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Communication

Palladium-Catalyzed *anti*-Michael-Type (Hetero)arylation of Acrylamides

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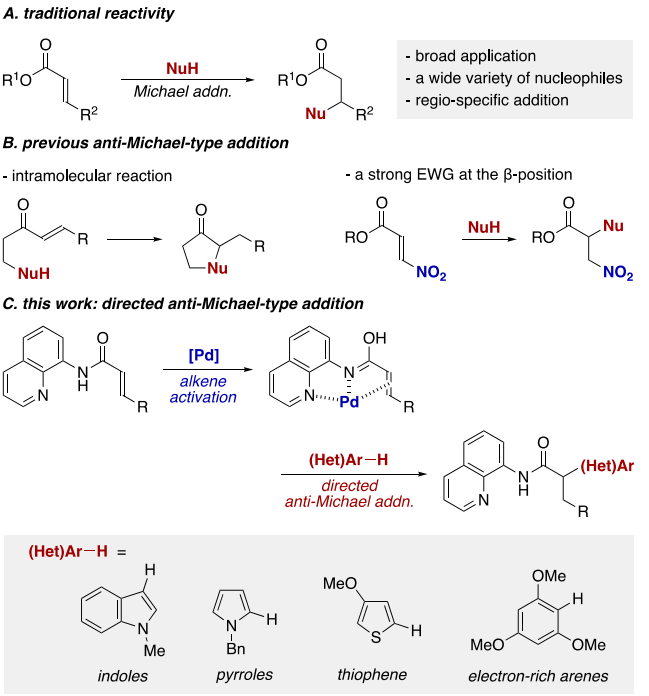
ABSTRACT: This paper reports a direct α-(hetero)arylation of acrylamides through an inverse electron-demand nucleophilic addition, specifically an *anti*-Michael-type addition. The introduction of a quinolyl directing group facilitates the nucleophilic addition of (hetero)arenes to the α-position of acrylamides. The quinolyl directing group effectively suppresses undesired β-hydrogen elimination and is removable for subsequent derivatization. The presented method provides an atom economical synthesis of α-(hetero)arylamide with a high degree of functional group tolerance.

Since Arthur Michael reported the conjugated addition of malonates to a cinnamate (Michael addition reaction) in 1887,[1,2] α,β-unsaturated carbonyl compounds have been widely employed as π-acceptors, forming carbon−carbon or carbon−heteroatom bonds at the β-position.[3−7] In stark contrast, the *anti*-Michael-type addition reaction, representing the α-addition of a nucleophile to an α,β-unsaturated carbonyl compound, is much less common. The scarcity of cases arises from the higher electrophilicity of the β-position compared to that of the α-position, necessitating the overwhelming of this unfavorable electronic bias for achieving the *anti*-Michael-type addition reaction (Scheme 1A). Previous reports on overcoming the electronic bias can be categorized into two strategies: (1) restricting the addition position by a substrate structure, such as an intramolecular reaction,[8,9] or (2) changing the electronic bias by introducing a strong electron-withdrawing group at the β-position (Scheme 1B).[10,11] Despite these strategies representing significant advances in *anti*-Michael-type addition reactions, applying the methodology to the complex molecule synthesis faces a crucial restriction; these strategies are significantly constrained by the structure of the starting materials.[8−12] Recently, transition-metal-catalyzed α-hydroarylations of α,β-unsaturated carbonyl compounds have emerged as a state-of-the-art methodology for accessing *anti*-Michael-type adducts.[13−15] Although these reactions offer rare solutions to critical challenges associated with *anti*-Michael-type addition reactions, certain limitations persist. For instance, the formation of β-adducts is occasionally observed.[13,15] In another case, the versatility of these reactions is limited by the aryl groups, necessitating the introduction of strong electron-withdrawing groups.[14] Consequently, intermolecular *anti*-Michael-type addition reactions with simple α,β-unsaturated carbonyl compounds, featuring alkyl/aryl groups or no substituent at the β-position, remain appealing yet challenging. If the *anti*-Michael-type addition reaction can proceed with simple α,β-unsaturated carbonyl compounds, it becomes an attractive and versatile methodology, providing α-substituted carbonyl compounds with high atom economy.[13−21] Therefore, our focus was directed toward investigating a general *anti*-Michael-type addition reaction using simple acrylamides.

Scheme 1. Previous *anti*-Michael-type Addition Reactions and This Work



In recent years, transition-metal-catalyzed substrate-directed hydrofunctionalization of unactivated alkenes has emerged as a

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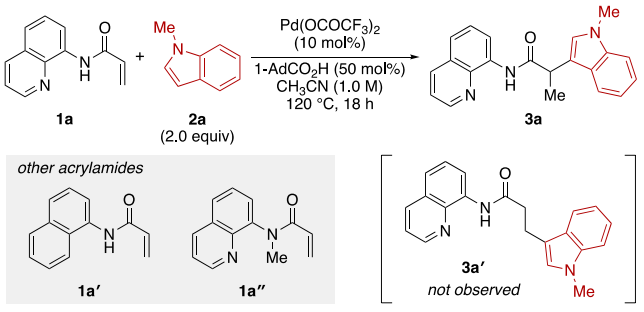
prominent tool in synthetic organic chemistry.[22−38] Particularly, the use of bidentate directing groups, such as an aminoquinoline group,[39−41] promotes a regioselective nucleometalation process with various carbon and heteroatom nucleophiles by suppressing undesired β-hydrogen elimination.[27−37] While these reactions established the regioselective addition of nucleophiles to unactivated alkenes (i.e., electronically unbiased alkenes) by generating a five-membered metallacycle, the efficiency of the strategy in an inverse electron-demand nucleophilic addition is unclear.[42] We envisioned that introducing an appropriate bidentate directing group would determine the regioselectivity of the addition step beyond the electronic bias of α,β-unsaturated carbonyl compounds. If successful, the novel intermolecular *anti*-Michael-type addition reaction could proceed without additional functional groups altering the steric or electronic properties of alkenes. Herein, we report a palladium-catalyzed *anti*-Michael-type (hetero)arylation of acrylamides with various arene nucleophiles, representing the first example of an *anti*-Michael-type addition reaction with simple acrylamides (Scheme 1C).

We initiated the *anti*-Michael-type heteroarylation of 1-methylindole (**2a**) to *N*-(quinolin-8-yl)acrylamide (**1a**) in the presence of $Pd(OAc)_2$ and 1-$AdCO_2H$ (Ad = adamantyl) in CH_3CN at 120 °C for 18 h, inspired by a previous report on the regioselective hydroamination of unactivated alkenes (Table 1).[27] Gratifyingly, the desired α-adduct was selectively formed, albeit with a low yield (entry 2). After extensive optimization of palladium catalysts, we identified that $Pd(OCOCF_3)_2$ was the optimal catalyst, affording **3a** in 80% yield (entry 1). The use of nickel catalysts, such as $Ni(OAc)_2{\cdot}4H_2O$, was ineffective for this reaction (entry 3). Surprisingly, the reaction in the absence of acid had a negligible effect on the yield, unlike previous palladium-catalyzed hydrofunctionalizations (entry 4).[27−37] Increasing the concentration improved the efficiency of the α-addition, furnishing **3a** in 90% isolated yield (entry 5). Several experiments demonstrated the robustness of the reaction system, with the addition of water or performing the reaction under air conditions having no significant impact on the yield (entries 6 and 7). Therefore, the chemical yield of this reaction was independent of a protic additive and atmospheric oxygen. Replacing the quinoline ring with a naphthalene ring (**1a′**) or blocking the N−H bond (**1a″**) prevented the reaction from proceeding, suggesting the bidentate directing group is essential (entries 8 and 9). The *anti*-Michal-type addition reaction necessitates a palladium complex to proceed (entry 10). Consequently, we identified the optimized reaction conditions as follows: **1a**, **2a** (2.0 equiv), $Pd(OCOCF_3)_2$ (10 mol %) in CH_3CN (2.0 M), 120 °C, 18 h.

Table 1. Optimization of Reaction Conditions[a]



entry	variation(s)	yield (%)[b]
1	none	80
2	$Pd(OAc)_2$ instead of $Pd(OCOCF_3)_2$	14
3	$Ni(OAc)_2{\cdot}4H_2O$ instead of $Pd(OCOCF_3)_2$	8
4	w/o 1-$AdCO_2H$	82
5	w/o 1-$AdCO_2H$, 2.0 M, 0.4 mmol scale	97 (90)
6	same as entry 5, with H_2O (2.0 equiv)	85
7	same as entry 5, under air	87
8	**1a′** instead of **1a**	0
9	**1a″** instead of **1a**	0
10	w/o $Pd(OCOCF_3)_2$	0

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (2.0 equiv), $Pd(OCOCF_3)_2$ (10 mol %) and 1-$AdCO_2H$ (50 mol %) were reacted in CH_3CN (1.0 M) at 120 °C for 18 h. [b]Yield was determined by ^1H NMR analysis using 1,2,4,5-tetramethylbenzene as an internal standard. The value in parentheses indicates the isolated yield.

With the optimized reaction conditions, we explored the substrate scope of this *anti*-Michael-type addition reaction with indole substrates (Table 2). Introducing alkyl substituents at the 1-position of an indole substrate did not affect the reactivity, providing **3a−c** in 72−90% yields. A 2 mmol scale reaction of **1a** and **2a** also gave **3a** in a similar yield compared to a 0.4 mmol scale. In contrast, 1-phenylindole reduced the yield dramatically to 24% yield, likely due to the lower nucleophilicity of the indole 3-position (**3d**). Interestingly, an unprotected indole provided the corresponding product **3e** without any side reactions, albeit with slightly diminished reactivity. A 2-phenylindole substrate reacted with **1a** smoothly to furnish **3g** in 91% yield, while a 2-methylindole reduced the yield of **3f** to 48% yield. Next, the effect of a substituent on the benzenoid moiety was examined. Indoles bearing a methyl substituent at the 4, 5, 6, and 7 positions rendered **3h−k** in 71−94% yields, indicating that the steric effect of the benzenoid moiety is negligible in this case. Indoles possessing electron-donating and -withdrawing groups at the 4−7 positions furnished **3l−s** in 52−89% yields. Notably, a 5-nitroindole, despite its lower nucleophilicity, produced **3s** in good yield. The reactivity of the *anti*-Michael-type addition reaction was dependent on the electronic property of the substituents, but *anti*-Michael adducts were still obtained even with electron-deficient nucleophiles. Various indole substrates could be employed as appropriate nucleophiles in this *anti*-Michael-type addition reaction.

We further explored the scope of β-substituted acrylamides with the optimized reaction conditions mentioned above. However, it failed to produce the *anti*-Michael adduct in an acceptable yield. Several acid additives were examined based on the previous report on the directed hydrofunctionalization of unactivated alkenes,[27−37] and the addition of a substoichiometric amount of 2,6-dichlorobenzoic acid turned cinnamamides into viable coupling partners. Cinnamamide gave **3t** in 81% yield. A methyl substituent on the benzene ring slightly affected the reactivity, affording **3u−w** in 64−88% yields. Unexpectedly, an *ortho*-substituted cinnamamide successfully transformed into **3w** in high yield despite the steric hindrance. Electron-rich cinnamamides rendered **3x−z** in 62−67% yields. The slight decrease in the reactivity of the electron-rich cinnamamides would be associated with the lower electrophilicity of the α-position. Interestingly, a phenolic functionality was tolerated in the reaction conditions to afford **3z** in 67% yield. Introducing an electron-withdrawing group on the benzene ring was beneficial in furnishing **3aa** and **3ab** with

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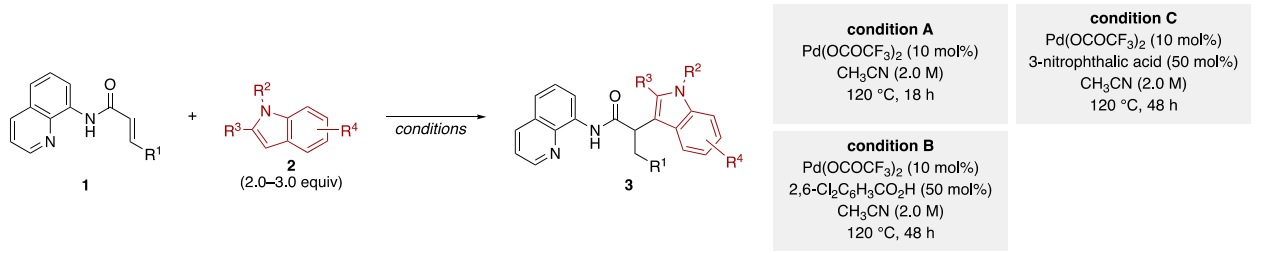
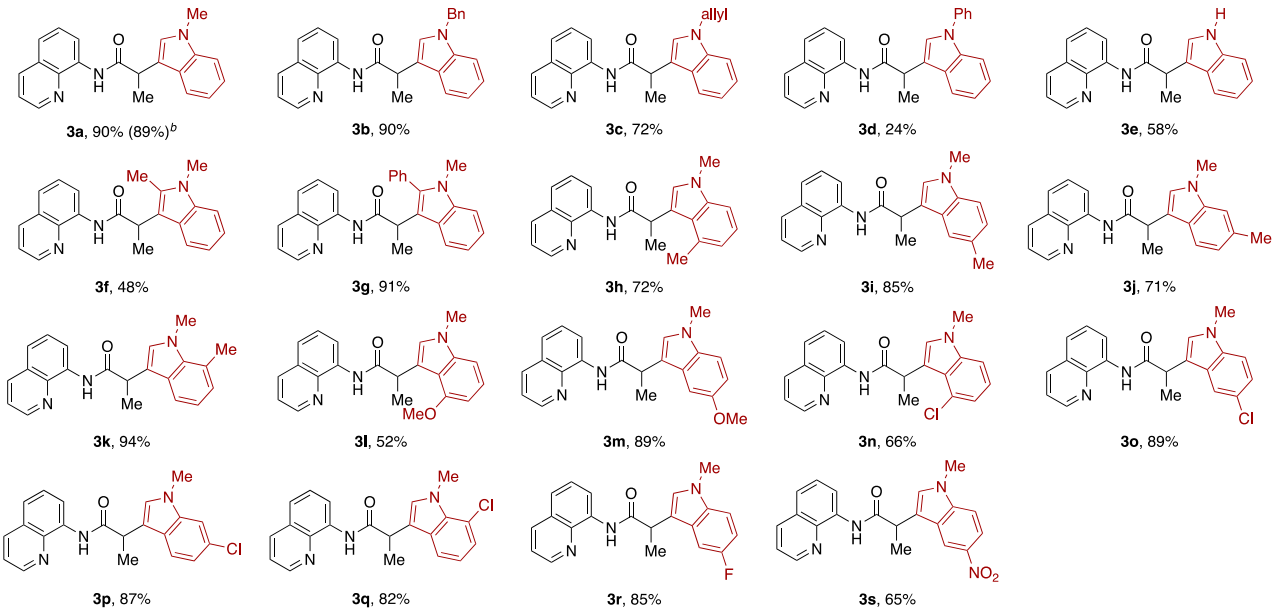
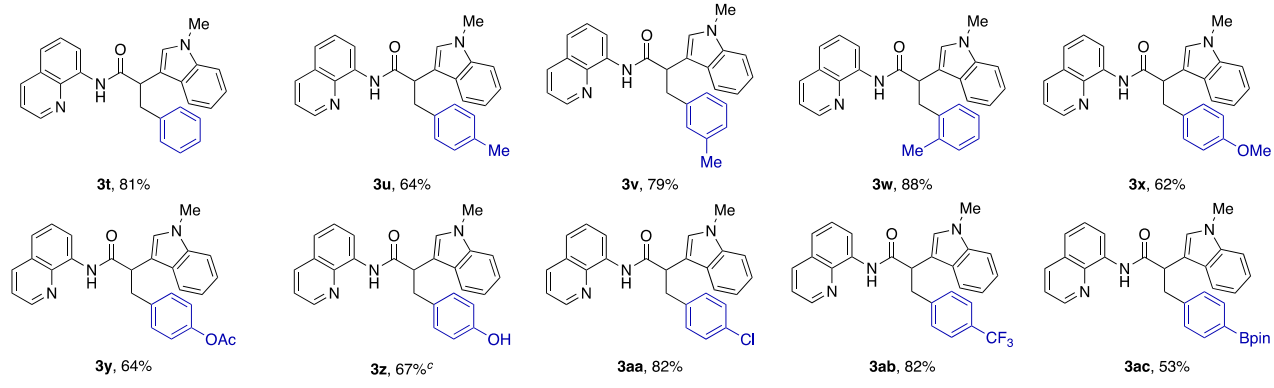
Table 2. Substrate Scope for Palladium-Catalyzed *anti*-Michael-Type Addition Reaction of Indoles[a]



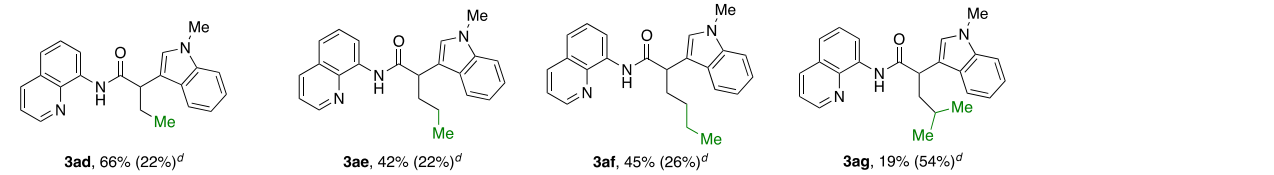
scope of 2 (condition A)



scope of 1 (R^1 = aryl, condition B)



scope of 1 (R^1 = alkyl, condition C)



[a]Reaction conditions A: **1a** (0.4 mmol), **2** (2.0 equiv) and $Pd(OCOCF_3)_2$ (10 mol %) were reacted in CH_3CN (2.0 M) at 120 °C for 18 h, unless otherwise noted. Reaction conditions B: **1** (0.4 mmol), **2a** (2.0 equiv), 2,6-dichlorobenzoic acid (50 mol %) and $Pd(OCOCF_3)_2$ (10 mol %) were reacted in CH_3CN (2.0 M) at 120 °C for 48 h, Reaction conditions C: **1** (0.4 mmol), **2a** (3.0 equiv), 3-nitrophthalic acid (50 mol %) and $Pd(OCOCF_3)_2$ (10 mol %) were reacted in CH_3CN (2.0 M) at 120 °C for 48 h. [b]2.0 mmol scale. [c]The reaction was performed in CH_3CN/DMF (3:1). [d]Yield of recovered starting material.

82% yields, respectively. An arylboronate moiety, which can be transformed into various functional groups by coupling reactions, remained intact (**3ac**). We then focused on the addition reaction to *β*-alkyl-substituted acrylamides. In this case, 3-nitrophthalic acid was used as an additive instead of 2,6-dichlorobenzoic acid. An *N*-(quinolin-8-yl)amide derived from crotonic acid reacted with **2a** in 66% as a sole product, and the isomerized *β*,*γ*-unsaturated starting material was not

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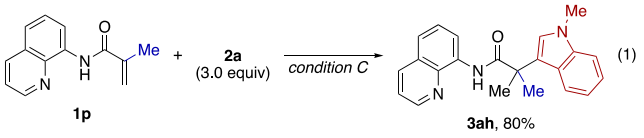
observed. Introducing a longer or a branched alkyl group at the β-position decreased the yield (**3ae**−**ag**), indicating that this *anti*-Michael-addition reaction is sensitive to the bulkiness of a β-alkyl substituent. Additionally, the amides with β-alkyl groups produced several byproducts, with the exception of **3ad**. However, the formation of β- and γ-adducts was not detected in these reactions. Although the scope of β-alkyl-substituted acrylamides is slightly limited, various kinds of indoles and acrylamides are applicable to the *anti*-Michael-type addition reaction with good functional group tolerance.

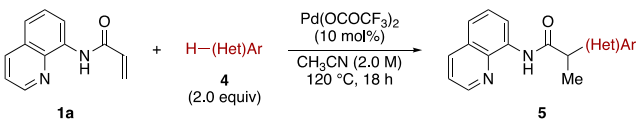
We then focused on exploring an *anti*-Michael-type addition to methacrylamide. Our investigations led to the successful synthesis of the desired amide **3ah** with an 80% yield (eq 1). This finding underscores the effectiveness of this method in synthesizing carbonyl compounds featuring a quaternary carbon center at the α-position.

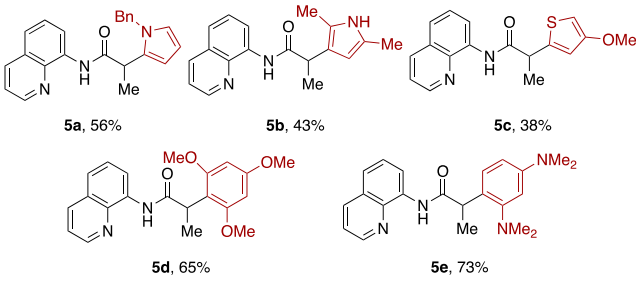


(1)

As indole substrates work as good nucleophiles for the *anti*-Michael-type addition reaction, we are next interested in using electron-rich arenes as nucleophiles (Table 3).[43,44] Subjecting

Table 3. *anti*-Michael-Type Addition Reaction of Electron-rich (Hetero)arenes[a]



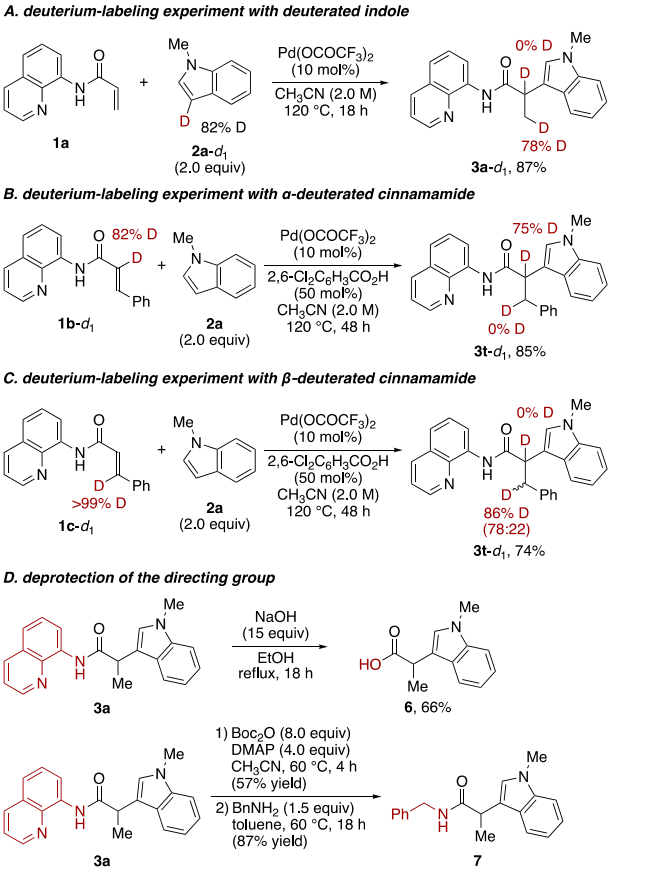


[a]Reaction conditions: **1a** (0.4 mmol), **4** (2.0 equiv), and Pd(OCOCF$_3$)$_2$ (10 mol %) were reacted in CH$_3$CN (2.0 M) at 120 °C for 18 h.

pyrrole substrates to the optimized reaction conditions for acrylamides promoted the desired *anti*-Michael-type addition reaction to furnish **5a** and **5b** in 56% and 43% yields, respectively. A thiophene substrate reacted with **1a** to afford **5c** in 38% yield. Electron-rich benzene derivatives also worked as good nucleophiles for the *anti*-Michael-type addition reaction (**5d** and **5e**). In all cases, β-addition of (hetero)arenes has not been observed, and the *anti*-Michael-type addition reaction selectively proceeded. Consequently, the generality of the nucleophiles could be broadened to electron-rich benzenes.

As an alkyl palladium intermediate is prone to undergo β-hydrogen elimination as a side reaction,[45−47] deuterium-labeling experiments were performed to evaluate the possibility of β-hydrogen elimination in this reaction pathway (Scheme 2). Subjecting **2a**-d_1 to the optimized reaction conditions for

Scheme 2. Deuterium-Labeling Experiments and Removal of Directing Group



nonsubstituted acrylamides revealed deuterium incorporation solely at the methyl group of **3a**-d_1 (Scheme 2A). Additionally, an α-deuterium atom of cinnamamide **1b**-d_1 was not transferred even after completing the reaction (Scheme 2B). These results indicated that β-hydrogen elimination did not proceed, likely suppressed by the use of a rigid bidentate directing group. To gain more insight into the reaction mechanism, a cinnamamide with a deuterium atom at the β-position was subjected to the reaction conditions. The results revealed a subtle reduction in deuteration, implying that C−H activation does not represent the predominant pathway in the *anti*-Michael-type addition reaction[48−51] (Scheme 2C). Next, the removal of the directing group was examined. Treating **3a** under the basic reaction conditions furnished the corresponding carboxylic acid **6** in 66% yield.[52] Furthermore, a two-step sequence successfully transformed **3a** into the secondary amide **7** (Scheme 2D).[53] These transformations of the directing group demonstrated the utility of this *anti*-Michael-type addition reaction.

A plausible reaction mechanism for the *anti*-Michael-type heteroarylation of indole **1a** to acrylamide **2a** is depicted in Scheme 3. Initially, Pd(OCOCF$_3$)$_2$ is trapped by the directing group, facilitating the subsequent nucleophilic addition of **1a** through π-Lewis acid activation. Subsequently, nucleopalladation occurs as **1a** attacks palladium complex **B** to afford alkylpalladium **C**, which is reluctant to undergo undesired β-hydrogen elimination. Finally, protodemetalation by CF$_3$CO$_2$H gives **3a** along with regenerating Pd(OCOCF$_3$)$_2$. In the case of β-substituted acrylamides, the protodemetalation step is likely accelerated by a carboxylic acid additive.

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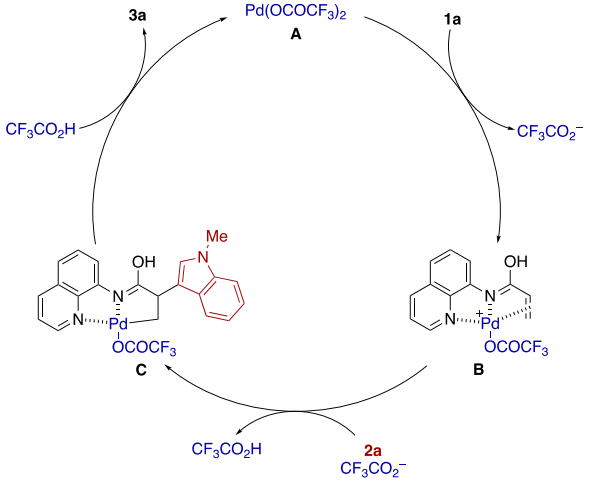
Scheme 3. Plausible Reaction Mechanism



In conclusion, we have successfully developed a novel palladium-catalyzed *anti*-Michael-type (hetero)arylation of acrylamides by employing a bidentate directing group. This methodology exhibits broad substrate compatibility, accommodating various arenes ranging from indoles to electron-rich arenes, leading to the formation of α-(hetero)arylated amides with high atom economy. Additionally, we demonstrated the removal of the quinolyl directing group through two derivatization processes. Our ongoing efforts in the laboratory involve more detailed mechanistic investigations and the expansion of the nucleophile scope.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c00841.

Experimental procedures, characterization data, COSY, HMQC, and HMBC spectra, and ^{1}H, ^{13}C, and ^{19}F NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Michael, A. Ueber die Addition von Natriumacetessig- und Natriummalonsäureäthern zu den Aethern ungesättigter Säuren. *J. Prakt. Chem.* **1887**, *35* (35), 349−356.

(2) Michael, A. Ueber die Addition von Natriumacetessig- und Natriummalonsäureäther zu den Aethern ungesättigter Säuren. *J. Prakt. Chem.* **1894**, *49* (49), 20−25.

(3) Comelles, J.; Moreno-Mañas, M.; Vallribera, A. Michael additions catalyzed by transition metals and lanthanide species. A review. *ARKIVOC* **2005**, *2005*, 207−238.

(4) Heravi, M. M.; Hajiabbasi, P. Recent advances in *C*-heteroatom bond forming by asymmetric Michael addition. *Mol. Divers.* **2014**, *18*, 411−439.

(5) Hui, C.; Pu, F.; Xu, J. Metal-Catalyzed Asymmetric Michael Addition in Natural Product Synthesis. *Chem.—Eur. J.* **2017**, *23*, 4023−4036.

(6) Reznikov, A. N.; Klimochkin, Y. N. Recent Developments in Highly Stereoselective Michael Addition Reactions Catalyzed by Metal Complexes. *Synthesis* **2020**, *52*, 781−795.

(7) Bakó, P.; Nemcsok, T.; Rapi, Z.; Keglevich, G. Enantioselective Michael Addition of Malonates to Enones. *Curr. Org. Chem.* **2020**, *24*, 746−773.

(8) Ferreira, M.; Sá, M. M. Formal [3 + 2] Annulation Involving Allylic Bromides and Thioureas. Synthesis of 2-Iminothiazolidines through a Base-Catalyzed Intramolecular *anti*-Michael Addition. *Adv. Synth. Catal.* **2015**, *357*, 829−833.

(9) Ferreira, M.; Munaretto, L. S.; Gouvêa, D. P.; Bortoluzzi, A. J.; Sá, M. M. Diversity-Oriented Synthesis of 2-Iminothiazolidines: Pushing the Boundaries of the Domino Nucleophilic Displacement/Intramolecular *anti*-Michael Addition Process. *Eur. J. Org. Chem.* **2022**, *2022*, No. e202101562.

(10) Ballini, R.; Bazán, N. A.; Bosica, G.; Palmieri, A. Uncatalyzed, anti-Michael addition of amines to β-nitroacrylates: practical, eco-friendly synthesis of β-nitro-α-amino esters. *Tetrahedron Lett.* **2008**, *49*, 3865−3867.

(11) Ballini, R.; Bosica, G.; Palmieri, A.; Bakhtiari, K. Solvent-Free, *anti*-Michael Addition of Active Methylene Derivatives to β-Nitroacrylates: Eco-Friendly, Chemoselective Synthesis of Polyfunctionalized Nitroalkanes. *Synlett* **2009**, *2009*, 268−270.

(12) Lewandowska, E. Substitution at the α-carbons of α,β-unsaturated carbonyl compounds: *anti*-Michael addition. *Tetrahedron* **2007**, *63*, 2107−2122.

(13) For α-hydroarylation of acrylates and acrylamides through migratory insertion of palladium hydride species, see: Vasquez, A. M.; Gurak, J. A., Jr.; Joe, C. L.; Cherney, E. C.; Engle, K. M. Catalytic α-Hydroarylation of Acrylates and Acrylamides via an Interrupted Hydrodehalogenation Reaction. *J. Am. Chem. Soc.* **2020**, *142*, 10477−10484.

(14) For α-hydroarylation of acrylates and acrylamides through migratory insertion of rhodium hydride species, see: Tran, G.; Hesp, K. D.; Mascitti, V.; Ellman, J. A. Base-Controlled Completely Selective Linear or Branched Rhodium-(I)-Catalyzed C−H *ortho*-Alkylation of Azines without Preactivation. *Angew. Chem., Int. Ed.* **2017**, *56*, 5899−5903.

(15) For α-hydroarylation of acrylates and acrylamides through migratory insertion of rhodium hydride species, see: Tran, G.; Confair, D.; Hesp, K. D.; Mascitti, V.; Ellman, J. A. C2-Selective Branched Alkylation of Benzimidazoles by Rhodium(I)-Catalyzed C−H Activation. *J. Org. Chem.* **2017**, *82*, 9243−9252.

(16) Culkin, D. A.; Hartwig, J. F. Palladium-Catalyzed α-Arylation of Carbonyl Compounds and Nitriles. *Acc. Chem. Res.* **2003**, *36*, 234−245.

(17) Sivanandan, S. T.; Shaji, A.; Ibnusaud, I.; Seechurn, C. C. C. J.; Colacot, T. J. Palladium-Catalyzed α-Arylation Reactions in Total Synthesis. *Eur. J. Org. Chem.* **2015**, *2015*, 38−49.

(18) Barde, E.; Guérinot, A.; Cossy, J. α-Arylation of Amides from α-Halo Amides Using Metal-Catalyzed Cross-Coupling Reactions. *Synthesis* **2019**, *51*, 178−184.

(19) Hao, Y.-J.; Hu, X.-S.; Zhou, Y.; Zhou, J.; Yu, J.-S. Catalytic Enantioselective α-Arylation of Carbonyl Enolates and Related Compounds. *ACS Catal.* **2020**, *10*, 955−993.
(20) Ostrowska, S.; Scattolin, T.; Nolan, S. P. *N*-Heterocyclic carbene complexes enabling the α-arylation of carbonyl compounds. *Chem. Commun.* **2021**, *57*, 4354−4375.
(21) Orlandi, M.; Escudero-Casao, M.; Licini, G. Transition-Metal-Catalyzed Enantioselective α-Arylation of Carbonyl Compounds to Give Tertiary Stereocenters. *Synthesis* **2021**, *53*, 4559−4566.
(22) Ickes, A. R.; Ensign, S. C.; Gupta, A. K.; Hull, K. L. Regio- and Chemoselective Intermolecular Hydroamination of AllylImines for the Synthesis of 1,2-Diamines. *J. Am. Chem. Soc.* **2014**, *136*, 11256−11259.
(23) Ensign, S. C.; Vanable, E. P.; Kortman, G. D.; Weir, L. J.; Hull, K. L. *Anti*-Markovnikov Hydroamination of Homoallylic Amines. *J. Am. Chem. Soc.* **2015**, *137*, 13748−13751.
(24) Vanable, E. P.; Kennemur, J. L.; Joyce, L. A.; Ruck, R. T.; Schultz, D. M.; Hull, K. L. Rhodium-Catalyzed Asymmetric Hydroamination of Allyl Amines. *J. Am. Chem. Soc.* **2019**, *141*, 739−742.
(25) Lee, B. J.; Ickes, A. R.; Gupta, A. K.; Ensign, S. C.; Ho, T. D.; Tarasewicz, A.; Vanable, E. P.; Kortman, G. D.; Hull, K. L. Synthesis of Unsymmetrical Vicinal Diamines via Directed Hydroamination. *Org. Lett.* **2022**, *24*, 5513−5518.
(26) Kim, S. W.; Wurm, T.; Brito, G. A.; Jung, W.-O.; Zbieg, J. R.; Stivala, C. E.; Krische, M. J. Hydroamination versus Allylic Amination in Iridium-Catalyzed Reactions of Allylic Acetates with Amines: 1,3-Aminoalcohols via Ester-Directed Regioselectivity. *J. Am. Chem. Soc.* **2018**, *140*, 9087−9090.
(27) Gurak, J. A., Jr.; Yang, K. S.; Liu, Z.; Engle, K. M. Directed, Regiocontrolled Hydroamination of Unactivated Alkenes via Protodepalladation. *J. Am. Chem. Soc.* **2016**, *138*, 5805−5808.
(28) Yang, K. S.; Gurak, J. A., Jr.; Liu, Z.; Engle, K. M. Catalytic, Regioselective Hydrocarbofunctionalization of Unactivated Alkenes with Diverse C−H Nucleophiles. *J. Am. Chem. Soc.* **2016**, *138*, 14705−14712.
(29) Gurak, J. A., Jr.; Tran, V. T.; Sroda, M. M.; Engle, K. M. N-alkylation of 2-pyridone derivatives via palladium(II)-catalyzed directed alkene hydroamination. *Tetrahedron* **2017**, *73*, 3636−3642.
(30) Gurak, J. A., Jr.; Engle, K. M. Regioselective Hydroamination Using a Directed Nucleopalladation/Protodepalladation Strategy. *Synlett* **2017**, *28*, 2057−2065.
(31) O'Duill, M. L.; Matsuura, R.; Wang, Y.; Turnbull, J. L.; Gurak, J. A., Jr.; Gao, D.-W.; Lu, G.; Liu, P.; Engle, K. M. Tridentate Directing Groups Stabilize 6-Membered Palladacycles in Catalytic Alkene Hydrofunctionalization. *J. Am. Chem. Soc.* **2017**, *139*, 15576−15579.
(32) Nimmagadda, S. K.; Liu, M.; Karunananda, M. K.; Gao, D.-W.; Apolinar, O.; Chen, J. S.; Liu, P.; Engle, K. M. Catalytic, Enantioselective α-Alkylation of Azlactones with Nonconjugated Alkenes by Directed Nucleopalladation. *Angew. Chem., Int. Ed.* **2019**, *58*, 3923−3927.
(33) Wang, X.; Li, Z.-Q.; Mai, B. K.; Gurak, J. A., Jr.; Xu, J. E.; Tran, V. T.; Ni, H.-Q.; Liu, Z.; Liu, Z.; Yang, K. S.; Xiang, R.; Liu, P.; Engle, K. M. Controlling cyclization pathways in palladium(II)-catalyzed intramolecular alkene hydrofunctionalization via substrate directivity. *Chem. Sci.* **2020**, *11*, 11307−11314.
(34) Simlandy, A. K.; Rodphon, W.; Alturaifi, T. M.; Mai, B. K.; Ni, H.-Q.; Gurak, J. A., Jr.; Liu, P.; Engle, K. M. Catalytic Addition of Nitroalkanes to Unactivated Alkenes via Directed Carbopalladation. *ACS Catal.* **2022**, *12*, 13755−13762.
(35) Wang, H.; Bai, Z.; Jiao, T.; Deng, Z.; Tong, H.; He, G.; Peng, Q.; Chen, G. Palladium-Catalyzed Amide-Directed Enantioselective Hydrocarbofunctionalization of Unactivated Alkenes Using a Chiral Monodentate Oxazoline Ligand. *J. Am. Chem. Soc.* **2018**, *140*, 3542−3546.
(36) Bai, Z.; Zheng, S.; Bai, Z.; Song, F.; Wang, H.; Peng, Q.; Chen, G.; He, G. Palladium-Catalyzed Amide-Directed Enantioselective Carboboration of Unactivated Alkenes Using a Chiral Monodentate Oxazoline Ligand. *ACS Catal.* **2019**, *9*, 6502−6509.
(37) Xia, L.; Wu, Y.; Lin, C.; Gao, F.; Shen, L. Palladium-Catalyzed Selective Hydroamination of Aliphatic Alkenes with Hydrazides. *Asian J. Org. Chem.* **2022**, *11*, No. e202100742.
(38) Ballav, N.; Dana, S.; Baidya, M. Palladium(II)-Catalyzed Regioselective Hydrocarbofunctionalization of *N*-Alkenyl Amides: Synthesis of Tryptamine Derivatives. *Org. Lett.* **2022**, *24*, 9228−9232.
(39) Rouquet, G.; Chatani, N. Catalytic Functionalization of $C(sp^2)$−H and $C(sp^3)$−H Bonds by Using Bidentate Directing Groups. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726−11743.
(40) Yadav, M. R.; Rit, R. K.; Shankar, M.; Sahoo, A. K. Reusable and Removable Directing Groups for $C(sp^2)$−H Bond Functionalization of Arenes. *Asian J. Org. Chem.* **2015**, *4*, 846−864.
(41) Fitzgerald, L. S.; O'Duill, M. L. A Guide to Directing Group Removal: 8-Aminoquinoline. *Chem.—Eur. J.* **2021**, *27*, 8411−8436.
(42) Guo, T.; Ding, Y.; Zhou, L.; Xu, H.; Loh, T.-P.; Wu, X. Palladium-Catalyzed anti-Michael Reductive Heck Reaction of α,β-Unsaturated Esters. *ACS Catal.* **2020**, *10*, 7262−7268.
(43) Schafroth, M. A.; Sarlah, D.; Krautwald, S.; Carreira, E. M. Iridium-Catalyzed Enantioselective Polyene Cyclization. *J. Am. Chem. Soc.* **2012**, *134*, 20276−20278.
(44) Cruz, F. A.; Zhu, Y.; Tercenio, Q. D.; Shen, Z.; Dong, V. M. Alkyne Hydroheteroarylation: Enantioselective Coupling of Indoles and Alkynes via Rh-Hydride Catalysis. *J. Am. Chem. Soc.* **2017**, *139*, 10641−10644.
(45) Jensen, K. H.; Sigman, M. S. Mechanistic approaches to palladium-catalyzed alkene difunctionalization reactions. *Org. Biomol. Chem.* **2008**, *6*, 4083−4088.
(46) McDonald, R. I.; Liu, G.; Stahl, S. S. Palladium(II)-Catalyzed Alkene Functionalization via Nucleopalladation: Stereochemical Pathways and Enantioselective Catalytic Applications. *Chem. Rev.* **2011**, *111*, 2981−3019.
(47) Giofré, S.; Molteni, L.; Beccalli, E. M. Asymmetric Pd(II)-Catalyzed C−O, C−N, C−C Bond Formation Using Alkenes as Substrates: Insight into Recent Enantioselective Developments. *Eur. J. Org. Chem.* **2023**, *26*, No. e202200976.
(48) Parella, R.; Babu, S. A. $Pd(OAc)_2$-Catalyzed, AgOAc-Promoted *Z* Selective Directed β-Arylation of Acrylamide Systems and Stereoselective Construction of *Z*-Cinnamamide Scaffolds. *J. Org. Chem.* **2015**, *80*, 12379−12396.
(49) Pan, J. L.; Chen, C.; Ma, Z.-G.; Zhou, J.; Wang, L.-R.; Zhang, S.-Y. Stereoselective Synthesis of *Z*-Vinylsilanes via Palladium-Catalyzed Direct Intermolecular Silylation of $C(sp^2)$−H Bonds. *Org. Lett.* **2017**, *19*, 5216−5219.
(50) Xiang, T.; Liu, Y.; Xu, Q.; He, K.; Pan, F. Palladium-Catalyzed Regio- and Diastereoselective Olefinic C−H Difluoromethylthiolation at Room Temperature. *J. Org. Chem.* **2022**, *87*, 3135−3144.
(51) Wang, J.; Hong, H.; Hu, D.; Liu, J.; Liu, W.; Shi, Y. Pd-catalyzed vinyl C−H amination with diaziridinone. *Org. Chem. Front.* **2024**, *11*, 484−488.
(52) Deng, G.; Chen, J.; Sun, W.; Bian, K.; Jiang, Y.; Loh, T.-P. Bioinspired Deamination of α-Amino Acid Derivatives Catalyzed by a Palladium/Nickel Complex. *Adv. Synth. Catal.* **2018**, *360*, 3900−3905.
(53) Ni, H. Q.; Rodphon, W.; Scherschel, N. F.; Yang, S.; Wang, F.; McAlpine, I. J.; Piercey, D. G.; Engle, K. M. *Anti*-Selective Cyclopropanation of Non-Conjugated Alkenes with Diverse Pronucleophiles via Directed Nucleopalladation. *ChemRxiv (Catalysis)* **2023**, DOI: 10.26434/chemrxiv-2023-b1bdb. (accessed 2024-05-08)