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Palladium(II)-Catalyzed Remote *meta*-C−H Functionalization of Aromatic Tertiary Amines

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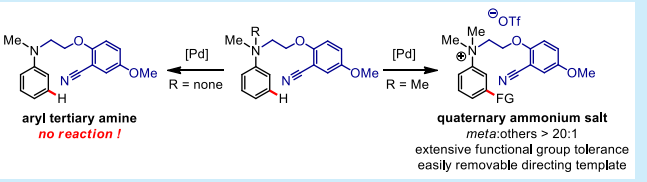
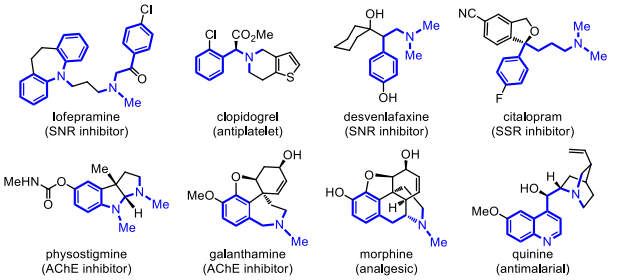
Supporting Information

ABSTRACT: Pd(II)-catalyzed remote C−H olefination of aromatic tertiary amines was achieved with high *meta* selectivity. With the assistance of an elaborated template, C−H functionalization of unreactive aryl tertiary amines, hindered by the p−π conjugation between the lone-pair electrons of the nitrogen atom and the phenyl ring, was realized with high *meta* regioselectivity via a quaternary ammonium salt assembly. The results demonstrate that apart from the distance and geometry of the template, the conformation of the arene substrate also plays a crucial role in the templated-assisted remote C−H functionalization.



As a key pharmacophore core, aryl tertiary amines are omnipresent in chemotherapeutic pharmaceuticals and naturally occurring alkaloids, which are commonly associated with significant pharmacological properties (Scheme 1). Direct

Scheme 1. Typical Pharmaceuticals Incorporating an Aryl Tertiary Amine Moiety



and site-selective transformation of the C−H bonds in this class of compounds will present new options for the retrosynthetic disconnection of natural products, late-stage modifications, and postsynthetic diversification of biologically significant pharmaceuticals. Aryl tertiary amines, e.g., *N*,*N*-dialkylaniline, are typically functionalized at the *ortho* and *para* positions via well-known electrophilic aromatic substitution (S_EAr) reactions.[1] Meanwhile, *ortho*-selective C−H functionalization of aryl tertiary amines could also proceed via directed *ortho* metalation (DoM) reactions[2] by means of the complex-induced proximity effect with organolithium reagents or via transition-metal-catalyzed *ortho*-C−H functionalization with the dialkylamino group as a directing group.[3] Relatively, catalytic *meta*-selective C−H functionalization[4] of aryl tertiary amines is greatly limited by their intrinsic electron biases.[5] Through the use of an elaborated template[6] covalently bound to the substrates, transition-metal-catalyzed *meta*-C−H functionalizations of aryl secondary amines have been achieved.[7,8] However, because they are devoid of an additional modified site, remote *meta*-C−H functionalization of aryl tertiary amines, especially for long-chain aryl amines, is yet to be explored.

In light of the extreme biological significance of aryl tertiary amine derivatives, we embarked on the development of *meta*-C−H functionalization for this class of compounds. Initially, in our attempts to investigate the intriguing possibility of template-directed *meta*-C−H functionalization, we encountered the following challenges: (1) the necessity to install a directing template via covalent binding to the substrate, (2) elaboration of a directing template to overcome the intrinsic *ortho*/*para* reactivity, and (3) facilitation of the removal of the template. During our recent work on palladium-catalyzed remote *meta*-C−H olefination of long-chain arene-tethered alcohols,[9] we observed unsuccessful C−H activation of aryl tertiary amines (Figure 1a), probably attributable to the presence of the lone-pair electrons on the nitrogen atom. To address this issue, we envisioned that installing the directing group on aryl tertiary amine via formation of a quaternary ammonium salt might give rise to a decreased electron-donating ability of the nitrogen atom (Figure 1b), thereby alleviating the electronic biases in the aryl ring. Nonetheless, another question arose therefrom: highly electron-deficient arene induced by the cationic quaternary ammonium salt is arguably resistant toward palladation, which entails a conformation-favored template to enable the *meta*-selective

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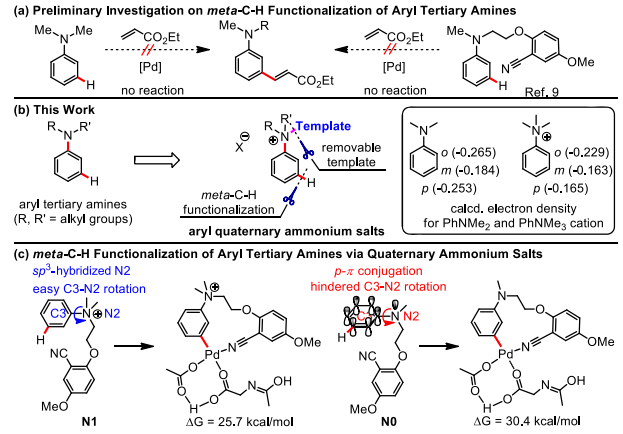
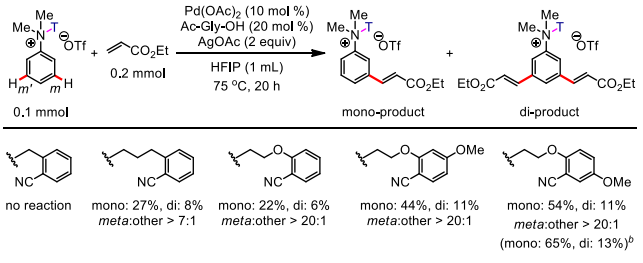


Figure 1. Directed *meta*-C−H functionalization of aryl tertiary amines.

C−H functionalization. Such challenges were overcome, and herein we disclose an approach for *meta*-C−H olefination of aryl tertiary amines using a template attached to the nitrogen atom via a quaternary ammonium salt linkage. Apart from *N*,*N*-dialkylanilines, the protocol is also compatible with long-chain aryl tertiary amines (vide infra). Importantly, the template can be readily accessed in a two-step sequence (see the Supporting Information for details) and selectively removed from the *meta*-C−H-functionalized products under mild conditions.

At the outset, to install a directing group on the substrates, we investigated various alkylation reagents, including alkyl halides, mesylates, tosylates, and triflates, for their ability to form a quaternary ammonium salts with *N*,*N*-dimethylaniline. Alkyl triflates proved to be the best choice. Therefore, nitrile-based templates with different chain lenghths and substitutions were successfully attached to *N*,*N*-dimethylaniline (Scheme 2),

Scheme 2. Development of a Template for *meta*-C−H Functionalization of Aromatic Tertiary Amines[a]

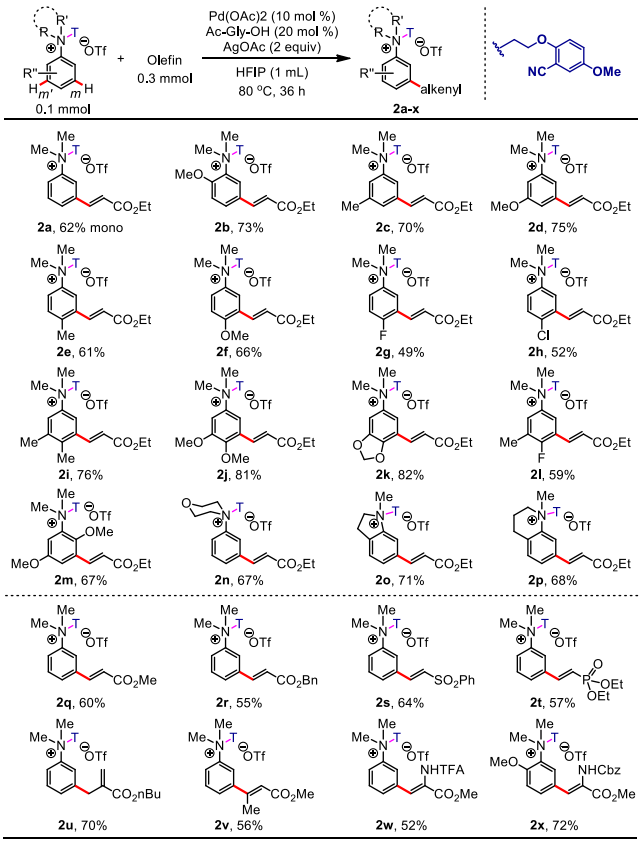


[a]Yield and selectivity determined by ^{1}H NMR analysis of the crude products. [b]Ethyl acrylate (0.3 mmol), 80 °C, 36 h.

affording the corresponding triflate salts in excellent yields. Following the previous reports,[8,9] the triflate salts obtained were subsequently subjected to a palladium-catalyzed C−H olefination reaction with ethyl acrylate. It was shown that both the chain linkage and electron density in the phenyl ring revealed a significant influence on the reactivity of directing *meta*-C−H activation in the resulting quaternary ammonium salts. The salt derived from *o*-cyano-4-methoxyphenoxyethyl triflate successfully delivered the olefinated products in 65% overall yield (mono, 54%; di, 11%) with exclusive regioselectivity (*meta*:others > 20:1). Further optimization of the reaction parameters (3 equiv of olefin, 80 °C, reaction time of 36 h) improved the yield to 78% (mono, 65%; di, 13%). Notably, the counteranion also plays an important role in the C−H olefintion reaction. In the presence of Br^- or I^- anion, no olefinated products were observed for this reaction.

Having identified the optimal template, we then examined the scope of this *meta*-selective C−H olefination reaction (Scheme 3). With the assistance of the template, different

Scheme 3. *meta*-C−H Olefination Reaction of Aryl Tertiary Amines via Quaternary Ammonium Salts[a]



[a]Isolated yields are shown. The regioselectivity was determined to be *meta*:others > 20:1 by ^{1}H NMR analysis using CH_2Br_2 as an internal standard.

ortho-, *meta*-, and *para*-substituted *N*,*N*-dimethylaniline-derived quaternary ammonium salts (**2b**−**h**) successfully delivered the desired C−H olefination products with exclusive *meta* selectivity (generally *meta*:others > 20:1). In addition to alkyl and alkoxyl groups, fluoro and chloro atoms (**2g** and **2h**) are also compatible with the protocol but give lower yields. Substrates incorporating two groups in different substitution patterns are well-tolerated (**2i**−**m**), affording the *meta*-olefinated products in good yields. Commonly, C−H olefination of substrates bearing electron-donating groups provide the olefinated products in higher yields. Notably, the protocol is also compatible with quaternary ammonium salts derived from cyclic tertiary amines (**2o** and **2p**), moieties widely existing in natural indole and quinoline alkaloids. In addition, the scope of olefin partners were also surveyed. Various *α*,*β*-unsaturated acrylates, sulfone, and phosphonate were reactive, affording the *meta*-olefinated products in good yields (**2q**−**t**). Under the reaction conditions, *α*- or *β*-substituted olefins also proved to be compatible substrates (**2u** and **2v**). Interestingly, C−H olefination with 2-

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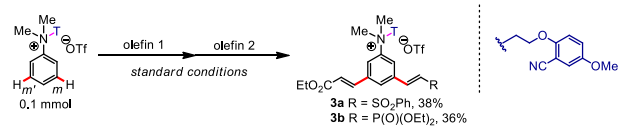
amidoacrylates provided the desired *meta*-substituted products successfully (**2w** and **2x**), making it possible to synthesize unnatural phenylalanines from aryl tertiary amines.

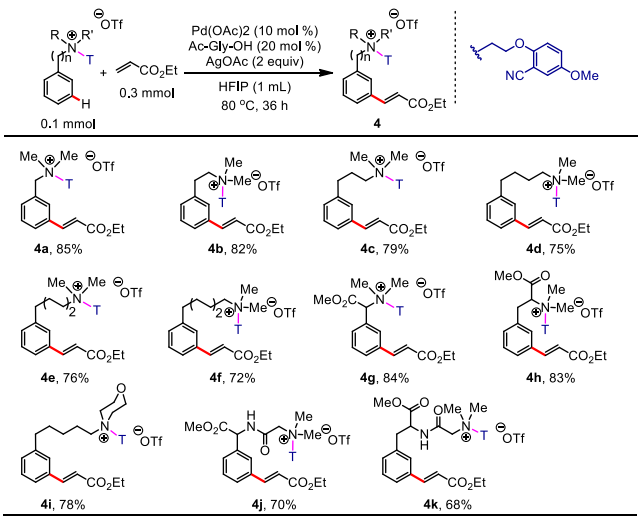
The presence of an acrylate group in the aryl quaternary ammonium salts further increases the steric congestion and electron-deficient property of the phenyl ring, and therefore, sequential diolefination of the remaining *meta* position significantly demonstrated the robust potential of the directing template (Scheme 4). More importantly, the template-assisted

Scheme 4. Template-Directed Sequential *meta,meta′*-Diolefination of Aryl Tertiary Amine



meta-C−H functionalization of quaternary ammonium salts is also applicable to widespread long-chain arene tertiary amines.[9,10] As shown in Scheme 5, *meta*-selective C−H

Scheme 5. *meta*-C−H Olefination of Distal Arene-Tethered Aryl Tertiary Amines via Quaternary Ammonium Salts[a]

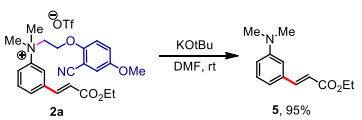


[a]Isolated yields are shown. The regioselectivity was determined to be *meta*:others > 20:1 by ^{1}H NMR analysis using CH_2Br_2 as an internal standard.

olefination of a variety of quaternary ammonium salts derived from distal arene-tethered tertiary amines, including amino acids (**4g** and **4h**) and dipeptides (**4j** and **4k**), proceeded smoothly to yield the desired olefination products.

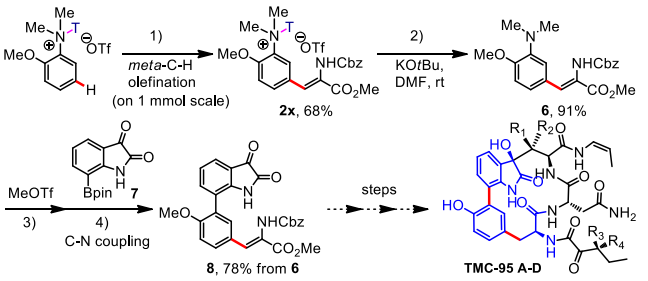
The 2-cyanophenoxyethyl directing group is easily removed from the corresponding quaternary ammonium salts via a Hofmann elimination[11] mediated by a base (e.g., KO*t*Bu) under mild conditions to produce the *meta*-substituted tertiary amines **5** (Scheme 6). In addition, the template-directed *meta*-

Scheme 6. Removal of the Template



C−H functionalization strategy also proved to be applicable to the synthesis of key building blocks of natural products (Scheme 7). Although direct Ni-catalyzed C−N coupling of

Scheme 7. Application to the Synthesis of Natural Products[a]



[a]For conditions, see the Supporting Information.

quaternary ammonium salt **2x** with arylboronic acid ester **7** suffered from removal of the directing group to give compound **6**, the key building block **8** for the natural antibiotic TMC-95[12] was easily accessed from 2-methoxy-*N*,*N*-dimethylaniline via a four-step sequence involving template-directed *meta*-C−H olefination, removal of the template, and C−N cross-coupling of the aryl trimethyl quaternary ammonium salt.[13] The synthetic strategy allows for easy modification of the biaryl unit and amino acid residue, facilitating the structure−activity relationship (SAR) study for this family of natural products.

To unravel the contrary reactivities of aryl tertiary amine **N0** and the corresponding aryl quaternary ammonium salt **N1** (Figure 1c) as well as the origin of the regioselectivity of the C−H activation process for **N1**, we computed the Gibbs free energies of the C−H activation steps and subsequent formation of intermediates **2-N1**-*m*, **2-N1**-*p*, and **2-N1**-*o* in the *meta*-, *para*-, and *ortho*-position pathways (Figure S1). The free energy of **2-N1**-*m* is lower than those of **2-N1**-*p* and **2-N1**-*o* by 2.7 and 4.0 kcal/mol, respectively, indicating that the *meta*-C−H activation product should be the major product, which is quite consistent with our experimental results (Figure 2). The exclusive *meta* selectivity is probably attributable to the

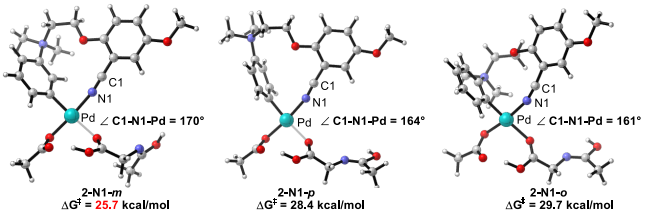


Figure 2. Optimized structures and Gibbs free energies of the intermediates **2-N1**-*m*, **2-N1**-*p*, and **2-N1**-*o*.

favored binding angle of the nitrile group to Pd in **2-N1**-*m* (∠C1−N1−Pd = 170°), which is close to the optimum nitrile ligand binding angle of 180°, while this angle is distorted to 164° in **2-N1**-*p* and 161° in **2-N1**-*o*.

The energy profile of the Pd(II)-catalyzed *meta*-C−H functionalization of quaternary ammonium salt **N1** is shown in Figure 3. MPAA-assisted C−H activation[14] via transition state **TS1-N1**-*m* requires an activation free energy of 25.7 kcal/mol to afford the intermediate **1-N1**-*m*. Notably, the intermediate **2-N1**-*m* has the same energy as the transition

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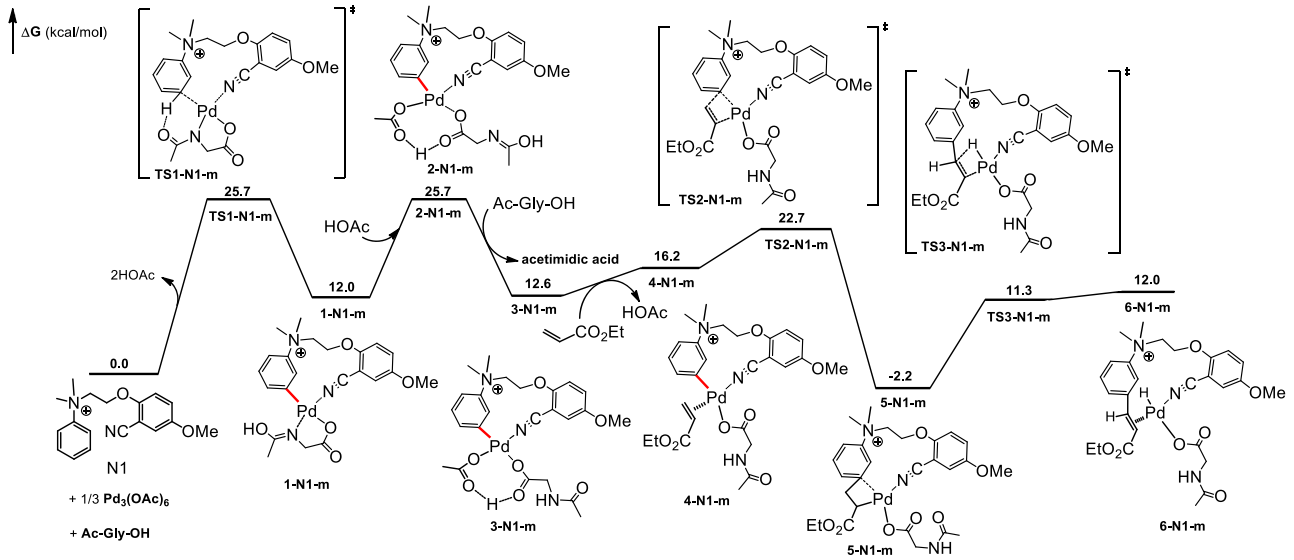

Figure 3. Energy profile for the Pd(II)-catalyzed reaction of quaternary ammonium salt **N1** with ethyl acrylate.

state **TS1-N1-*m***, implying that **2-N1-*m*** may be an active species. Following ligand exchange between the acetimidic acid and another MPAA, the proton of MPAA is simultaneously transferred to the acetate group to form **3-N1-*m***. Subsequently, acetic acid in **3-N1-*m*** leaves from the Pd center to vacate a coordination site for the migratory insertion of ethyl acrylate to afford intermediate **5-N1-*m***, followed by β-H elimination via transition state **TS3-N1-*m*** to generate the product complex **6-N1-*m***. Both ethyl acrylate insertion and β-H elimination are facile and have lower energy barriers (10.1 and 13.5 kcal/mol, respectively) than the C−H activation step. Reductive elimination of the resulting Pd(II) hydride **6-N1-*m*** affords the Pd(0) species and releases the C−H functionalization product. Finally, oxidation of the Pd(0) species to the active Pd(II) catalyst is enabled by silver acetate.

In sharp contrast, for aryl tertiary amine **N0** in Figure 1c, the rate-determining species **TS1-N0-*m***, **2-N0-*o***, and **2-N0-*p*** have much higher free energies (31.4, 31.3, and 34.9 kcal/mol, respectively) than the rate-determining **2-N1-*m*** in the *meta*-C−H activation pathway of quaternary ammonium salt **N1** (Figure S7), implying that the three C−H activation pathways of tertiary amine **N0** are disfavored. On the basis of the observation that the presence of an *N*-alkyl-substituted morpholine group did not poison the Pd catalyst under the same reaction conditions,[9] to a large extent such an opposite reactivity can be attributed to the intrinsic conformation biases of the tertiary amine and quaternary ammonium salt (Figures S2 and S8). The stabilizing p−π conjugation between the lone-pair electrons on the N atom of tertiary amine **N0** and the phenyl ring makes the palladacycles in **TS1-N0-*m***, **2-N0-*o***, and **2-N0-*p*** difficult to assemble (Figure 1c).

In summary, we have developed a versatile template approach for Pd(II)-catalyzed *meta*-selective C−H activation of aryl tertiary amines. With the assistance of an elaborated template, C−H functionalization of unreactive aryl tertiary amines, stabilized by the p−π conjugation between the lone-pair electrons of the nitrogen atom and the phenyl ring, are realized with exclusive *meta* selectivity via a quaternary ammonium salt assembly. The significantly different reactivities of the aryl tertiary amines and quaternary ammonium salts suggests that apart from the distance and geometry of the template, a compatible conformation of the arene substrate is also essential for the template-assisted remote C−H functionalization reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00499.

Experimental procedures, characterization data, NMR spectra for new compounds, and computational details (PDF)

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Notes

The authors declare no competing financial interest.

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