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Remote C–H Activation of Various *N*-Heterocycles Using a Single Template

Guoqiang Yang, Dajian Zhu, Peng Wang, Ri-Yuan Tang, and Jin-Quan Yu*

In Memory of Professor Ronald Breslow

Abstract: A single simple *ortho*-sulfonyl benzonitrile template was developed to achieve remote C–H olefination of six different classes of *N*-heterocycles. We demonstrate that, by varying precatalysts and conditions, the same template can be applied to the remote C–H activation of six structurally distinct heterocyclic scaffolds, and the site-selectivity can be predicted based on distance and geometry. Furthermore, this new development shows that template-directed remote C–H activation are possible via macrocyclopalladation processes with smaller ring sizes.

Achieving site selectivity is crucial for developing synthetically useful C–H activation reactions. In synthetic substrates or intermediates, there often exist multiple C–H bonds with similar electronic properties and steric environments, and yet functionalization of different C–H bonds could lead to completely different structures due to the distal and geometrical relationship between the newly introduced functional groups and the preexisting ones. Pre-coordination with existing functional groups has been extensively used to direct selective activation of proximal C–H bonds as exemplified by *ortho*-C–H functionalizations.[1] The importance and challenge of remote C–H functionalizations was articulated in Breslow's inspirational works.[2] However, selective functionalization of remote C–H bonds remains a significant challenge due to the difficulties for forming a macrocyclic, especially cyclophane-like pre-transition states. Non-directed *meta*-selective C–H functionalization reactions have been achieved by virtue of sterically or electronically biased properties of the arene substrates which are generally not compatible with mono-substituted arenes.[3] Several different approaches have recently been employed successfully in remote C–H activation.[4-8] Our group has developed a template-based methodology for *meta*-selective C–H activation in which the site selectivity is achieved by the precise recognition of the distance and geometry between the directing atom and the C–H bonds.[5] Since this approach uses distance and geometry as the key differentiation parameters, it is not surprising that one particular template designed for a class of substrates may not be adaptable to others. Indeed, various templates were designed for different substrates such as phenols, alcohols, indoline, and acids (Figure 1).[5] In general, these templates are only applicable to one class of substrates and are relatively large in size. Herein, we report a simple template that can direct the remote C–H olefinations of six structurally distinct *N*-heterocycles. The use of different precatalysts is crucial when applying to different substrates. Moreover, the *ortho*-sulfonyl benzonitrile template can be readily removed under mild conditions.

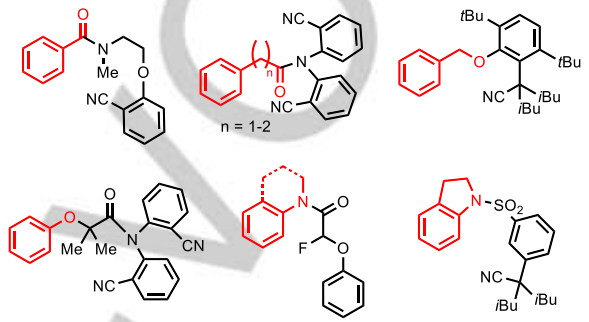
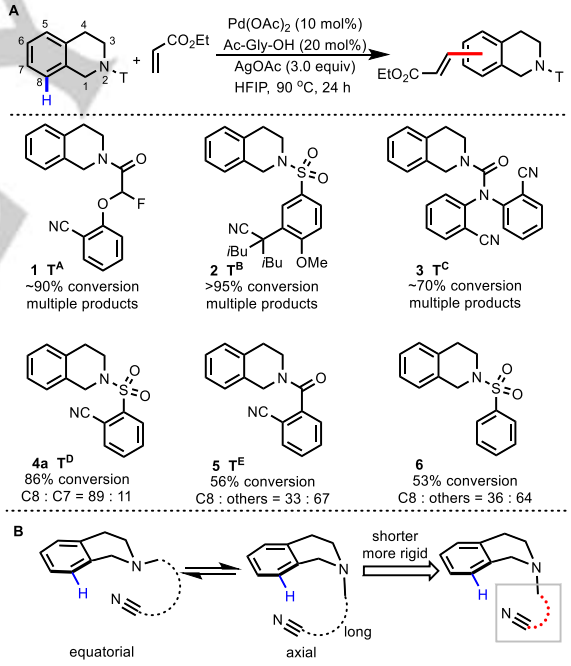


Figure 1. Representative substrate classes used for template-directed *meta*-C–H functionalization.



Scheme 1. Development of the template. Reaction conditions: substrate (0.1 mmol), ethyl acrylate (1.5 equiv), $Pd(OAc)_2$ (10 mol%), Ac-Gly-OH (20 mol%), AgOAc (3.0 equiv), HFIP (1.0 mL), 90 °C, 24 h. Conversions were determined by ^1H NMR using CH_2Br_2 as internal standard. Selectivities were determined by ^1H NMR after simple preparative TLC.

Since tetrahydroisoquinoline is an important heterocyclic skeleton of pharmaceutical and natural products, we began to develop a template for selective C8–H activation of tetrahydroisoquinoline, in which the C7 position is favored by the Friedel-Crafts reaction and electrophilic substitution (Scheme 1A).[9] Screening of our previously reported templates are either not reactive or unselective as shown in **1**–**3** (Scheme 1A). We

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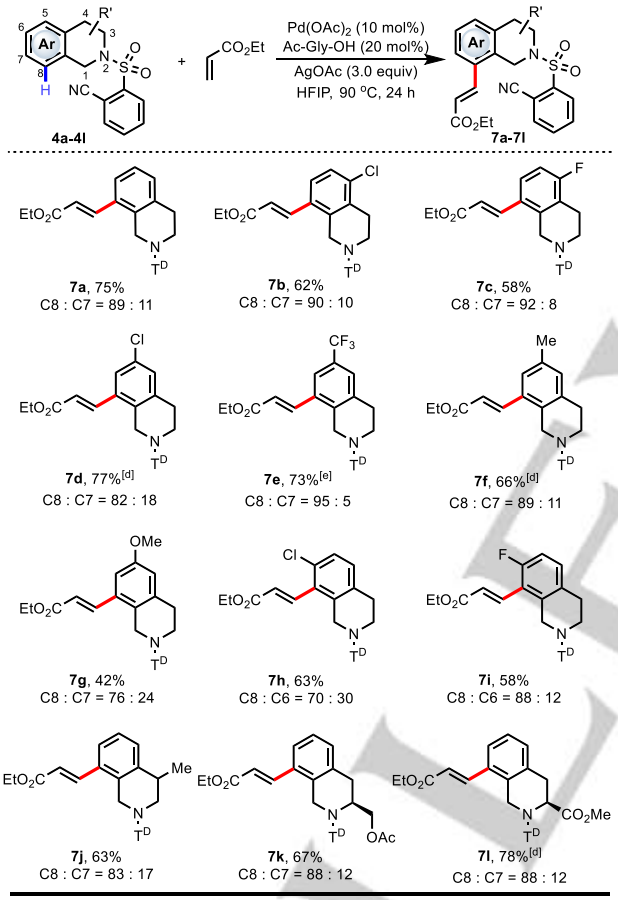
reasoned that the nitrogen in the tetrahydroisoquinoline is conformationally less rigid than that in the tetrahydroquinoline and the nitrile group could reach other C–H bonds in axial position when long template was used, hence the design of a shorter and more rigid nitrile template may be required (Scheme 1B). Therefore, a simple *ortho*-sulfonyl benzonitrile template **T^{D}** was tested. To our delight, substrate **4** bearing this template showed good reactivity and selectivity. Notably, this template is commercially available, alternatively can be readily prepared from saccharin in a single step.[10] Replacement of the sulfonyl by a carbonyl group in the template gave poor selectivity and lower reactivity (**5**, Scheme 1). The absence of the nitrile group led to loss of selectivity demonstrating the essential role of the directing template.

Table 1. Scope of tetrahydroisoquinoline substrates.[a,b,c]

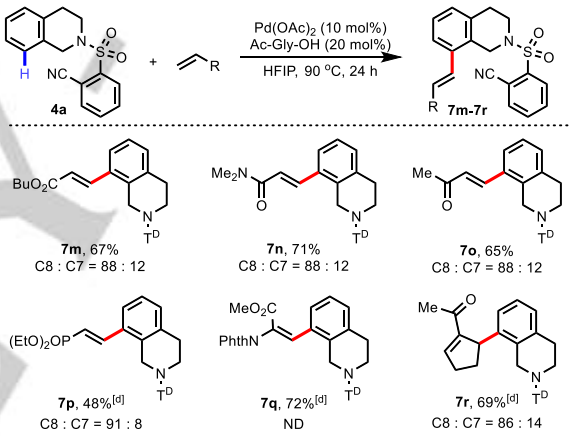


[a] Reaction conditions: **4** (0.2 mmol), ethyl acrylate (1.5 equiv), $Pd(OAc)_2$ (10 mol%), Ac-Gly-OH (20 mol%), AgOAc (3.0 equiv), HFIP (2.0 mL), 90 °C, 24 h. [b] Yield of the isolated mixture of isomers. [c] Regioselectivity was determined by ^{1}H NMR after simple preparative TLC purification for removal of di-olefinated products (<10% yield). Trace amounts of other isomers were observed in some cases (see the SI). [d] 36 h. [e] 48 h.

With the template **T^{D}** identified, we investigated the scope of the tetrahydrosioquinnoline substrate (Table 1). Electron-withdrawing groups at the C5 and C6 positions are tolerated (**7b**-**e**). Substrate **4f** bearing a weak electron-donating group Me at the C6 position showed similar results to that of **4a**. However, the presence of a methoxyl group at the C6 position likely decreases the C8-selectivity due to its known *ortho*-directing effect. Interestingly, the sterically-hindered substrates **4h** and **4i** are also compatible with this procedure, giving their corresponding substituted products, albeit poor selectivity was observed for **7h** due to steric hindrance. Substituents at C3 and C4 positions have a slight effect on the reaction outcome (**7j**-**l**). Olefination of C1-substituted tetrahydroisoquinoline, however, gave the desired product with poor selectivity (see the supporting information for details).

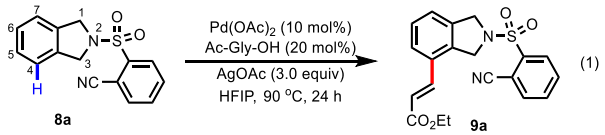
We also briefly examined the olefin scope using substrate **4a** (Table 2). Olefin coupling partners such as α,β-unsaturated esters, amides, ketones, and phosphonates afforded the corresponding C8-olefinated products in moderate to good yields and with good selectivities (**7m**-**7p**). A dehydro-α-amino acid was also tolerated to the reaction conditions (**7q**). Notably, olefination with a trisubstituted cyclic olefin coupling partner also proceeded smoothly, although the desired product was obtained with slightly lower selectivity as a result of increased steric hindrance (**7r**).

Table 2. Scope of olefin partners.[a,b,c]



[a] Conditions: as Table 1. [b] Yield of the isolated mixture of isomers. [c] Regioselectivity was determined by ^{1}H NMR after simple preparative TLC purification for removal of di-olefinated products (<10% yield). Trace amounts of other isomers were observed in some cases (see the SI). [d] 36 h. [e] ND = Not determined.

Next, we attempted to apply this template to the C4-selective olefination of isoindoline (Eq. 1). However, poor selectivity was observed under the previous conditions for the C8-selective olefination of tetrahydroisoquinoline. Interestingly, site-selectivity was significantly improved in the absence of Ac-Gly-OH ligand, although the yield was lower. Several isoindoline substrates are compatible with the new conditions (Table 3, **9b**-**d**). It has been elucidated by computational and kinetic studies that the absence of Ac-Gly-OH ligand switched a monomeric Pd pathway to Pd−Ag heterodimeric mechanism.[11] The aforementioned results show that template-directed remote C–H activation are possible via macrocyclopalladation processes with a small ring size.



with Ac-Gly-OH: 63% NMR yield, C4 : C5 = 52 : 48
without Ac-Gly-OH: 54% NMR yield, C4 : C5 = 88 : 12

To further test the generality of this template, we investigated remote selective C–H olefinations of indoline, indole and tetrahydroquinoline. We are also curious whether the site selectivity can be predicted precisely by the distance (10 or 11-membered organometallic rings) (Figure 2).

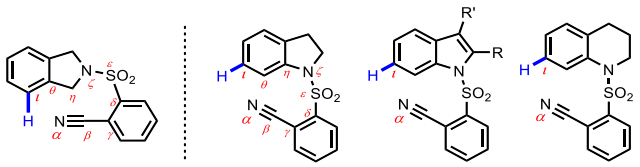
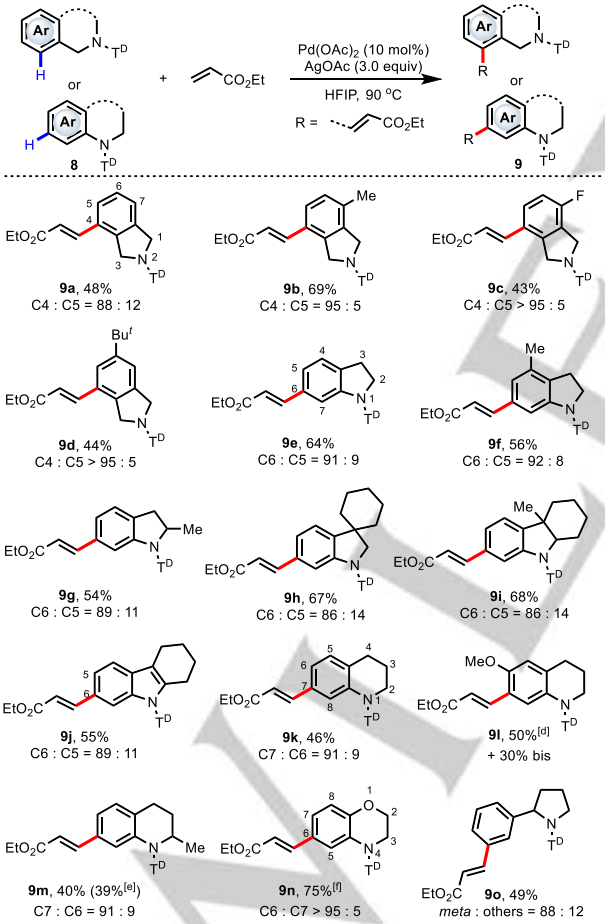


Figure 2. Distance between nitriles and C–H bonds of heterocycles.

Table 3. Scope of other *N*-heterocycle substrates.[a,b,c]

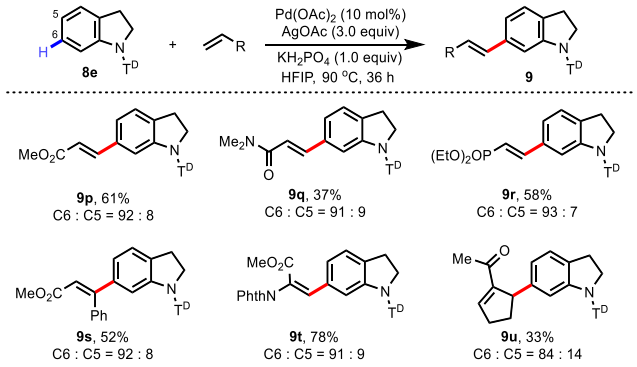


[a] Reaction conditions: **8** (0.2 mmol), ethyl acrylate (2.0 equiv), $Pd(OAc)_2$ (10 mol%), AgOAc (3.0 equiv), KH_2PO_4 (1.0 equiv) (for isoindoline substrates, without KH_2PO_4), HFIP (6.0 mL), 90 °C, 24 h. [b] Yield of the isolated mixture of isomers. [c] Regioselectivity was determined by ^{1}H NMR. [d] HFIP (2.0 mL), ethyl acrylate (4.0 equiv). 30% yield of bis-tetrahydroquinoline product (β,β-diarylation of olefin) was isolated, see the SI. [e] 0.5 gram scale. [f] HFIP (2.0 mL), ethyl acrylate (2.5 equiv).

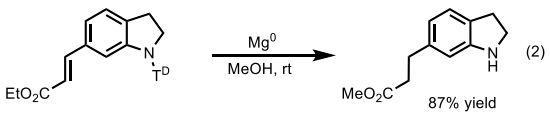
Remote C–H olefination of indoline and indole substrates gave products **9e**-**9j** with the site selectivity that is expected from the distance (Table 3). The new template $\mathbf{T^D}$ can also be applied to the remote-selective C–H olefination of tetrahydroquinolines (**9k**-**9m**). It is worth-noting that of the previous templates $\mathbf{T^A}$ is only compatible for tetrahydroquinoline and $\mathbf{T^B}$ is only suitable for indoline. A half-gram scale reaction of **8m** showed the scalability of the present protocol. Similarly, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine substrate **8n** can also be olefinated at the C6 position in good yield with high site-selectivity. Finally, olefination of a 2-phenylpyrrolidine substrate gave the *meta*-coupled product **9o** with good selectivity and modest yield. Considering the diverse structures of the aforementioned *N*-heterocycles, these results demonstrate the generality of using distance to predict selectivity in template-directed remote C–H activation.

The indoline substrate **8e** was chosen for investigating the olefin scope of the remote selective C–H activation (Table 4). Both α,β-unsaturated ester and phosphonate coupled well to give the desired olefination products in moderate yields with good site selectivities (**9p**, **9r**). The α,β-unsaturated amide partner showed similar selectivity but lower reactivity (**9q**). We were pleased to find that the olefination of *trans*-methyl cinnamate, which was a poor olefin partner for C8-selective remote C–H activation of tetrahydroisoquinoline, provided the C6-olefinated product **9s** in moderate yield. The dehydro-α-amino acid ester is also compatible under these Ac-Gly-OH free conditions (**9t**). However, reaction with a trisubstituted cyclic olefin provides the corresponding C6-allylated product in only 33% yield and with moderate selectivity (**9u**). The template $\mathbf{T^D}$ is readily removed by treatment with magnesium turnings in methanol at room temperature with concomitant reduction of the olefin and transesterification (Eq. 2).

Table 4. Olefin scope for indoline substrate.[a,b,c]



[a] Conditions: as Table 3. [b] Yield of the isolated mixture of isomers. [c] Regioselectivity was determined by ^{1}H NMR.



In conclusion, we have developed a simple U-shaped template that displayed promising generality for structurally distinct heterocycle scaffolds. The use of MPAA ligands was crucial to expand the substrate scope. The directing template can be removed by a common deprotection method. Although our new template is not superior than previous templates individually designed for four types of substrates, the versatility of this single template to accommodate six different classes of heterocycles is a significant step forward towards the development of more general templates for other substrates.

Acknowledgements

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Keywords: C–H activation • olefination • palladium • *N*-heterocycle • remote

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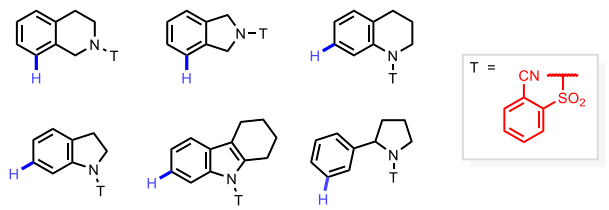

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