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Selective C–H Olefination of Indolines (C5) and Tetrahydroquinolines (C6) by Pd/S,O-Ligand Catalysis

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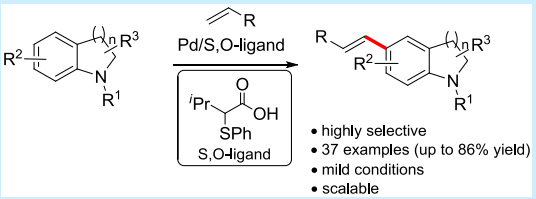
Supporting Information

ABSTRACT: Herein, we report a highly selective C–H olefination of directing-group-free indolines (C5) and tetrahydroquinolines (C6) by Pd/S,O-ligand catalysis. In the presence of the S,O-ligand, a wide range of challenging indolines, tetrahydroquinolines, and olefins was efficiently olefinated under mild reaction conditions. The synthetic potential of this methodology was demonstrated by the efficient olefination of several indoline-based natural products.



Indolines and tetrahydroquinolines (THQs) are ubiquitous structures in natural products and pharmaceuticals.[1] The development of new methodologies that permit the selective C–H functionalization of these structures could considerably widen the extent of current strategies for diversity-oriented synthesis in medicinal chemistry.[2] In this context, two main strategies to achieve efficient and selective C(sp^2)–H functionalization reactions of indolines and THQs were employed. The first approach consists of the use of directing groups attached to the nitrogen atom, which leads to functionalized C7-indolines and C8-THQs (Figure 1a),[3] while the second one provides C6-indolines and C7-THQs by using templates attached to the nitrogen atom (Figure 1b).[4] In the particular case of indolines, the selective C5 functionalization was accomplished via (a) Ru(II)-catalyzed difluoromethylation,[5] (b) Au(I)-catalyzed alkylation,[6] and (c) Zn(II)-catalyzed Michael-type Friedel–Crafts alkylation (Figure 1c).[7] In these examples, only alkyl groups are introduced, and the substrate scope is limited to neutral or electron-rich indolines. To the best of our knowledge, general strategies to selectively obtain C5-olefinated indolines and C6-olefinated THQs are still elusive.[8] Herein, we report the first C5–H olefination of indolines and C6–H olefination of THQs by Pd/S,O-ligand catalysis (Figure 1d). The reaction in the presence of the S,O-ligand proceeds efficiently with a wide range of indolines, THQs, and olefins, providing the desired olefinated products with excellent selectivity and high yields.

Recently, we found out that the C–H olefination of a variety of aromatic compounds can be promoted by the presence of bidentate S,O-ligands.[9] In particular, we reported the first general *para*-selective C–H olefination of aromatic amines. Thus, we hypothesized that a selective C–H olefination of indolines and THQs, which are ubiquitous moieties in natural products, could be achieved in the presence of our Pd/S,O-ligand catalyst.

First, we evaluated the reactivity of different *N*-protected (Me, Bn, Boc) indolines under conditions similar to the ones used in the C–H olefination of anilines (see Supporting Information, Table S1).[9d] We observed that *N*-methyl indoline (**1a**) provided the highest yield (38%) and C5 selectivity and that indolines were less reactive than anilines as well as more sensitive to higher temperatures. Thus, different temperatures, reaction times, and stoichiometries were tested to obtain a compromise between reactivity and stability. Finally, the

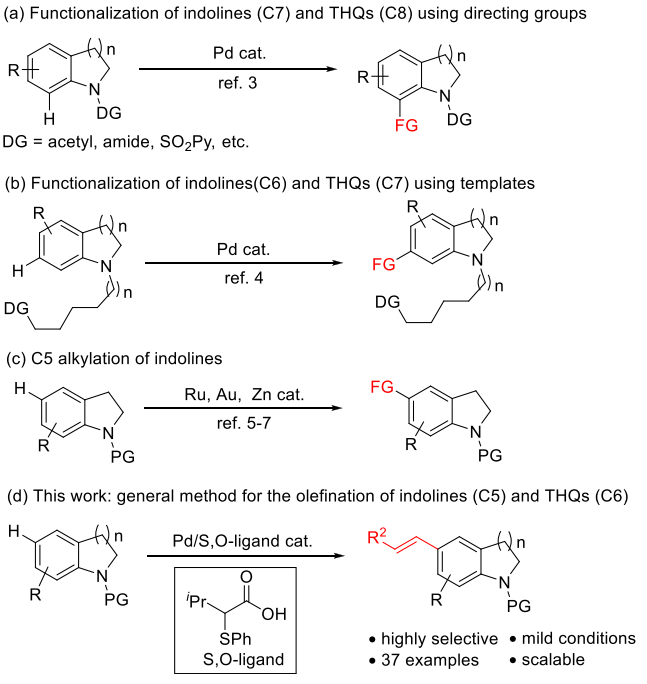


Figure 1. Metal-catalyzed selective C–H functionalization of indolines and THQs.

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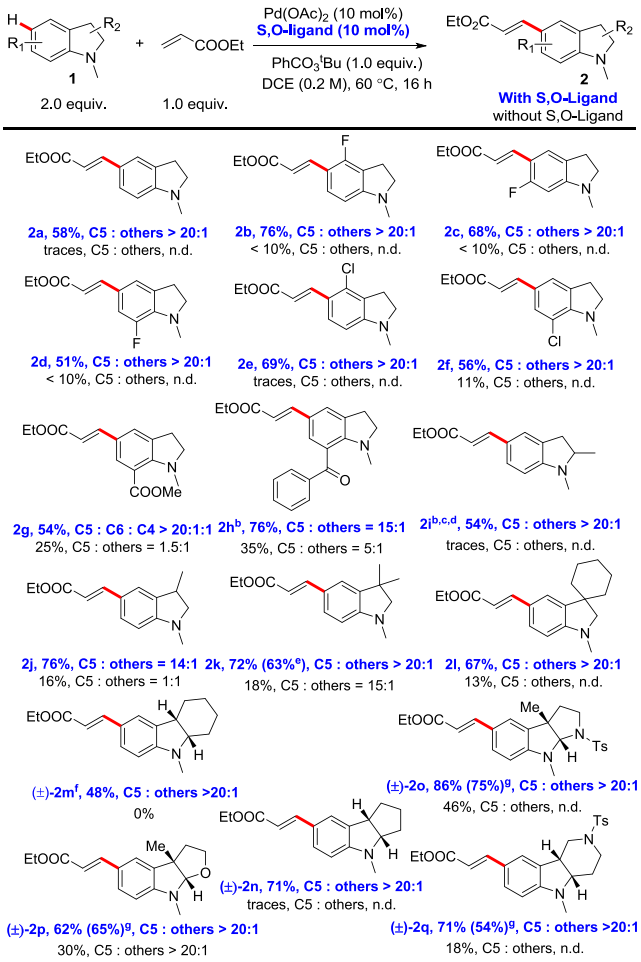
reaction of *N*-methyl indoline (**1a**) (2 equiv) under the optimized reaction conditions (Scheme 1) provided the

Scheme 1. C5 C−H Olefination of *N*-Methyl Indolines[a]



[a]Isolated yields. Selectivities were determined by ^{1}H NMR analysis of the crude mixture. [b]A mixture of DCE and HFB (1:4, v/v) was used as solvent. [c]The reaction was performed at 80 °C. [d]The reaction time was 8 h. [e]4.0 mmol scale. [f]A mixture of DCE and HFB (1:1, v/v) was used as the solvent. [g]1.0 equiv of indoline substrate and 2.0 equiv of ethyl acrylate were used.

desired C5 olefinated product in 58% isolated yield and with excellent C5 selectivity (20 > 1). With the optimal reaction conditions in hand, we studied the substrate scope of a variety of *N*-methyl indolines.

First, we explored the reaction of *N*-methyl indolines bearing electron donating substituents (Me, OMe) in the aromatic ring. To our surprise, the olefinated indoline products were obtained in low yields (see Supporting Information, Table S8), in contrast to the reactivity observed when using *N*,*N*-dialkyl anilines.[9d,10] Then, we tested a variety of indolines bearing electron withdrawing substituents. The reaction of *N*-methyl 4-, 6-, and 7-fluoroindolines (**1b−d**) provided the desired C-5 olefinated products in good yields (76−51%) and perfect selectivities (20 > 1). The slightly lower yield obtained with 7-fluoroindoline (**1d**) can be explained by the deactivation ability of the fluorine atom at the *meta* position. The same trend was observed when chlorine-substituted substrates were used. The reaction of *N*-methyl 4-chloroindoline (**1e**) furnished the C5-olefinated product in 69% yield, while the *N*-methyl 7-chloroindoline olefinated product **2f** was obtained in slightly lower yield (56%). Synthetically useful yield (54%) and good selectivity (20 > 1) were obtained in the reaction of the methyl 1-methylindoline-7-carboxylate (**1g**). Substrate **1h**, which has a benzoyl group at the 7-position, delivered the olefinated product in 76% isolated yield with slightly lower C5-selectivity (15:1).

Next, we evaluated indolines substituted at C2 and/or C3 positions, which are scaffolds present in a wide range of natural products and pharmaceuticals.[1] The reaction of *N*-methyl 2-methylindoline (**1i**) provided the olefinated product in 54% yield and perfect C5-selectivity. Interestingly, when the methyl group is present at the C3 position instead of at C2 position, higher yield (76%) and lower C5-selectivity (14:1) was observed (**2j**, Scheme 1). Good yields (72−67%) and perfect selectivities were obtained using 3,3-dialkyl indolines **1k** and **1l**. The reaction of 2,3-indoline-fused cyclohexane **1m** and cyclopentane **1n** furnished the olefinated products in 48 and 71% yields, respectively, with perfect C5-selectivity. When the pyrroloindoline **1o** skeleton that is found in many natural products and pharmaceuticals was used under standard reaction conditions, the olefinated pyrroloindoline **2o** was obtained in 86% isolated yield and with excellent selectivity. The reaction of the furoindoline derivative **1p** provided the C5-olefinated product in 62% isolated yield. Finally, the olefinated product **2q**, obtained from the reaction of tetrahydro-9-pyridoindoline, was isolated in 71% yield with perfect selectivity. To prove the scalability of this transformation, we performed the reaction of 3,3-dimethyl indoline **1k** on a 4.0 mmol scale, which provided the olefinated product **2k** in 63 yield.

The crucial role of the S,O-ligand in the reaction was demonstrated by comparing the results of the reaction with and without the ligand (Scheme 1). In all cases, the presence of the S,O-ligand was key to obtain the olefinated products in good yield and excellent selectivity.

After demonstrating the efficiency of our catalytic system in promoting the C−H olefination of indolines, we investigated the olefination of tetrahydroquinolines (Scheme 2). The reaction of *N*-methyl THQ **3a** under the optimal reaction conditions (for optimization of reaction conditions, see the Supporting Information, Tables S9−S11) provided the olefinated product **4a** in 73% isolated yield with perfect selectivity. In contrast with the reactivity observed for indolines bearing methyl groups in the aromatic ring, *N*-methyl 5-methyl THQ **3b** and *N*-methyl 7-methyl THQ **3c** were olefinated in 50 and 54% yield, respectively. The reaction of *N*-methyl 2,2,4,7-tetramethyl THQ (**3d**) furnished the olefinated product in 62% isolated yield. Then, we performed the reactions of more electron poor THQs. Under optimal conditions, *N*-methyl 7-chloro THQ (**3e**) and *N*-methyl 2,3-dihydro-1*H*-quinolin-4-one (**3f**) were olefinated in 53 and 56% yield, respectively, and with excellent selectivity. Reactions with spirotetrahydroquinolines **3g** and **3h** provided the olefinated products in 73 and 71% yield. Finally, we tested the reaction of *N*-methyl 8-chloro THQ (**3i**). As expected, this substrate gave only a trace amount of olefinated product, in line with the reactivity observed with *N*,*N*-dimethyl *ortho*-substituted anilines.[9d] Our previous DFT calculations proved that the lack of reactivity of *ortho*-substituent anilines is due to the twist of the nitrogen atom out of the plane, deactivating the aniline. To prove that the same situation occurred in this case, we performed the reaction of the unprotected 8-chloro THQ

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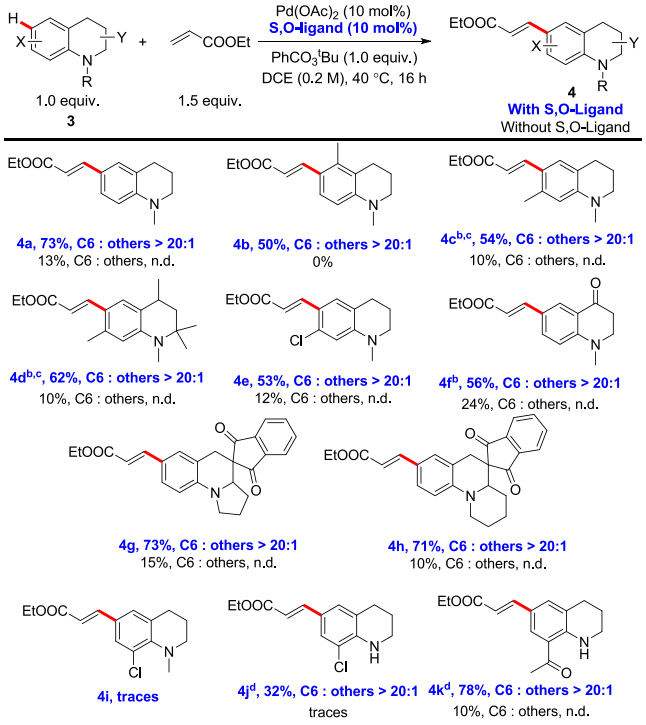
Scheme 2. C6 C−H Olefination of *N*-Methyl THQs[a]



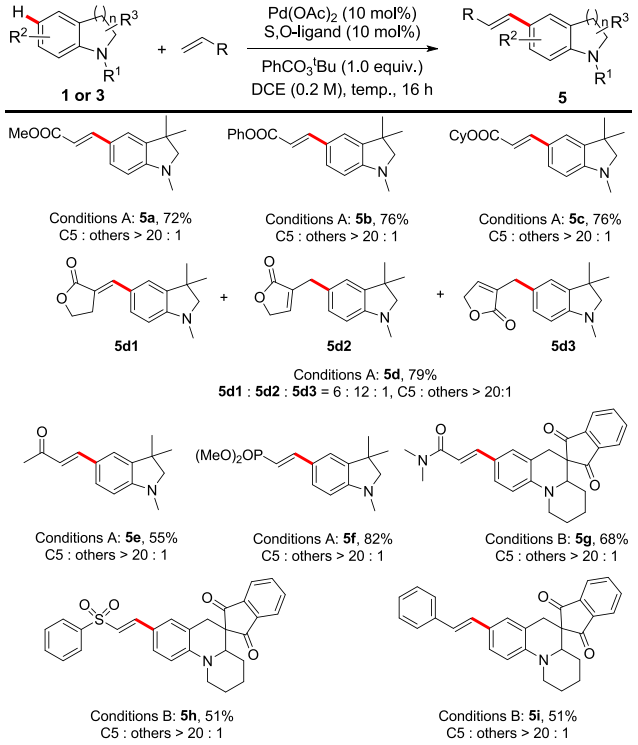
[a]Isolated yields. Selectivities were determined by ^{1}H NMR analysis of the crude mixture. [b]Reaction was performed at 50 °C. [c]1,4-Dioxane was used as the solvent. [d]Reaction was performed at 80 °C.

3j, which provided the olefinated product in 32% isolated yield. Although the reaction was still not efficient, the higher yield obtained for the unprotected THQ in comparison with the protected one **3i** confirms that the same situation occurred. Indeed, the reaction of the unprotected 8-etanone THQ (**3k**) furnished the olefinated product in 78% yield. Again, the key role of the S,O-ligand in the reaction was confirmed by comparing the results of the reaction with and without the ligand.

Next, we evaluated the scope of olefins, as shown in Scheme 3. The reaction of *N*-methyl 3,3-dimethyl indoline (**1k**) with several olefins, including methyl, phenyl, and cyclohexyl acrylates, furnished the olefinated products **5a−c** in high yields (72−76%) and selectivities. α-Methylene-γ-butyrolactone afforded compound **5d** in 79% yield as a mixture of **5d1**, **5d2**, and **5d3** in a ratio 6:12:1. Other activated olefins such as methyl vinyl ketone and vinylphosphonate were also used, providing the olefinated products **5e** and **5f** in 55 and 82% yields, respectively. We also tested the C−H olefination using the spirotetrahydroquinoline **3h**. The reaction using vinyl amide and vinyl sulfonate provided the corresponding olefinated products **5g** and **5h**, respectively, in synthetically useful yields (51−68%). To our delight, the challenging substrate styrene was also a suitable olefin for this reaction, providing the olefinated product **5i** in 51% yield.

In conclusion, we developed the first C5−H olefination of indolines and C6−H olefination of THQs by Pd/S,O-ligand catalysis. The reaction in the presence of the S,O-ligand proceeded efficiently with a wide range of indolines, THQs, and olefins, providing the desired olefinated products with excellent selectivity and high yields. Further applications and mechanistic studies are currently ongoing in our laboratory.

Scheme 3. Scope of Olefins[a]



[a]Reaction conditions: (A) **1k** (0.5 mmol), olefin (0.25 mmol), $Pd(OAc)_2$ (10 mol %), S,O-ligand (10 mol %), $PhCO_3{}^tBu$ (1.0 equiv) in DCE (1.25 mL) at 60 °C for 16 h; (B) **3h** (0.25 mmol), olefin (0.375 mmol), $Pd(OAc)_2$ (10 mol %), S,O-ligand (10 mol %), $PhCO_3{}^tBu$ (1.0 equiv) in DCE (1.25 mL) at 40 °C for 16 h. Isolated yields. Selectivities were determined by ^{1}H NMR analysis of the crude mixture.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03505.

General information, synthesis of indoline and quinoline substrates, reaction optimization for the C5 C−H olefination of indolines, general procedure for Pd-catalyzed C5 C−H olefination of indolines, reaction optimization for the C6 C−H olefination of tetrahydroquinolines, general procedure for Pd-catalyzed C6 C−H olefination of tetrahydroquinolines, general procedure for the evaluation of olefins, large scale reaction of Pd-catalyzed C5 C−H olefination of 1,3,3-trimethylindoline, ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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