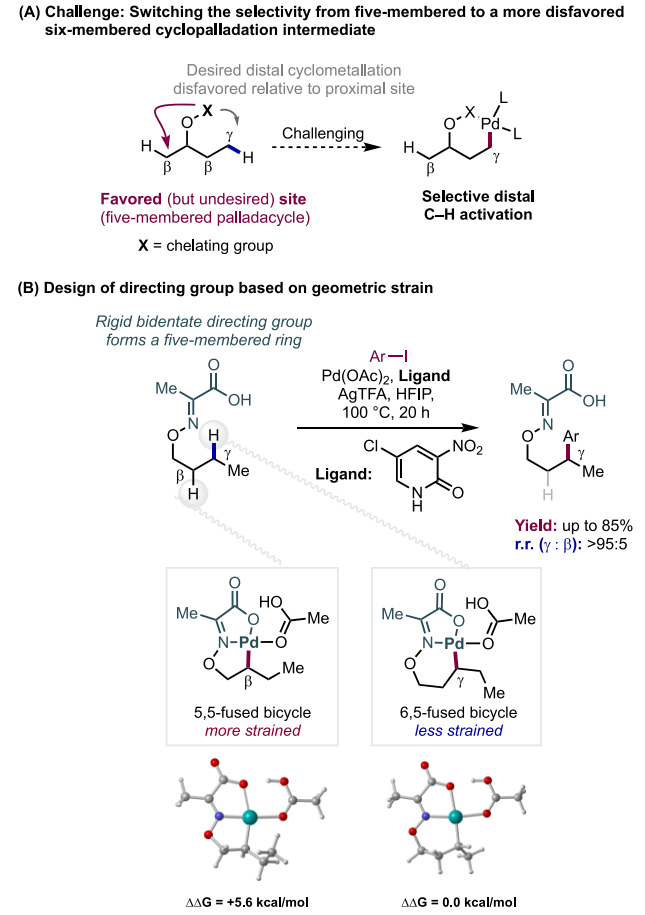
Scheme 36. *Meta*-Selective C−H Borylation Mediated by Ion-Pairing Interactions



considering whether it was possible to selectively target the γ-C(sp^3)−H over the more proximal β-C(sp^3)−H neighbor (Scheme 37A). As the regioselectivity in palladium-catalyzed C(sp^3)−H activation reactions is generally controlled by the preferential generation of five-membered palladacyclic intermediates, the reversal of the canonical site-selectivity must therefore arise from designing a directing group that *energetically disfavors the formation of the five-membered palladacycle in preference for the six-membered analog*. For remote arene functionalizations, we noted that the rigidity of the aryl ring plays an important role in entropically favoring the generation of the macrocyclophane transition state. With inherently flexible aliphatic substrates for C(sp^3)−H functionalization, we hypothesized that employing rigidifying elements in the directing group (i.e., rich in sp^2 character) could be an effective strategy to minimize the entropic cost of generating the cyclometalated intermediate. This could then generate a

Scheme 37. Reversing Conventional Site-Selectivity through Geometric Factors in C(sp^3)−H Arylation of Alcohols



rigid five-membered directing group-palladium complex to target the desired C(sp^3)−H bond. In this case, the generation of a five-membered palladacycle (arising from the canonical β-C(sp^3)−H activation) fused to a rigid five-membered directing group chelate is hypothesized to be more strained than the atypical six-membered analog arising from γ-C(sp^3)−H activation.

Based on this blueprint, we designed a rigid pyruvic acid-derived directing group capable of generating a five-membered palladium chelate. In conjunction with aryl iodide coupling partners, we were pleased to see a *complete* reversal of site-selectivity to afford γ-arylated products for a variety of primary and secondary C(sp^3)−H bonds (Scheme 37B),[65] affirming our hypothesis that such a rigid directing group disfavors the formation of the more strained 5,5-fused palladacycle in favor of the less strained 6,5-fused palladacycle. Indeed, the 5,5-fused palladacycle was calculated to be disfavored relative to the 6,5-fused species by 5.6 kcal/mol at the reaction temperature.[19] In the emerging, and more challenging, field of transition metal-catalyzed C(sp^3)−H functionalization, this promising result indicates the feasibility of incorporating carefully considered geometric parameters as a starting point for the design of new and adventurous site-selective remote C(sp^3)−H functionalization processes.

7. CONCLUSION AND OUTLOOK

As an eminent approach, C−H activation represents a potentially transformative method that can simplify the

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construction and/or facilitate the diversification of complex molecules in a straightforward manner. In this perspective, we highlight that achieving one of the most challenging regioselective transformations—the differentiation and functionalization of remote C−H bonds—is a venture not only possible, but also practical and translatable across a wide variety of contexts. We proposed that this challenge could be distilled down to two design parameters: the *distance* and *geometry* of the catalyst binding site relative to the target C−H bond, where the careful optimization of both variables is crucial for achieving the desired selectivity of the transformation. In the absence of substrate-imposed steric and electronic biases, these two parameters determinatively moderate the relative energies between competing cyclophane-like macrocyclic transition states, and therefore the selectivity for one remote C−H bond over another. The wide applicability of this philosophy can be seen through its realization across a series of anchoring functional groups, achieving a wide range of positionally selective functionalizations. Furthermore, alternation of directing motifs on these templates allowed for the broadening of coupling partners competent for these transformations. Finally, we demonstrate that these design principles can be translated into more challenging C(sp^3)−H functionalization contexts, where directing group design can overturn the inherent selectivity of a substrate. Although the need for covalent attachment of templates remains a limitation of this approach, this perspective has demonstrated several promising strategies harnessing non-covalent interaction for template attachment. These include metal/Lewis acid coordination,[56−59] hydrogen-bonding,[60] and ion-pairing interactions[61−63] to assemble the requisite macrocyclophane transition states.

These emergent strategies can guide the development of more effective template-directed strategies that can systematically target any aromatic C−H bond without the need for covalent anchoring. Adding an extra dimension to this challenge is the vast gap that remains in the selective aliphatic C−H functionalization repertoire. The substrate's innate flexibility, the strength of the target C−H bond and the challenging coupling process demand an even greater consideration of these design parameters in order to effectively architect its selective functionalization. These formidable challenges render the field of site-selective C−H functionalization an ever-fertile environment for chemical innovation. Building on the already venerable repertoire of selective remote C−H transformations illustrated in this perspective, one can hope that the vision of molecular editing can be realized in the not-too-distant future: a future where chemists, like molecular carpenters, have all the necessary tools at their disposal to freely and selectively modify a target structure at any site, in any order.

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Notes

The authors declare no competing financial interest.

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