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Conformation-Induced Remote *meta*-C–H Activation of Amines

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Abstract

Achieving site selectivity in C–H functionalization is a long-standing challenge in organic synthesis. The small differences in intrinsic reactivity of C–H bonds in a given organic molecule often lead to poor discrimination by a catalyst. One solution to this problem is to distinguish C–H bonds based on their location with respect to a particular functional group. In this context, the activation of C–H bonds 5 or 6 bonds away from a functional group via cyclometalation has been extensively studied.^{1–13} However, directed activation of C–H bonds that are distal (>6 bonds away) from functional groups has remained difficult, especially when the target C–H bonds are geometrically inaccessible through directed metalation due to the ring strain encountered in cyclometalation.^{14,15} Herein we report a recyclable template that directs the olefination and acetoxylation of distal *meta*-C–H bonds (as far as 11 bonds away) of anilines and benzylic amines. Remarkably, this template is able to direct the *meta*-selective C–H functionalization of bicyclic heterocycles *via* highly strained tricyclic cyclophane-like palladated intermediates. X-ray and NMR studies reveal that the conformational biases induced by a single fluorine substitution in the template can be enhanced by a ligand to switch from *ortho*- to *meta*-selectivity.

The selective functionalization of inert C–H bonds at different sites of organic molecules provides an opportunity for the introduction of diverse structural modifications and the development of novel retrosynthetic disconnections. However, the widespread application of C–H functionalization in organic synthesis is hampered by a lack of catalysts, reagents, and methodologies that enable the site-selective functionalization of C–H bonds, which often have very subtle differences in intrinsic reactivity. Our group has broadly focused on the development of metal-catalyzed C–H activation reactions that are directed by weakly coordinating functional groups.¹ In analogy to the principles of proximity-driven metalation,² this type of methodology enables the selective functionalization of C–H bonds that are 5–6 bonds away from the directing atom through cyclometalation.^{3–13} While this approach has enabled the discovery of numerous transformations over the past decade, the

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Author Contributions R.-Y.T. and G. L. performed the experiments and developed the reactions. R.-Y.T. and J.-Q.Y. designed the templates. J.-Q.Y. conceived this concept and prepared this manuscript with feedback from R.-Y.T. and G. L.

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functionalization of C–H bonds that are located farther away from the coordinating functional group remains a largely unsolved problem in organic synthesis, especially when their locations do not permit cyclometalation due to geometric strain.^{14–18}

Recently we developed an end-on coordinating nitrile-based template that is able to direct the remote Pd(II)-catalyzed *meta*-selective C–H functionalizations.^{14,15} This discovery led us to explore three key questions: (a) whether this new end-on template approach can be applied to other substrate classes, (b) whether other types of transformations using different catalytic manifolds can be achieved using end-on templates, and (c) whether there are critical and general underlying principles for the design of an effective template to direct remote C–H activation. In this context, we recognized that the selective activation of C–H bonds at C7 of tetrahydroquinolines is a conceptually intriguing and synthetically important challenge. A novel template will be required to accommodate a highly strained intermediate with a tricyclic cyclophane structure (Fig. 1).

Herein, we report the rational design of a nitrile-containing template that directs C7-selective C–H activation of tetrahydroquinolines (Fig. 1). By systematically modifying the structure of the template, we identified the template conformation as a critical factor in favoring remote *meta*- or proximate *ortho*-selectivity (Fig. 1B). Remarkably, by tuning the properties of the Pd(II) catalyst through use of *N*-acetyl-glycine (Ac-Gly-OH) as a ligand, the pre-existing conformational bias in the template can be further amplified to achieve remote *meta*-C–H olefination in excellent yield and with high levels of site selectivity (Fig. 1C). This optimized template is broadly applicable to the remote C–H activation of 2-phenylpyrrolidines, 2-phenylpiperidines, and other aniline-type substrates, despite the intrinsic electronic biases in these substrates that favor *ortho*-functionalization (Fig. 1D). In addition to *meta*-C–H olefination via a Pd(II)/Pd(0) redox cycle, we were also able to demonstrate *meta*-C–H acetoxylation via Pd(II)/Pd(IV) catalysis using this template. This template can be easily installed and later recycled, similar to chiral auxiliaries that are widely used in organic synthesis, such as the venerable Evans oxazolidinone. This work paves the way for practical applications of remote C–H activation through template control.

Results and discussion

In 2012 our group disclosed a procedure for the *meta*-selective olefination of hydrocinnamic acids using a novel end-on 2-aminobenzonitrile template.¹⁴ Crucial for the *meta*-selectivity, the directing nitrile group is in extended conjugation with the carbonyl moiety of the substrate, which positions the nitrile group in close proximity to and coplanar with the target *meta*-C–H bond. However, in translating this insight to the *meta*-selective olefination of tetrahydroquinolines, we needed to design an entirely novel end-on template and we faced several significant challenges in determining the optimal structural design. First, as shown in Figure 1, the hypothetical palladation intermediate would involve a highly strained intermediate with a tricyclic cyclophane structure. Second, although a simple amide linkage is desirable for practical attachment of the template, we were cognizant that the amide group could potentially favor the activation of the *ortho*-(C8) position, an established mode of reactivity for anilide-type substrates.¹⁹ Moreover, amine substituents are well-known *ortho/para* directors in electrophilic aromatic substitution reactions, including electrophilic

palladation. Third, in order to avoid the pitfall of over-engineering, we hoped to develop a simple amide template with a sp^3 hybridized backbone without having to build in an extended conjugation. We recognized such a template could lead our substrates to exist in multiple inter-converting conformations, each with a low equilibrium population. This would translate into a high entropic barrier for formation of the highly organized transition state required for cyclopalladation. As such we aimed to acquire an improved understanding of how the conformation of non-constrained atoms in a template can be manipulated to favor remote C–H activation. In addition, we hoped to develop a catalyst to recognize and harness subtle conformational biases and amplify pre-existing template-induced preferences for *meta*-selectivity.

To begin our investigation, we attached the simple nitrile templates **T**₁–**T**₃ to tetrahydroquinoline and tested these substrates in a model reaction, the Pd(II)-catalyzed C–H olefination (Fig. 2a, 2b). While the reaction of **1** did not provide any olefinated products, **2** and **3** afforded intractable mixtures of positional isomers. The addition of our previously identified ligand, Ac-Gly-OH, did not improve the level of selectivity with these templates. We attributed the poor site selectivity to either a lack of conformational rigidity in the template backbones (**T**₁, **T**₂) or the template being too short to reach the target C–H bond (**T**₃). We subsequently explored the α -hydroxy template structure (**T**₄, **T**₅ and **T**₆) and observed an encouraging trend favoring C7 selectivity in C–H olefination (Fig. 2b). While exclusive C8-olefination was observed using template **T**₄ (substrate **4**), the use of template **T**₅ (substrate **5**) and **T**₆ (substrate **6a**) afforded C7-olefinated product in 11% and 20% selectivity, respectively. Although the level of *meta*-selectivity was still poor with these templates, the observation that a single fluorine substituent **T**₆ nearly doubles the *meta*-selectivity prompted us to investigate the origin of this phenomenon.

As fluorine substituents can lead to dramatic changes in molecular conformation,^{20,21} we studied the conformations of **4**–**6** in the solid state and in solution. X-ray crystal structures of **4** and **5** showed that the carbonyl group is perfectly oriented to perform *ortho*-C–H activation. However, in the X-ray crystal structure of **6** the carbonyl group is oriented away from C7, which presumably makes it better-suited for the nitrile moiety to approach the *meta*-C–H bond (C8). NOE studies showed that a similar conformational trend is present in solution (see Supplementary Information). Steric hindrance from the *gem*-dimethyl substituents in **4** likely raises the activation energy for amide N–C bond rotation, leading to highly restricted interconversion between the pro-*ortho* (ground state) and pro-*meta* conformations. In contrast the amide C–N bond in **5** can more freely rotate, leading to some of the *meta*-C–H olefination product. Importantly, introduction of the α -fluorine substitution in **6** leads to a conformational switch wherein the carbonyl group is directed away from the *ortho*-C–H bond. Increased level of this conformation seems to improve the rate of *meta*-C–H activation; however a low barrier for interconversion between the pro-*meta* and pro-*ortho* conformers still results in substantial levels of *ortho*-C–H activation.

We reasoned that the *meta*-selectivity of **6** could be amplified by the use of a bulkier and more electron-rich catalyst since the C7 position is less sterically hindered and more electron-poor than C8.²² In fact, we were delighted to find that the use of Ac-Gly-OH as a ligand in conjunction with template **T**₆ improves the level of *meta*-selectivity from 20% to

92% (Fig. 2b). After deprotection the *meta*-olefinated product **7a** was isolated in 75% yield. Under these ligand-enhanced reaction conditions the *meta*-selectivity of substrate **5** is also dramatically improved (11% to 84%). In contrast, olefination of substrate **4** with Ac-Gly-OH as a ligand provides the olefinated product with 91% *ortho*-selectivity (92% yield). These results suggest that, while the Ac-Gly-OH ligand can promote *meta*-selectivity, the appropriate conformation of the template is a prerequisite for achieving high levels of *meta*-selectivity. We have also tested the analogue of **T6** that contains α -difluoro substituents attempting to further improve the *meta*-selectivity. Similar yield and *meta*-selectivity to that of **T6** was obtained indicating that electronic effect does not play a major role in controlling *meta*-selectivity (see Supplementary Information).

Having established an optimal system for *meta*-selective C–H olefination, we proceeded to investigate the scope of tetrahydroquinolines (Fig. 2c). Substitution at C2 improves the *meta*-selectivity (**7b**, 97:3). Substitution at the C5 and C6 positions were well tolerated (**7c–7f**). C8 substitution decreases the level of *meta*-selectivity to (78:22), presumably due to the steric hindrance of the C7 position (**7g**). Dihydrobenzoxazine **6h** was also selectively olefinated at the *meta*-position to give the desired product in 71% isolated yield (**7h**). It is worth-noting that the C7 positions of these heterocyclic skeletons are very difficult to functionalize and this methodology could enable the synthesis of a new subclass of these medically-active heterocycles.

We subsequently explored the use of our template system in the *meta*-selective olefination of anilines. de Vries and van Leeuwen reported the directed *ortho*-C–H olefination of acetanilides, thereby demonstrating the high reactivity of the *ortho*-position of these substrates towards palladation.¹⁹ A *meta*-selective C–H olefination of anilines would offer a complementary retrosynthetic disconnection for the synthesis of substituted anilines. Thus, aniline was attached to the optimized template **T6** and subjected to the established olefination conditions (Fig. 3). A mixture of mono- and di-olefinated products **9a_{mono}** and **9a_{di}** is obtained in 88% combined yield with 99% *meta*-selectivity, suggesting that this template can successfully override an electronic bias towards *ortho*-palladation. A variety of electron-rich and electron-poor *meta*-substituted anilines give the mono-olefinated products in good to high yields with the *meta*-selectivity ranging from 94–99% (**9b–9g**). *ortho*-Substituted anilines are selectively olefinated at the less hindered position to give mono-olefinated products (**9h_{mono}** and **9i_{mono}**) accompanied by small amounts of the di-olefinated byproducts. Despite the steric hindrance, excellent *meta*-selectivity is also obtained for a number of *para*-substituted anilines, albeit with varied mono/di selectivity (**9j–9o**). Poly-substituted anilines were also smoothly olefinated at the remaining *meta*-positions to afford anilines **9p–9r** containing complex 1,2,3,5-substitution patterns. *Meta*-olefination of **8d** was also carried out using 5 mol% Pd(OAc)₂ to give the desired product **9d** in 60% isolated yield (see Supplementary Information). The replacement of the *N*-methyl group by a readily removable benzyl-type protecting group was also tolerated, thus improving the utility of this reaction (**9s** and **9t**). The hydrogenolysis of the benzyl-type protecting group also reduced the installed olefin unit to corresponding alkyl (see Supplementary Information). Finally, a range of olefin coupling partners, including 1,2-di-substituted olefins, were shown to be

compatible with this transformation demonstrating broader scope than the majority of directed *ortho*-C–H olefination reactions (**9b₁₋₇**).

The utility of our template-directed remote C–H activation approach in developing other types of C–C and C–heteroatom bond-forming reactions via different catalytic manifolds remains to be demonstrated. Thus, amine substrate **8a** was subjected to various C–H oxidation reaction conditions (Fig. 4a). Notably, these transformations proceed via a Pd(II)/Pd(IV) redox chemistry as opposed to the Pd(0)/Pd(II) catalytic cycle of C–H olefination. We were delighted to find that the use of PhI(OAc)₂ oxidant⁸ affords *meta*-acetoxyated amine **10a** as the major product in 60% isolated yield. Excellent levels of *meta*-selectivity (90-98%) are obtained with various substituted anilines. A variety of *ortho*-, *meta*-, and *para*-substituents are tolerated in this transformation (**10b-10j**) although more electron-withdrawing substituents lead to a depreciation in yield (**10f**, **10g**). *meta*-Selective acetoxylation of an *ortho,meta*-disubstituted aniline was also successful (**10q**). The versatility of our newly developed methodology is further demonstrated by the *meta*-selective acetoxylation of acyclic and cyclic benzylamines (Fig. 4d). Notably, the C–H bonds that are cleaved in these in benzylamine substrates are 11 bonds away from the directing nitrogen atom, representing the longest distance involved in a directed C–H activation reported to date. *meta*-Selective acetoxylation of 2-phenylpyrrolidine **11c** and 2-phenylpiperidine **11d** are potentially powerful methodologies for accessing diverse structures of medicinally important heterocycles. The hydrolytic removal of the template also converted the acetate to hydroxyl group in one-pot (see Supplementary Information).

Preliminary mechanistic studies on the acetoxylation of aniline also revealed that conformation of templates, again, plays a decisive role in controlling the site selectivity. Control experiments showed that Ac-Gly-OH had only a minor beneficial effect on the yield of acetoxylation and a negligible influence on the site selectivity. Remarkably, we found that the levels of *meta*-selectivities of the acetoxylation of aniline were 46%, 66% and 92% respectively when templates **T₄**, **T₅** and **T₆** were used in the absence of an amino acid ligand, reflecting the intrinsic conformational biases of these templates very clearly (See Supplementary Information).

In summary, we have developed a versatile template approach to direct the remote *meta*-C–H bond activation of tetrahydroquinoline, benzoxazines, anilines, benzylamines, 2-phenylpyrrolidines and 2-phenylpiperidines, all of which are privileged architectures in drug discovery. Template **T₆** can be readily installed via acylation of the amine substrates with the commercially available 2-(2-cyanophenoxy)-2-fluoroacetic acid (Aldrich catalog number: 791369). Due to their electronic biases, these amine substrates are incompatible with other known approaches for *meta*-C–H activation.²³⁻³⁰ We demonstrate that small conformational biases can be amplified by the judicious use of an amino acid ligand to significantly enhance *meta*-selectivity, although the precise role of the α -fluoro group on the template conformation remains hypothetical at this stage.

Methods Summary

General procedure for template-directed *meta*-selective C–H olefination

A 35-mL sealed tube (with a Teflon cap) equipped with a magnetic stir bar was charged with amide substrate (0.10 mmol, 1.0 equiv.), Pd(OAc)₂ (2.3 mg, 0.01 mmol, 10 mol%), Ac-Gly-OH (2.4 mg, 0.02 mmol, 20 mol%) and AgOAc (50 mg, 0.30 mmol, 3.0 equiv.). HFIP (0.5 mL) was added to the mixture, followed by ethyl acrylate (1.2–2.0 equiv.) and finally another portion of HFIP (0.5 mL). The tube was then capped and submerged into a pre-heated 90 °C oil bath. The reaction was stirred for 24 to 48 h and cooled to room temperature. The crude reaction mixture was diluted with EtOAc (5 mL) and filtered through a short pad of Celite. The sealed tube and Celite pad were washed with an additional 20 mL of EtOAc. The filtrate was concentrated *in vacuo*, and the resulting residue was purified by preparative TLC using hexanes/EtOAc/DCM as the eluent. The positional selectivity was determined by GCMS with a flame ionization detector and by ¹H NMR analysis of the unpurified reaction mixture. Full experimental details and characterization of new compounds can be found in the Supplementary Information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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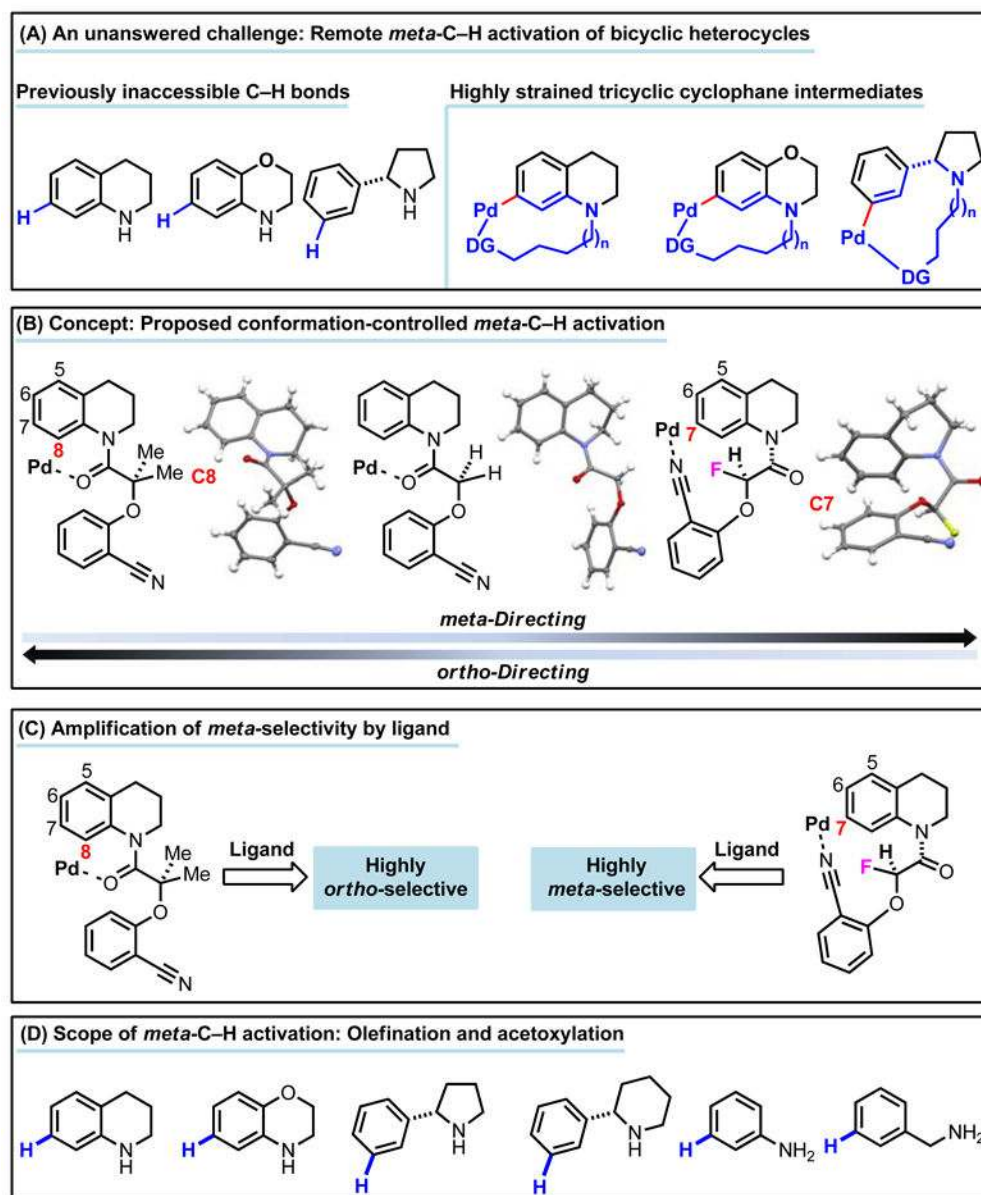


Figure 1. Design of a versatile template to direct *meta*-C–H activation

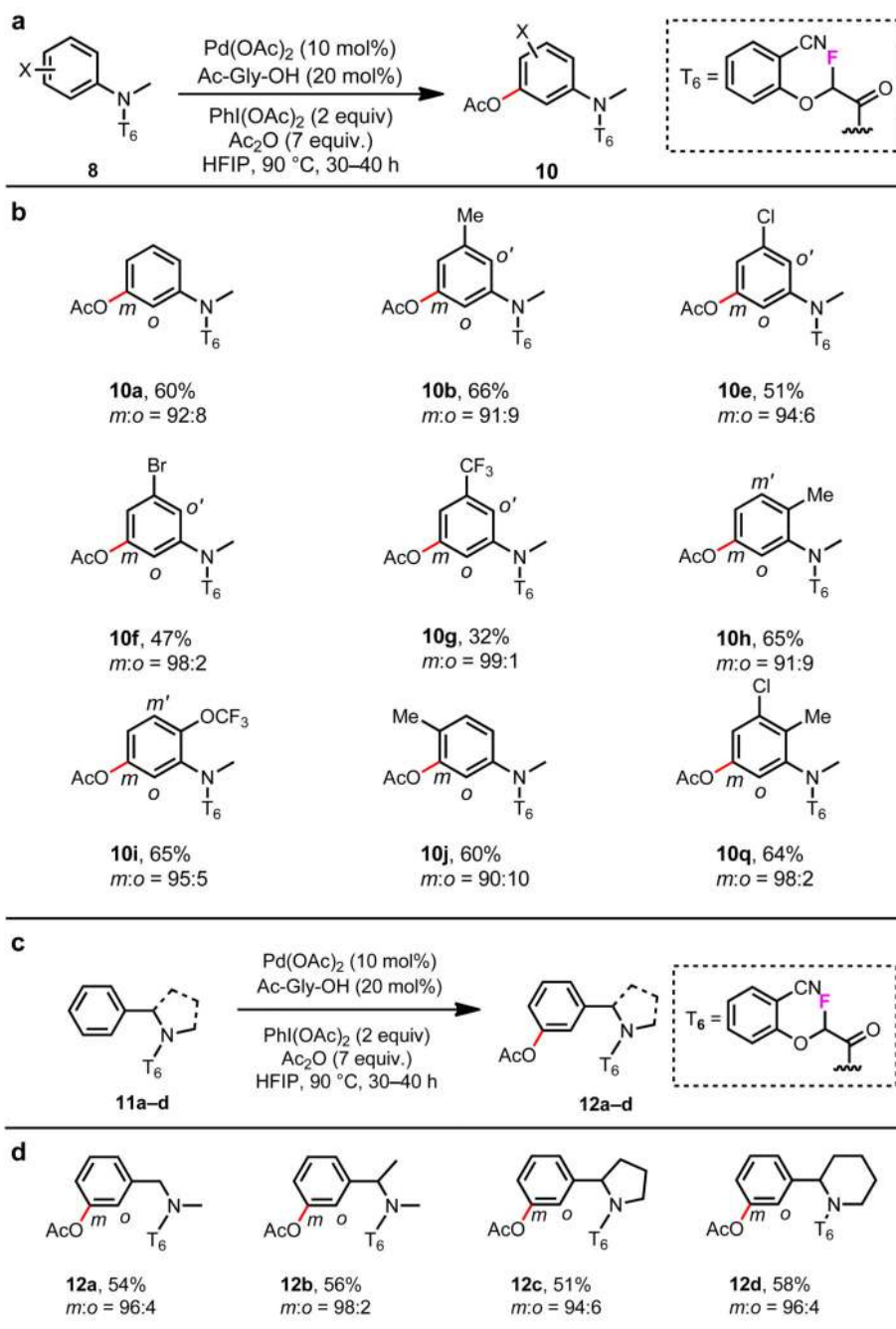


Figure 2. Development of templates to direct *meta*-C–H olefination

a) Olefination of tetrahydroquinoline derivatives; **b)** Six representative templates designed to screen the *meta*-C–H olefination; **c)** Tetrahydroquinolines with a variety of substitution patterns appended with template **T₆** (**6a–6h**) undergo facile *meta*-C–H olefination. The yields of **2** and **3** are NMR yields with CH₂Br₂ as internal standard. The selectivity is not determined due to multiple olefinated products detected. The isolated yields of other olefinated products are shown along with the selectivity (combined yields shown in **b**). See Supplementary Information for experimental details. Selectivity of the olefinated products

was determined by ^1H NMR analysis or GCMS analysis using flame ionization detector; the variance is estimated to be within 5%. HFIP = hexafluoroisopropanol.

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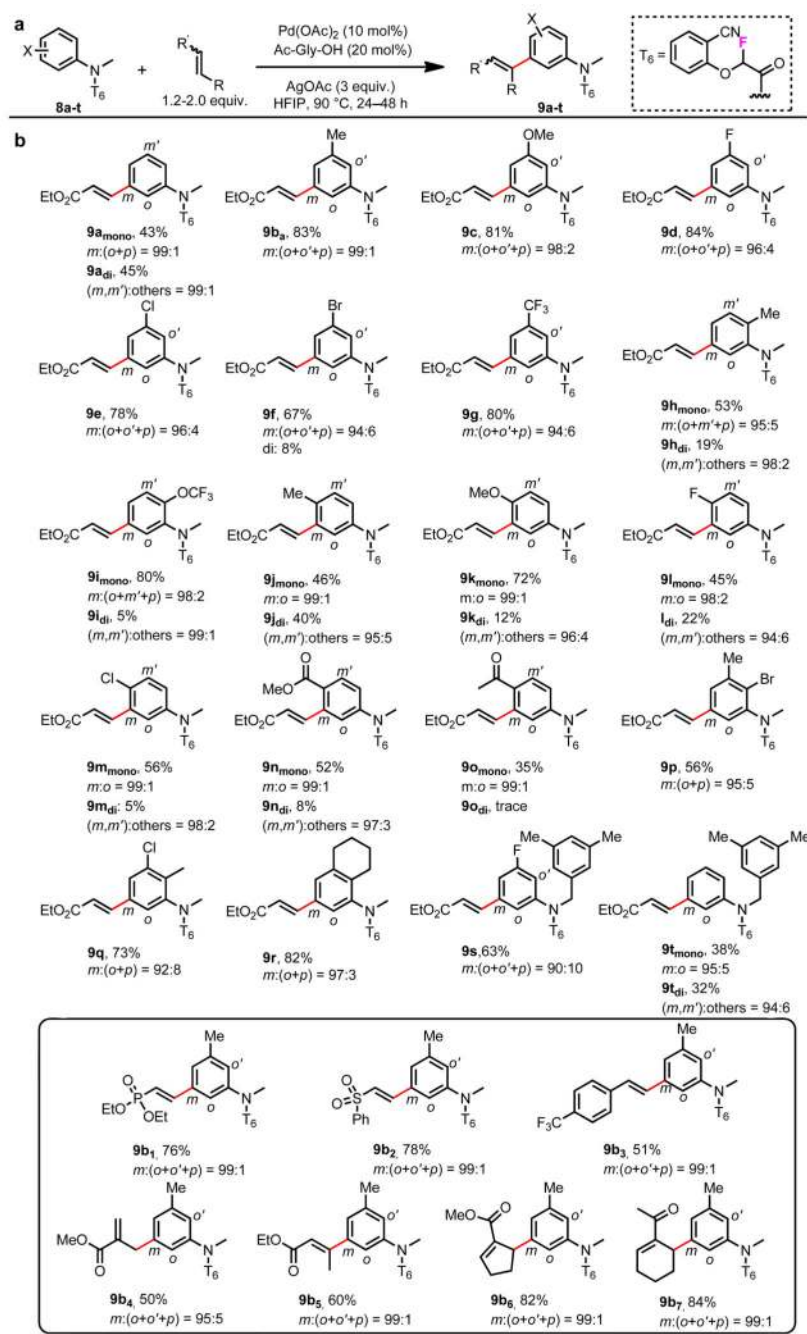


Figure 3. Template-directed remote C–H olefination of *N*-methylanilines

a) Anilines with a variety of substitution patterns were found to undergo facile *meta*-C–H olefination; **b)** In the box, electron-deficient olefins and various di- and tri-substituted olefins were compatible with this transformation. The isolated yields of the mono-olefinated product (and also the isolated yields of the di-olefinated product, when applicable) are shown along with the selectivity. See Supplementary Information for experimental details. Selectivity of the mono- and di-olefinated products was determined by ^1H NMR analysis

and GCMS analysis using a flame ionization detector; the variance is estimated to be less than 5%.

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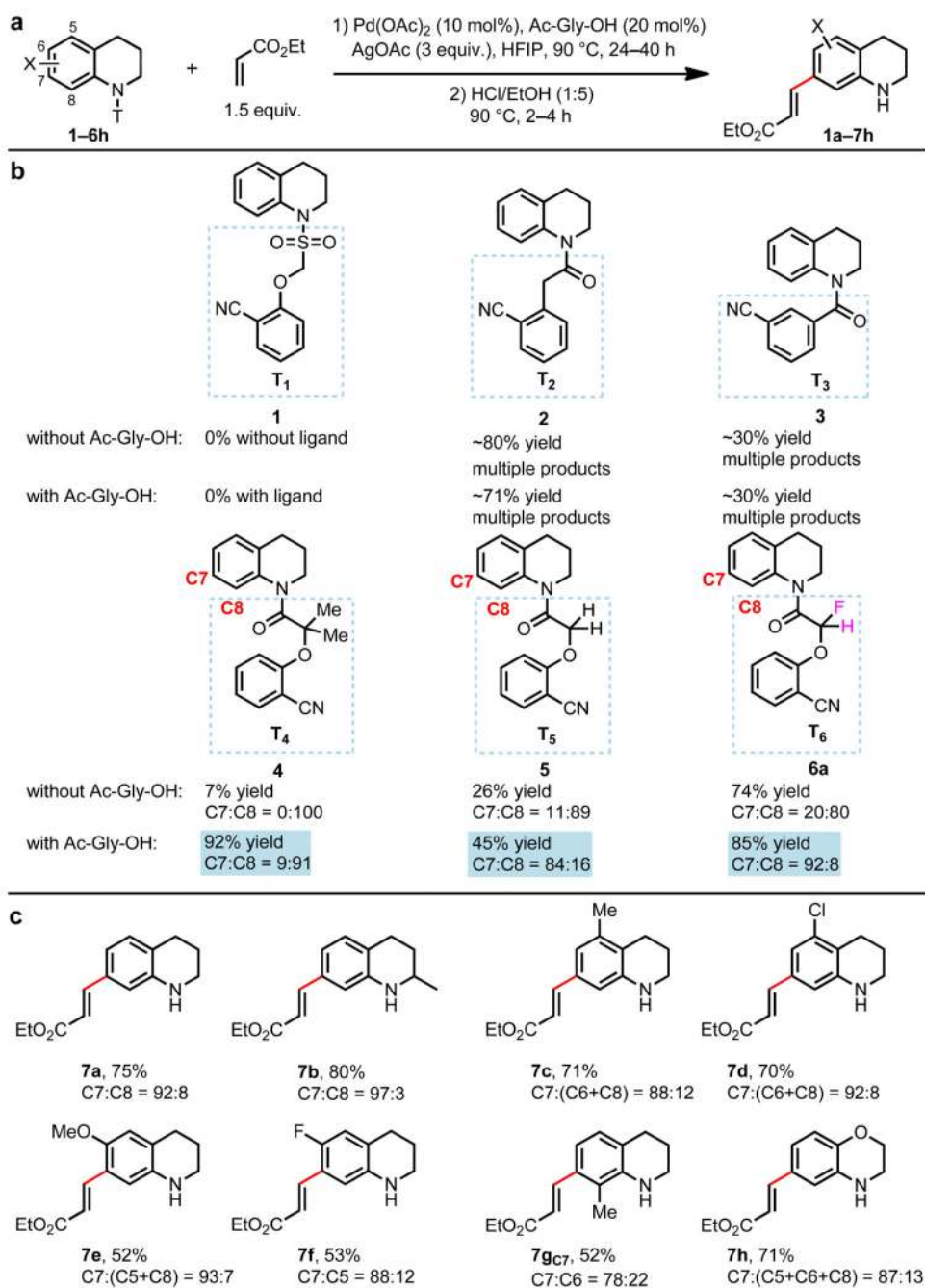


Figure 4. meta-Selective C–H acetoxylation of N-methylanilines and benzylamine derivatives

a) Anilines (**8**) with a variety of substitution patterns undergo facile *meta*-C–H acetoxylation; **b)** The isolated yield of the acetoxylation product is shown along with the selectivity; **c)** Benzylamines derivatives (**11a–d**) were found to undergo facile *meta*-C–H acetoxylation; **d)** The isolated yield of the acetoxylation product is shown along with the selectivity. See Supplementary Information for experimental details.

Selectivity of the acetoxyated products was determined by ^1H NMR analysis and GCMS analysis using a flame ionization detector; the variance is estimated to be less than 5%.

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