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Pd(II)-Catalyzed *meta*-C−H Olefination, Arylation, and Acetoxylation of Indolines Using a U-Shaped Template

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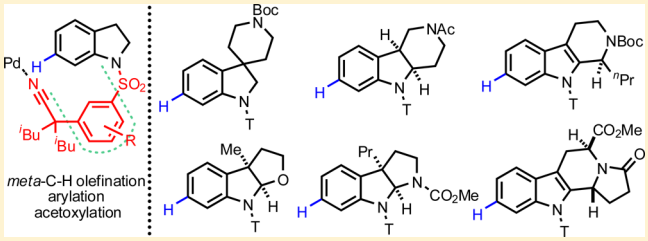
Supporting Information

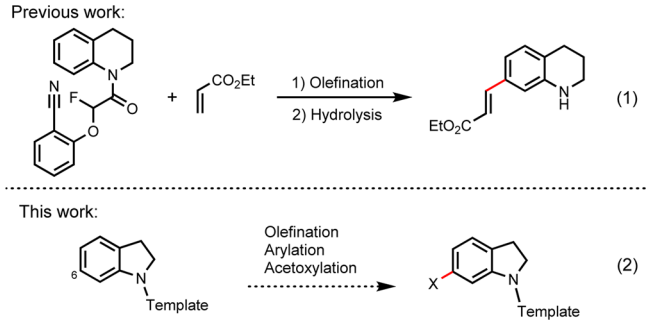
ABSTRACT: *meta*-C−H olefination, arylation, and acetoxylation of indolines have been developed using nitrile-containing templates. The combination of a monoprotected amino acid ligand and the nitrile template attached at the indolinyl nitrogen via a sulfonamide linkage is crucial for the *meta*-selective C−H functionalization of electron-rich indolines that are otherwise highly reactive toward electrophilic palladation at the *para*-positions. A wide range of synthetically important and advanced indoline analogues are selectively functionalized at the *meta*-positions.



1. INTRODUCTION

Rigorous control of site selectivity is critically important for C−H activation reactions to find broad synthetic applications. Selective recognition of C−H bonds by virtue of their distance and geometric relationship to an existing functional group is potentially a broadly applicable approach for harnessing the synthetic utility of C−H activation. While the principles and tactics for achieving *ortho*-selective C−H functionalization have been established over the past three decades,[1] *meta*-selective C−H functionalization remains a significant challenge. Examples of using steric or electronic factors to obtain *meta*-selectivity have been reported primarily for disubstituted arenes.[2,3] We have recently developed a number of readily removable U-shaped nitrile templates to promote the *meta*-selective C−H olefination, arylation, and acetoxylation of three classes of organic aromatic compounds: alcohols, carboxylic acids, and amines.[4,5] Importantly, with this strategy the resultant *meta*-selectivity is independent of the substitution pattern and electronic nature of the substrate. Instead, the reaction recognizes the distance and geometric relationship of the target C−H bonds with respect to the amine functionality. The success of this approach hinges upon the combined use of a weakly coordinating U-shaped template with a monoprotected amino acid ligand.

In light of the biological importance of indoline-based alkaloids,[6] we embarked on the development of *meta*-C−H functionalizations of indolines. Unfortunately, the previously developed templates for other amines, including tetrahydroquinolines (eq 1), do not afford *meta*-selectivity for indoline substrates, presumably due to both conformational and electronic properties of indolines. Herein, we report the first example of *meta*-C−H olefination, cross-coupling, and acetoxylation of indolines using a template attached to the indolinyl nitrogen via a removable sulfonamide linkage (eq 2).



In our effort to develop methods for the *meta*-selective C−H functionalization of arenes, electron-rich phenols, anilines, and tetrahydroquinolines have proved especially challenging due to their intrinsic electronic bias in favor of *ortho*- and *para*-selective reactivity. To overcome this intrinsic reactivity, we have designed a number of U-shaped nitrile-containing templates that enable a highly *meta*-selective functionalization of these arenes.[4b,d] Interestingly, we found that these same templates are ineffective for the *meta*-selective palladation of indolines; an inability to outcompete *ortho*- and *para*-electrophilic palladation leads to a mixture of regioisomers (see Table 1, $\mathbf{T_A}$). Previous physical organic experiments using charge transfer have established that the indoline nitrogen has a higher degree of planarization than the tetrahydroquinoline nitrogen, leading to a more pronounced electron-donating effect of the nitrogen in indolines.[7] Studies in both solution and

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gas phase suggest that different levels of planarity of the alicyclic ring could affect the electron density of the fused aryl ring.[8]

The stronger electron-donating ability of the indolinyl nitrogen is likely responsible for the observed *ortho*- and *para*-reactivity.[9] To override this intrinsic site-selectivity, we focused on the development of a novel nitrile-containing template based on two key design principles. First, a more electron-withdrawing template would reduce the electron density at the *ortho*- and *para*-positions of the indoline substrate, and second, a maximization of the Thorpe–Ingold effect in the template backbone would enhance the directing power of the nitrile (Figure 1).

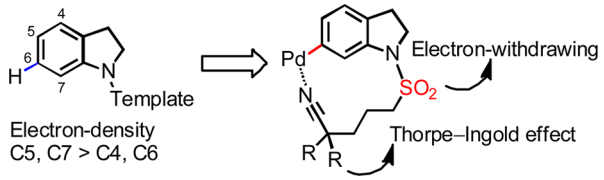


Figure 1. Design of template.

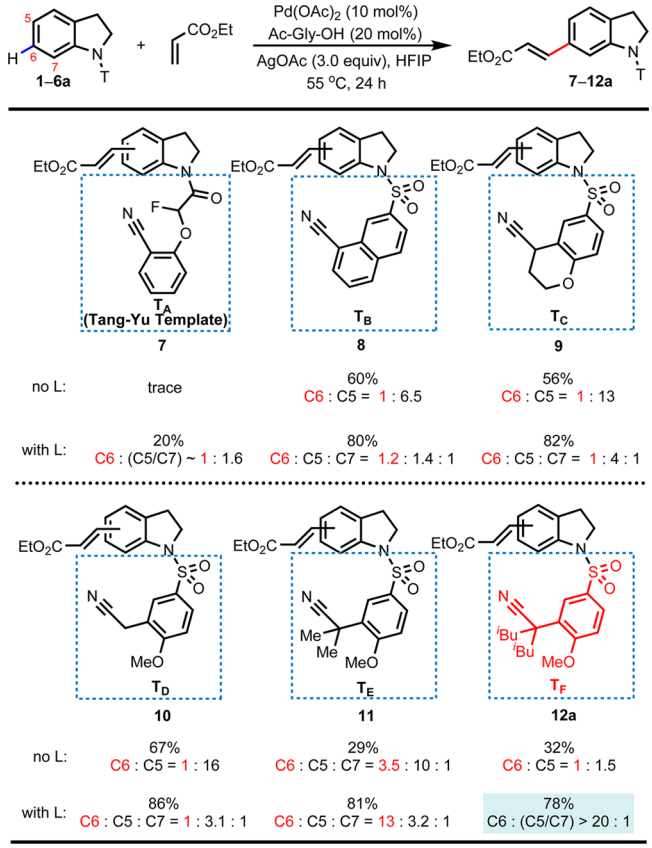
2. RESULTS AND DISCUSSION

We focused our attention on the design of a sulfonyl-based template due to its intrinsic electron-withdrawing nature. Results from a number of templates show that the sheer electron-withdrawing effects of the sulfonyl groups are not sufficient for the directed *meta*-reactivity to override the intrinsic *para*-reactivity (Table 1, $\mathbf{T_B}$–$\mathbf{T_D}$). However, we found that the conformation of the template can be tuned by the incorporation of geminal dialkyl groups alpha to the directing nitrile. This modification greatly improves the *meta*-directing power of the template, presumably via an enhanced Thorpe–Ingold effect ($\mathbf{T_E}$, $\mathbf{T_F}$). A ratio of C6:C5 = 1:1.5 was obtained with $\mathbf{T_F}$. A clear trend in favor of the *meta*-selectivity was observed from $\mathbf{T_D}$ to $\mathbf{T_F}$. The addition of the Ac-Gly-OH ligand significantly improves the *meta*-selectivity with all of these templates, which can be tentatively explained on the basis of a switch of the C–H activation mechanism from the electrophilic palladation to a concerted deprotonation/metalation pathway.[4f,10] The combination of template $\mathbf{T_F}$ and Ac-Gly-OH ligand provides a *meta*-selectivity (C6:others) of >20:1. Thus, substrate **6a** bearing template $\mathbf{T_F}$ was stirred with 2.5 equiv of ethyl acrylate, 10 mol% of $Pd(OAc)_2$, 20 mol% of Ac-Gly-OH, and 3.0 equiv of AgOAc in 1 mL of HFIP at 55 °C for 24 h to provide the desired product **12a** in 78% yield.

In a pair of control experiments performed with or without ligand, olefination of the indoline **13**, protected with a simple benzenesulfonyl group, predominantly gave the *para*-olefinated indoline product **14**, albeit in poor yields (Scheme 1). The low yield is not surprising, considering that the reactivity of nondirected aryl C–H activation is generally low unless excess arene is used. This result demonstrates the importance of the directing effect of the nitrile templating group.

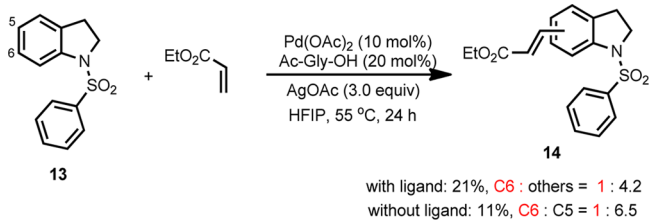
With this optimized template in hand, we examined the scope of this *meta*-selective C–H olefination reaction (Table 2). Substrates containing a variety of substituents at the C4 or C5 position of the aryl ring afford the desired products in good yields and with excellent *meta*-selectivity (**12b**–**12h**). The presence of a fluorine atom at the C4 position likely decreases the *meta*-selectivity due to its known *ortho*-directing effect (**12d**). The olefination of C5-substituted substrates required an

Table 1. Screening of Templates[a,b]



[a]0.1 mmol scale, 2.5 equiv of ethyl acrylate, 10 mol% of $Pd(OAc)_2$, 20 mol% of Ac-Gly-OH, 3.0 equiv of AgOAc, 1 mL of HFIP, 55 °C, 24 h. [b]The total yield and regioselectivity were determined by crude ^1H NMR.

Scheme 1. Control Experiments



elevated reaction temperature (80 °C) due to the lower reactivity of these substrates (**12e**–**12h**). The tolerance of a strongly electron-withdrawing ester group at the C5 position is noteworthy (**12h**). Olefination of 7-methylindoline, however, gave poor *meta*-selectivity (see Supporting Information), with *para*-olefination taking place as a significant competing pathway. Apparently, the substitution at C7 hampered the assembly of the macrocyclic transition state of the directed C–H activation due to steric hindrance.

Prompted by the structures of indoline-containing natural products, we investigated the compatibility of this *meta*-selective olefination with C2 and C3 substitutions. We were pleased to find that indolines containing a methyl group at the C2 or C3 position are olefinated in good yields and with good *meta*-selectivities (**12i**–**12k**). C2,3-fused rings are well tolerated (**12l**–**12o**), and indolines containing spiro rings at the C3 position are also olefinated in good yields and with good *meta*-

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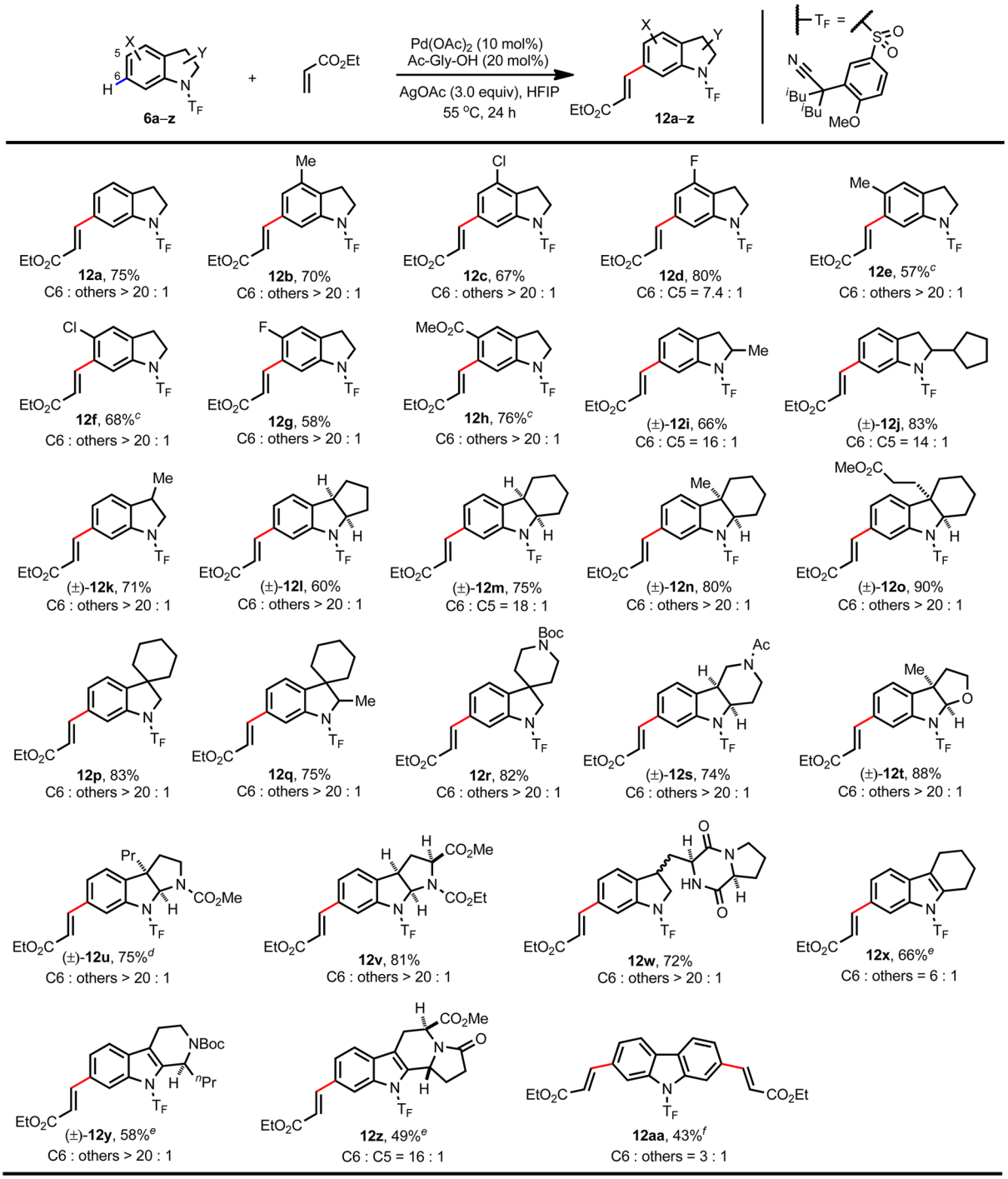
Table 2. Scope of Indoline and Indole Substrates[a,b]



[a]0.1 mmol scale, 2.5 equiv of olefin, 10 mol% of $Pd(OAc)_2$, 20 mol% of Ac-Gly-OH, 3.0 equiv of AgOAc, 1 mL of HFIP, 55 °C, 24 h. [b]Isolated yield for mono-olefinated product. Regioselectivity was determined by crude ^1H NMR. [c]80 °C. [d]0.05 mmol scale, 60 °C, 36 h. [e]70 °C. [f]3.0 equiv of olefin, 4.0 equiv of AgOAc.

selectivities (**12p**, **12q**). The presence of an additional piperidine ring is also tolerated (**12r**, **12s**). Compound **12r** bears the core of a potent P2Y1 antagonist.[11] Furoindolines and pyrroloindolines are also *meta*-olefinated to provide the desired products in good yields (**12t**–**12v**). The reaction of a diketopiperazine substrate gave the *meta*-olefinated product **12w** in good yield. Indoles are also compatible with this *meta*-olefination protocol, albeit in lower yields and with lower selectivities (**12x**–**12z**). Notably, these furoindoline (**12t**), pyrroloindoline (**12u**, **12v**),[12] and tetrahydro-*β*-carboline (**12y**, **12z**)[13] structural motifs are embedded in a range of biologically important natural products or drug candidates. Interestingly, medicinally important carbazole is olefinated to give the diolefinated product **12aa** in moderate yield and with moderate *meta*-selectivity.[14]

A wide range of olefins is compatible with this transformation, allowing for diversification of the *meta*-position substituent (Table 3). A variety of *α*,*β*-unsaturated terminal

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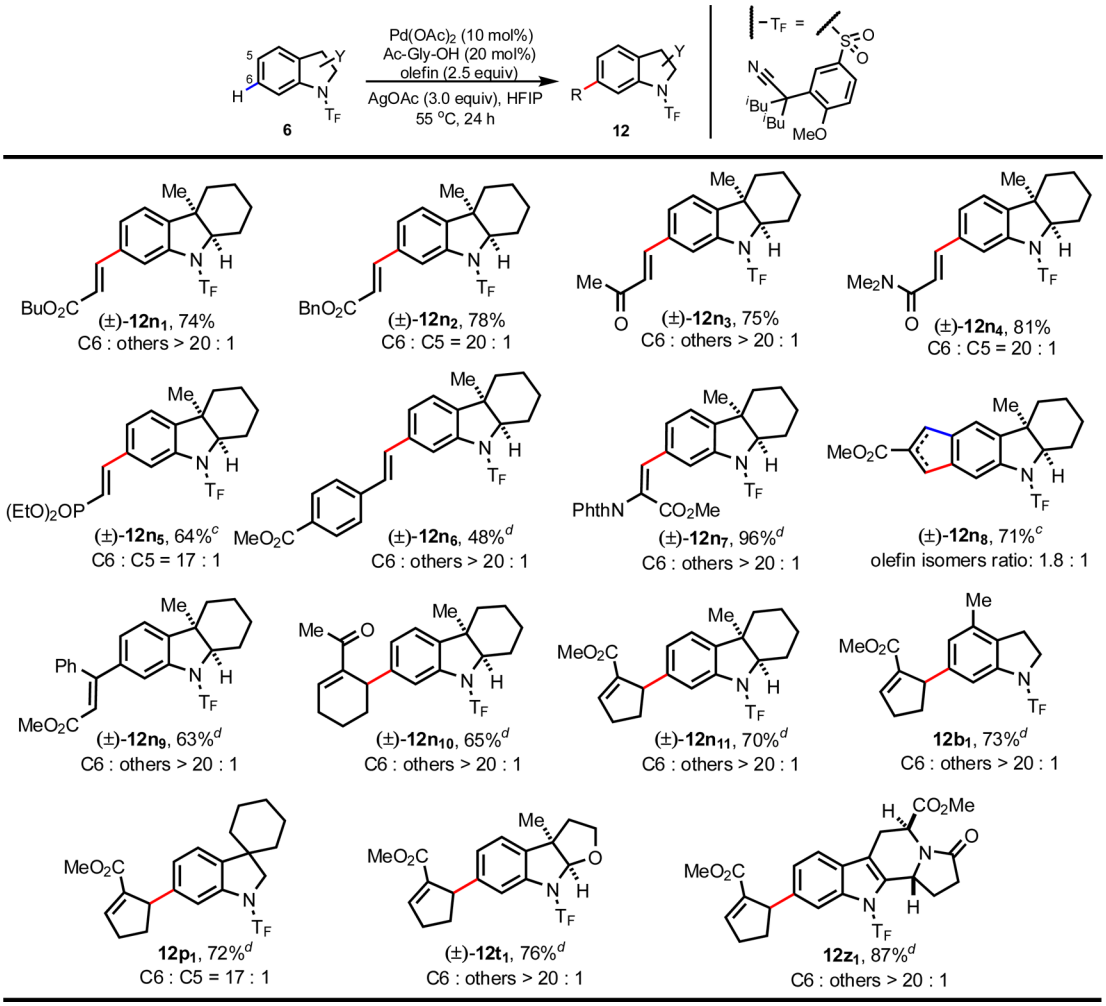
Table 3. Scope of Olefin Coupling Partners[a,b]



[a]0.1 mmol scale, 2.5 equiv of olefin, 10 mol% of $Pd(OAc)_2$, 20 mol% of Ac-Gly-OH, 3.0 equiv of AgOAc, 1 mL of HFIP, 55 °C, 24 h. [b]Isolated yield for mono-olefinated product. Regioselectivity was determined by crude ^{1}H NMR. [c]70 °C. [d]90 °C.

olefins[15] react with **6n** to give the desired products selectively in good yields (**12n$_1$**−**12n$_5$**). While styrene is not an effective coupling partner under these conditions, the presence of an electron-withdrawing 4-methoxycarbonyl group on the aryl ring improved the yield to 48% (**12n$_6$**). A dehydro-α-amino acid is an excellent coupling partner, affording high yield and selectivity (**12n$_7$**). Interestingly, two isomeric cyclization products are isolated in 71% yield when methyl α-methyl acrylate is used as the olefin partner (**12n$_8$**). Formation of this product likely proceeds via intramolecular olefination at the *para*-position of the initially *meta*-olefinated product. The olefination with *trans*-methyl cinnamate also gives the trisubstituted olefin product in good yield and with good selectivity (**12n$_9$**). Reactions with trisubstituted cyclic olefins proceed to provide *meta*-allylated products in good yields (**12n$_{10}$**, **12n$_{11}$**). Other indoline and indole substrates are also compatible with this trisubstituted cyclic olefin coupling partner (**12b$_1$**, **12p$_1$**, **12t$_1$**, **12z$_1$**).

To demonstrate the versatility of this template approach for diverse *meta*-C−H functionalizations of indolines, we subjected a number of indoline substrates **6** to previously developed C−H cross-coupling conditions.[4c] Arylation with various arylboronic acid pinacol esters proceeded to give the *meta*-arylated indolines in synthetically useful yields (Table 4). These *meta*-arylated indolines are actively pursued targets in medicinal chemistry.[16]

Considering the biological importance of the *meta*-hydroxylated indolines,[17] we also attempted the *meta*-acetoxylation reaction using the well-established oxidation conditions (Table 5).[18] While the *meta*-acetoxylated indolines were obtained as the major products, substantial amounts of *para*-acetoxylated indolines (~10%) were also formed due to the electrophilic palladation at the electron-rich C5 position under these conditions. As expected, the nonsubstituted indoline **6a** is not compatible with these oxidation conditions, as the indoline ring is readily oxidized to give a mixture of unidentified compounds. The use of milder oxidants and further optimizations are currently being carried out to overcome these limitations.

The template is readily removed by treatment with magnesium turnings in methanol at room temperature, with the olefin being reduced at the same time. Thus, the *meta*-alkylated products **18n** and **18p** are obtained in 78% and 89% yields, respectively, following this deprotection procedure (eqs 3 and 4). The template attached to the indole product **12y** was removed under basic conditions (eq 5). Since the Boc and ester groups were also deprotected, the free amines and carboxylic acid were reprotected in one pot for ease of isolation.

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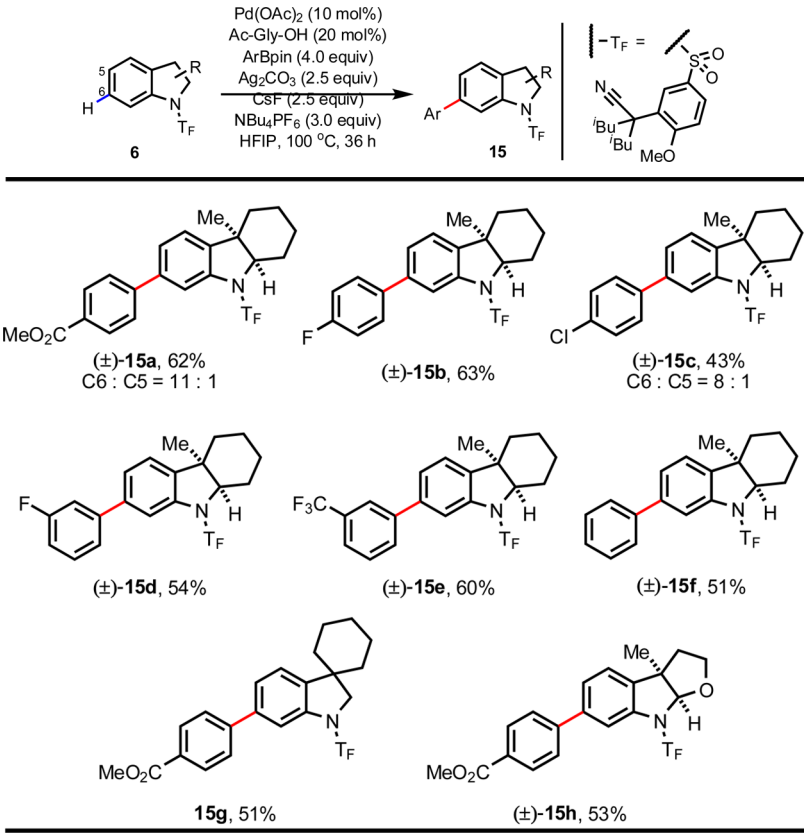
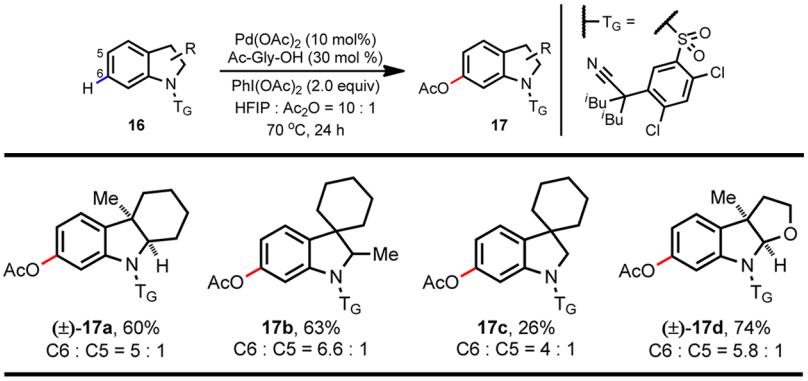
Table 4. *meta*-Arylation of Indolines[a,b]



[a]0.1 mmol scale, 4.0 equiv of ArBpin, 10 mol% of $Pd(OAc)_2$, 20 mol% of Ac-Gly-OH, 2.5 equiv of Ag_2CO_3, 2.5 equiv of CsF, 3.0 equiv of NBu_4PF_6, 1 mL of HFIP, 100 °C, 36 h. [b]Isolated yield. For **15a** and **15c**, regioselectivity was determined by crude ^1H NMR. For others, the regioselectivity could not be determined by crude ^1H NMR.

Table 5. *meta*-Acetoxylation of Indolines[a,b]



[a]0.1 mmol scale, 2.0 equiv of $PhI(OAc)_2$, 10 mol% of $Pd(OAc)_2$, 30 mol% of Ac-Gly-OH, 1 mL of HFIP, 0.1 mL of Ac_2O, 70 °C, 24 h. [b]Isolated yield. Regioselectivity was determined by crude ^1H NMR.

3. CONCLUSION

In conclusion, we have developed the first example of *meta*-C−H activation of indolines using a U-shaped nitrile template attached to the indoline via a sulfonamide linkage. A range of diverse C−H functionalizations at the *meta*-position directed by the nitrile template outcompete the inherently preferred electrophilic palladation at the C7 and C5 positions. This method provides a useful tool for the preparation of a wide range of *meta*-substituted indoline analogues, including biologically important natural products and drug molecules.

4. EXPERIMENTAL SECTION

General Procedure for the Pd(II)-Catalyzed *meta*-C−H Olefination of Indolines and Indoles (Tables 2 and 3). An 8 mL tube equipped with a magnetic stir bar was charged with substrate **6** (0.1 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%), AgOAc (50.1 mg, 0.3 mmol, 3.0 equiv), olefin (0.25 mmol, 2.5 equiv), and HFIP (1.0 mL). The tube was sealed and stirred at room temperature for 10 min. It was then heated to 55, 60, 70, 80, or 90 °C. The reaction was stirred for 24 h and cooled to room temperature. The reaction mixture was diluted with EtOAc (2 mL) and filtered through a pad of silica gel. The tube and silica gel were washed with an additional 10 mL of EtOAc.

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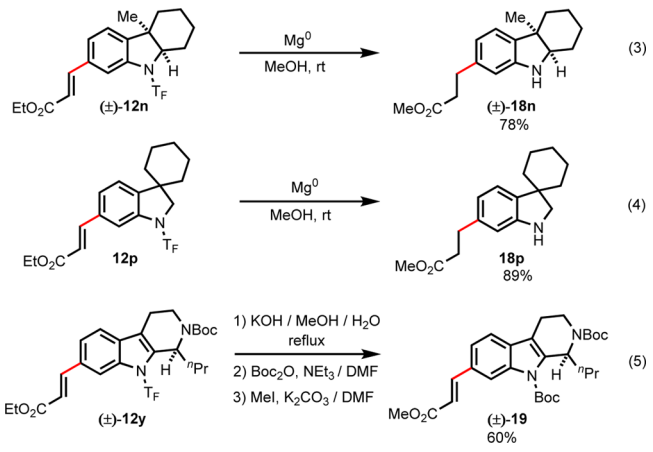

The filtrate was concentrated in vacuo, and the resulting residue was purified by preparative TLC using hexane/EtOAc or CH_2Cl_2/hexane/EtOAc as the eluent.

General Procedure for the Pd(II)-Catalyzed *meta*-C−H Cross-Coupling of Indolines (Table 4). An 8 mL tube equipped with a magnetic stir bar was charged with substrate **6** (0.1 mmol, 1.0 equiv), ArBpin (0.4 mmol, 4.0 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 10 mol %), Ac-Gly-OH (2.4 mg, 0.02 mmol, 20 mol%), Ag_2CO_3 (68.5 mg, 0.25 mmol, 2.5 equiv), CsF (38 mg, 0.25 mmol, 2.5 equiv), NBu_4PF_6 (116 mg, 0.3 mmol, 3.0 equiv), and HFIP (1.0 mL). The tube was sealed and stirred at room temperature for 10 min. It was then heated to 100 °C and stirred for 36 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (2 mL) and filtered through a pad of silica gel. The tube and silica gel were washed with an additional 10 mL of EtOAc. The filtrate was concentrated in vacuo, and the resulting residue was purified by preparative TLC using hexane/EtOAc as the eluent.

General Procedure for the Pd(II)-Catalyzed *meta*-C−H Acetoxylation of Indolines (Table 5). An 8 mL tube equipped with a magnetic stir bar was charged with substrate **16** (0.1 mmol, 1.0 equiv), $PhI(OAc)_2$ (64.4 mg, 0.2 mmol, 2.0 equiv), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 10 mol%), Ac-Gly-OH (3.5 mg, 0.03 mmol, 30 mol%), Ac_2O (0.1 mL), and HFIP (1.0 mL). The tube was sealed and stirred at room temperature for 10 min. It was then heated to 70 °C and stirred for 24 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (2 mL) and filtered through a pad of silica gel. The tube and silica gel were washed with an additional 10 mL of EtOAc. The filtrate was concentrated in vacuo, and the resulting residue was purified by preparative TLC using hexane/EtOAc as the eluent.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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