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Palladium-Catalyzed γ,γ′-Diarylation of Free Alkenyl Amines

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Cite This: J. Am. Chem. Soc. 2021, 143, 10352−10360
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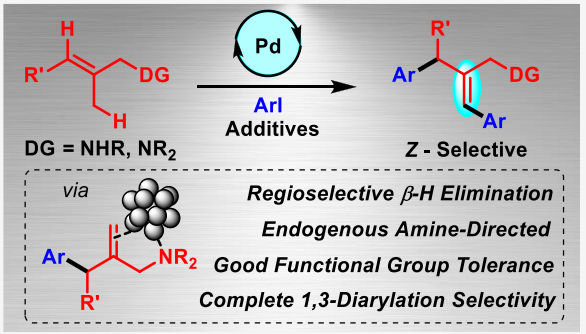
ABSTRACT: The direct difunctionalization of alkenes is an effective way to construct multiple C−C bonds in one-pot using a single functional group. The regioselective dicarbofunctionalization of alkenes is therefore an important area of research to rapidly obtain complex organic molecules. Herein, we report a palladium-catalyzed γ,γ′-diarylation of free alkenyl amines through interrupted chain walking for the synthesis of *Z*-selective alkenyl amines. Notably, while 1,3-dicarbofunctionalization of allyl groups is well precedented, the present disclosure allows 1,3-dicarbofunctionalization of highly substituted allylamines to give highly *Z*-selective trisubsubstituted olefin products. This cascade reaction operates via an unprotected amine-directed Mizoroki−Heck (MH) pathway featuring a β-hydride elimination to selectively chain walk to furnish a new terminal olefin which then generates the *cis*-selective alkenyl amines around the sterically crowded allyl moiety. This operationally simple protocol is applicable to a variety of cyclic, branched, and linear secondary and tertiary alkenylamines, and has a broad substrate scope with regard to the arene coupling partner as well. Mechanistic studies have been performed to help elucidate the mechanism, including the presence of a likely unproductive side C−H activation pathway.

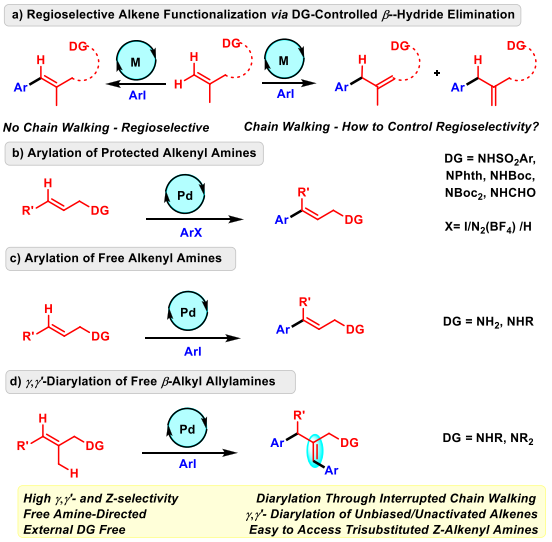


INTRODUCTION

Alkenes are important feedstocks in synthetic chemistry due to their versatility; they are inherently nucleophilic but can easily be made electrophilic by the addition of certain functional groups or catalysts.[1−3] Alkenes can also serve as activating groups for adjacent C−H bonds, allowing even greater synthetic utility.[4−7] One of the biggest challenges for alkene functionalization is to achieve regioselectivity.[8−12] While this is easily overcome for terminal olefins[13−16] and cyclization reactions,[17,18] internal alkenes often undergo poor regiochemically selective reactions without the aid of activating functional groups. This has spawned a significant research enterprise exploring how to achieve regioselective transformations in electronically unbiased alkenes.[19−23] For transition metal-catalyzed reactions, one of the most effective strategies has been the use of directing groups (DGs). A directing group can be thought of as an auxiliary ligand on the substrate that coordinates to the metal, thereby driving the regioselectivity through the formation of the most accessible cyclometalated intermediate. Because many metal−alkyl species can undergo β-hydride elimination and reinsertion, so-called chain walking can even lead to significant changes in regioselectivity but still under the control of the DG (Scheme 1a).[24−28] Several different DGs have been applied to alkene functionalization,[29−32] 1,2-difunctionalization,[33−37] and 1,3-difunctionalization (by taking advantage of chain walking).[38]

Notably, unprotected alkenylamines have not traditionally been targets for alkene functionalization or difunctionalization

Scheme 1. Directed Mizoroki-Heck Reactions on Allylic Substrates



Received: April 23, 2021
Published: June 23, 2021

https://doi.org/10.1021/jacs.1c04261
J. Am. Chem. Soc. 2021, 143, 10352−10360

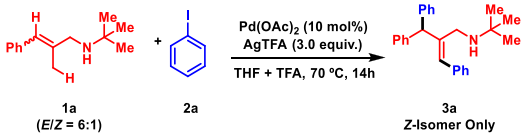
reactions (although tertiary or N/O-substituted alkenylamines are commonly prepared via hydroamination).[39−41] This is due to primary or secondary alkenylamines being prone to oxidation,[42] allylic deamination,[43] and intramolecular cyclization of the alkene,[44−46] issues which are not as significant when the alkene is part of an aromatic ring.[47] Protected alkenylamines have therefore been the preferred entry point for these reactions, serving as substrates for regioselective Mizoroki-Heck (Scheme 1b),[48−51] 1,1-difunctionalization,[52] 1,2-difunctionalization,[53] and even 1,3-difunctionalization reactions.[38] Specifically, the protecting group is generally regarded as also providing a directing effect in these reactions. However, as with all DG-mediated reactions, the need for installation and subsequent removal of the DG significantly increases the process mass intensity and step economy of these transformations, decreasing their industrial relevance.[54]

While transient DGs have been explored that obviate some of these concerns for transition metal-catalyzed organometallic derivatization of amines via C−H activation,[55−59] the instances of transient DGs for alkene functionalization are still relatively limited and not generally applied to amines. On the basis of our interest in amine functionalization,[60,61] we recently reported a CO_2-mediated regioselective Mizoroki-Heck reaction of unprotected allylamines (Scheme 1c).[62] The method provided rapid access to 3,3-difunctionalized allylamines and worked with terminal allyl, cinnamyl, and even aliphatic alkenylamines. Notably, no chain walking was observed, owing to the directing effect of the amine group. Considering the ability of Pd-insertion intermediates to chain walk, we wondered if the high γ-selectivity for these allylamine substrates could be diverted toward selective 1,3-difunctionalization upon the addition of a β-alkyl substituent. Many difunctionalization reactions proceed in a 1,2-fashion where the metalated intermediate intercepts an additional nucleophile or electrophile, followed by a second cross-coupling.[63−65] One of the challenges to overcome in this area is actually competitive β-hydride elimination,[66,67] which when overcome can enable 1,1-[68,69] or 1,3-[70] difunctionalization. However, we hypothesized that in our case, the amine could facilitate direct arylation at the γ-position, followed by chain walking via regioselective β-hydride elimination, which would then facilitate a second arylation at γ' to furnish the γ,γ'-diarylated products (Scheme 1d).

METHODOLOGY AND RESULTS

We began our study on the γ,γ'-diarylation of β-alkylallylamines using (*E*)-*N*-(*tert*-butyl)-2-methyl-3-phenylprop-2-en-1-amine (**1a**) and iodobenzene (**2a**) as model substrates. In the presence of $Pd(OAc)_2$ and AgTFA and with the use of a solvent mixture of THF and TFA, in the ratio of 8:2 at 70 °C for 14 h, product **3a** was obtained in 73% yield (Table 1, **Entry 1**) (see Support Information for experimental details). Although the *E*/*Z* ratio of the starting material was only 6:1, the reaction is completely selective for the *Z*-product. Notably, while our previous report on the Pd-catalyzed Mizoroki-Heck reaction of allylamines demonstrated a key role for CO_2 as a protecting group, in the present transformation, CO_2 offered no significant advantage. As the most significant decomposition products from that study were found to be oxidation of the allylic C−N bond, we hypothesize that in the present system, the added group at the β-position slows this degradation pathway sterically,[71,72] thereby obviating the need for CO_2 as a protecting group.

Table 1. Optimization of Reaction Conditions[a]



entry	reaction conditions[a]	yield (%)
1	Standard conditions	73
2	$Pd(acac)_2$ instead of $Pd(OAc)_2$	43
3	$Pd(dba)_2$ instead of $Pd(OAc)_2$	68
4	$PdCl_2(PPh_3)_2$ instead of $Pd(OAc)_2$	71
5	$Pd(OAc)_2$ omitted	<4
6	AgOAc instead of AgTFA	55
7	Ag_2CO_3 instead of AgTFA	43
8	AgO instead of AgTFA	64
9	Ag_2SO_4 instead of AgTFA	67
10	$AgNO_3$ instead of AgTFA	<4
11	AgTFA omitted	<4
12	Toluene instead of THF	48
13	DCE instead of THF	46
14	MeCN instead of THF	<4
15	TFA omitted	<4
16	Reaction Performed at 50 °C	40
17	Reaction Performed at 90 °C	68
18	Reaction time was 5 h	39

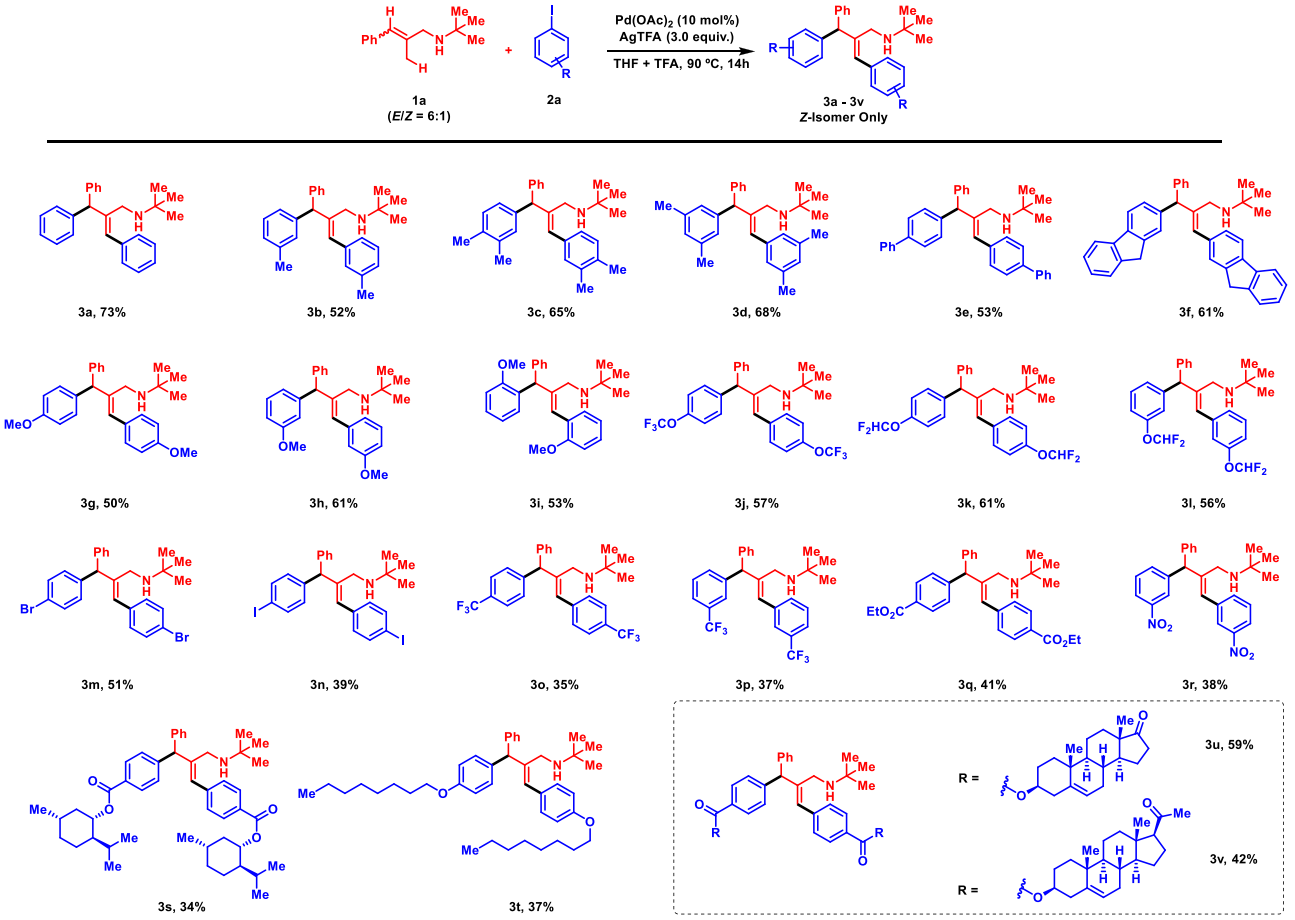
[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (10 mol %), AgTFA (0.45 mmol), and mixture of THF:TFA (8:2) 1 mL, heated at 70 °C for 14 h.

The amine is actually the superior functional group for this transformation, as several protected amines either decomposed or gave mixtures of products (see SI for details), although picolinamides have previously been used for 1,3-diarylation of methacryl groups.[73] Among a variety of different palladium precatalysts, $Pd(OAc)_2$ proved to give the best results (**Entries 1−4**). Other transition metal catalysts were unsuccessful for this transformation (see SI for details). Furthermore, in the absence of Pd, no product was observed (**Entry 5**).

Although silver has several proposed roles in C−H arylation reactions involving aryl iodides,[74−76] in this chemistry we assumed that it might be required to activate the C−I bond and to sequester the byproduct iodide as AgI. We observed a critical role for Ag, as the presence and identity of the silver salt were important, with AgTFA giving the best yield of **3a** (**Entries 6−10**). As expected, when Ag was omitted, no product was observed (**Entry 11**). Although THF proved to be the optimal solvent, toluene and DCE both yielded the product, albeit in lower yields, while acetonitrile was completely ineffective (**Entries 12−14**). Despite the effectiveness of a mixture of THF and TFA in the ratio of 8:2 (1 mL), other mixtures of these two solvents also yielded the product (see SI). However, omission of TFA led to no product formation (**Entry 15**). In this case, between 50 and 60% of the starting material could be recovered on different trials, suggesting a role for TFA beyond just protecting the amine through protonation.[77−79] Lowering the temperature led to decreased yield, although starting material was also recovered (**Entry 16**) suggesting simply poor reaction efficiency at the lower temperature. The reaction was tolerant of increased temperatures, and performance of the reaction at 90 °C gave the γ,γ'-diarylated product in 68% yield (**Entry 17**). A

https://doi.org/10.1021/jacs.1c04261
J. Am. Chem. Soc. 2021, 143, 10352−10360

Table 2. Scope of Aryl Iodide for γ,γ′-Diarylation of α-Methyl Cinnamylamines[a]



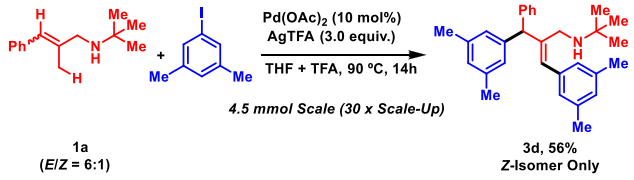
[a]All reactions were performed on 0.15 mmol scale with 4 eq of aryl halide in 1 mL of solvent (8:2 THF:TFA mixture), in at least duplicate, and the average yield reported.

shortening of the reaction time to 5 h also led to lower product yield (**Entry 18**).

With our optimized reaction conditions in hand, we next investigated the γ,γ′-diarylation of model substrate (*E*)-*N*-(*tert*-butyl)-2-methyl-3-phenylprop-2-en-1-amine (**1a**) with various iodoarenes. In addition to simple phenyl (Table 2, **3a**), we could readily install mono or disubstituted arenes containing relatively electronically neutral substituents (**3b**−**3d**) in good yields and also with complete *Z*-selectivity. While the NMR data showed reasonably clearly that the two newly installed arenes were installed at the γ,γ′-positions, X-ray analysis of **3d·HCl** further confirmed the regioselectivity of the products (see SI). Various conjugated iodoarenes such as biphenyl and fluorene also worked in the reaction, giving the desired products in 53% and 61% yields, respectively (**3e** and **3f**). Sterically accessible *meta* and *para*-substituted iodoanisole proved to be viable coupling partners, as was the more sterically hindered *ortho*-iodoanisole (**3g**−**3i**).

The present reaction conditions were also compatible for ethereal CF_3 or CHF_2 groups as well as halides (**3j**−**3n**). Electron deficient groups such as trifluoromethyls, esters, or nitro groups were also tolerated (**3o**−**3r**). Highly lipophilic coupling partners, such as a mentholate ester or octyloxybenzene, were also suitable substrates (**3s** and **3t**). We were pleased to find that even steroid esters derived from *trans*-androsterone and epiandrosterone also worked well under the reaction conditions (**3u** and **3v**). Having established the substrate scope for this methodology, we next wanted to demonstrate that it could be scaled-up effectively. This is necessary considering the heterogeneity of these reactions due to the significant amount of precipitate that forms during the reaction. Using **3d** as our target, we increased the reaction scale from 0.15 to 4.5 mmol or an increase of 30-fold. Gratifyingly, the product was still obtained in 56% isolated yield (Scheme 2).

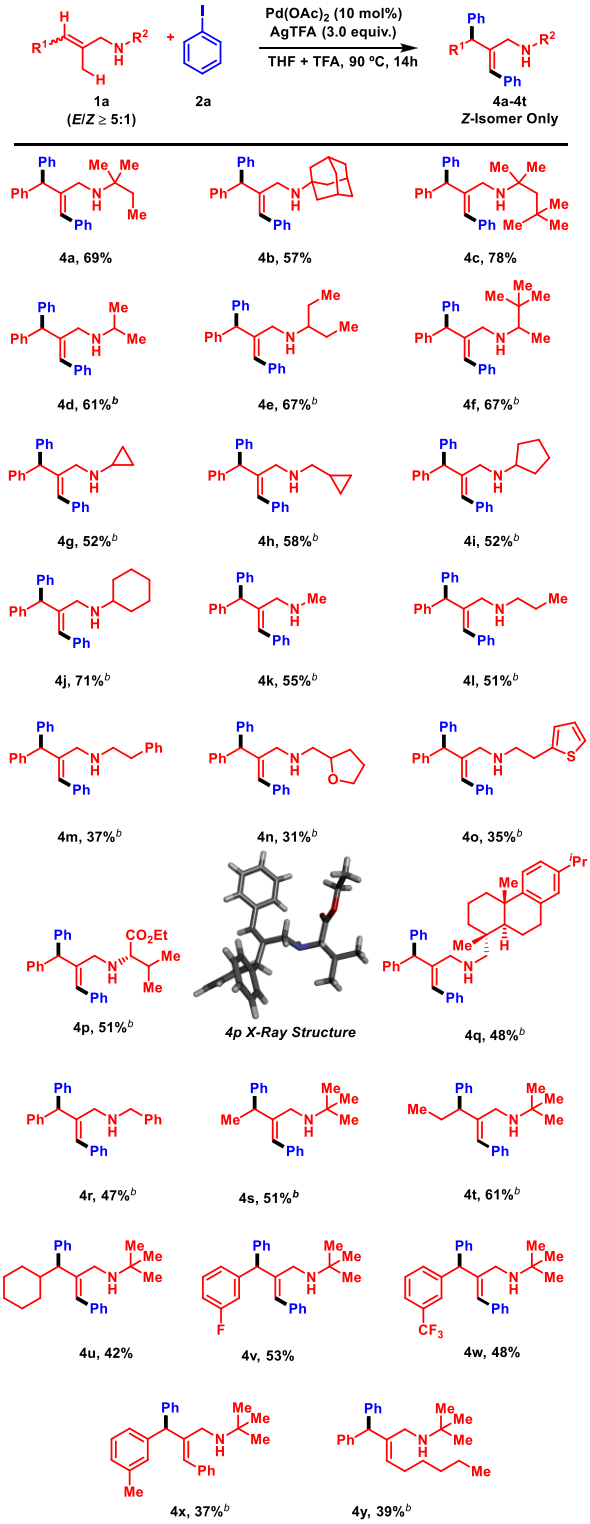
Scheme 2. Reaction Scale-Up



We next studied the scope of secondary amines under the optimized conditions (Table 3). The reactions upon sterically hindered amines proceeded smoothly and afforded the γ,γ′-diarylation amine products (**4a**−**4c**) in up to 78% yield. Notably, we observed regioselective 1,3-diarylation products only and no γ′,γ′-diarylation that might be postulated to arise through migration of the alkene and subsequent diarylation of

https://doi.org/10.1021/jacs.1c04261
J. Am. Chem. Soc. 2021, 143, 10352−10360

Table 3. Scope of γ,γ'-Diarylation of α-Methyl Cinnamylamines[a]



[a]All reactions were performed on a 0.15 mmol scale with 4 eq of aryl halide in 1 mL of solvent (8:2 THF:TFA mixture) and in triplicate with the average yield reported. [b]Ag_2SO_4 (1.5 equiv)

the terminal olefin or a competitive C−H activation. Surprisingly, when we performed the reaction with the less sterically hindered (*E*)-*N*-isopropyl-2-methyl-3-phenylprop-2-en-1-amine, product **4a** was not observed. After rescreening the reaction conditions (see SI), we found that simply replacing the silver trifluoroacetate with silver sulfate was sufficient to allow less sterically hindered substrates to be diarylated, although the reason for this is currently unclear. Under the revised conditions, various branched and carbocyclic secondary amines gave the expected products (**4d**−**4j**) in good yields. Gratifyingly, simple linear alkyl chains also afforded the desired products in moderate isolated yields under the Ag_2SO_4 conditions (**4k**−**4m**). Other secondary amines containing heterocycles such as tetrahydrofuran or thiophane (**4n** and **4o**) can also be regioselectively arylated under these conditions. A valine ester-derivatized substrate could also be used under the revised reaction conditions (**4p**). We could even use the reaction to selectively arylate a leelamine derivative (**4q**). While carbonyl-based protecting groups were not viable substrates, a Bn-protected product could also be prepared (**4r**).

We anticipated that chelation control would only allow chain walking to generate the β,γ'-olefin prior to the second arylation. As expected, when aliphatic substituents were present at the γ-position, arylation was still observed exclusively at the γ,γ'-positions, with no chain walking to other sites (**4s**−**4u**). The diarylation also occurs when other aryl substituents are present at the γ-position (**4v** and **4w**). When there is an arene at both the γ and γ'-positions already, then one arene is added at the γ-position while the double bond shifts to the β,γ'-position (**4x**). In the case of a β-alkyl substituted substrate, where the second arylation was not expected to occur, the reaction proceeded and still gave complete *Z*-selectivity for the formation of the β,γ'-olefin product (**4y**) as judged by the crude ^{1}H NMR of the reaction mixture prior to purification.

Considering the sensitivity of the conditions to the level of substitution of the secondary amines, at least with regard to what silver salt was necessary to best promote the diarylation reaction, we wondered how easily the reaction could be extended to other more or less bulky amines. We therefore sought to evaluate the scope of tertiary amines and found that simple (*E*)-*N*,*N*-diethyl-2-methyl-3-phenylprop-2-en-1-amine (**5a**) could be readily diarylated with representative iodoarenes under the reaction conditions (Table 4; **6a**−**6d**). Cyclic tertiary amine substrates based on morpholine and piperidine also gave the desired products using the silver sulfate conditions (**6e** and **6f**). Despite our efforts, we were unable to find effective conditions for the diarylation of primary β-alkyl cinnamylamines due to their apparent decomposition during the reaction.

We next embarked on studying the mechanism to delineate a plausible catalytic pathway. In this regard, several control experiments were performed under the standard conditions (Scheme 3). Key questions to address included the determination of whether the *cis* and *trans* isomers interconverted prior to the arylation reactions, whether or not there is a background C−H activation reaction, and whether or not the arylation occurs through an inertion or a reductive elimination pathway. To establish whether or not isomerization or C−H bond activation occurs on the alkenyl amine substrates, we carried out the reaction using deuterated trifluoroacetic acid in the absence of an aryl iodide coupling partner (Scheme 3a). After performing the reaction, we found that no alkene isomerization had occurred with the free amine as a directing group.[80] Meanwhile, the *trans*-starting material was partially deuterated at the γ-position, while the *cis*-starting

https://doi.org/10.1021/jacs.1c04261
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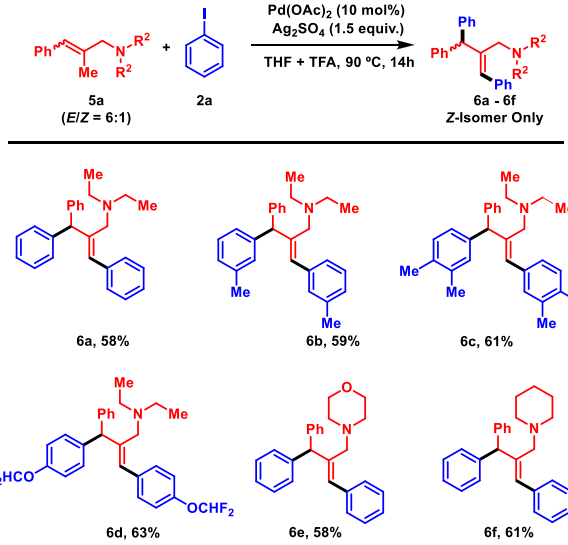
Table 4. Scope of Aryl Iodide and Tertiary Amines for γ,γ′-Diarylation of α-Methyl Cinnamylamines[a]



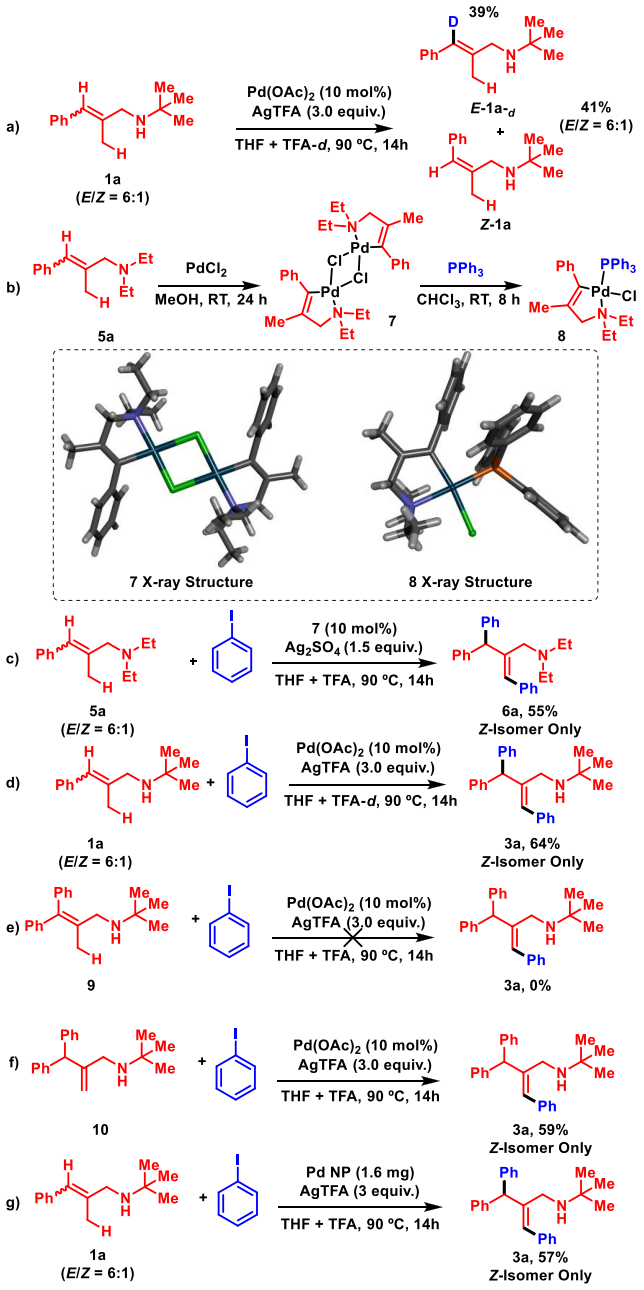
[a]All reactions were performed on a 0.15 mmol scale with 4 eq of aryl halide in 1 mL of solvent (8:2 THF:TFA mixture) and in triplicate with the average yield reported.

material was not. Neither isomer experienced any deuterium enrichment at the γ′-CH_3. These experiments point toward the reversible C−H activation of the *trans* but not the *cis* substrate and rule out reversible/productive C−H activation at the γ′-position.

To provide more direct evidence of C−H bond activation, we subjected **3a** to $PdCl_2$ in methanol. From this reaction, we found that five-membered-ring palladacycle dimer **7** could be isolated (Scheme 3b); notably, the reaction was less clean when we performed the reaction with $Pd(OAc)_2$, possibly due to the formation of a mixture higher order Pd-amine complexes.[81] As expected, treatment of the dimer with PPh_3 gave rise to mononuclear palladacycle **8**. When **7** was used in place of $Pd(OAc)_2$ under the standard reaction conditions, the expected product **5a** was observed in 55% yield (Scheme 3c). Although this does not directly indicate whether the reaction can be initiated through a C−H activation event, it does show that formation of the C−H activation intermediate does not siphon catalyst into a nonproductive reaction pathway. When **7** was combined with silver trifluoroacetate and phenyl iodide under modified reaction conditions (at 50 °C), only starting material was recovered.

To further elucidate the potential for intermediate **7** to have a role in the reaction, we conducted the reaction under deuterated media (Scheme 3d). Despite the partial enrichment observed in the absence of the aryl iodide coupling partner, no deuteration was observed when the reaction was carried out. This suggests that the first arylation outcompetes the reversible C−H activation step. We next synthesized the expected product of the γ-C(sp^2)−H activation reaction, **9**, and used it under the standard conditions (Scheme 3e). In this case, no product was formed, with the starting material being largely recovered. Since the reaction does not proceed from the trisubstituted alkene **9**, we reasoned that after insertion the β-hydride elimination occurs exclusively to give the less substituted olefin **10**, which would then participate in the second arylation reaction. To ensure this was possible, we next

Scheme 3. Mechanistic Studies



synthesized **10** and submitted it to the standard reaction conditions (Scheme 3f) and found product **3a** in an isolated yield of 59%.

Conventionally, the more conjugated alkene would be expected to form, which begged the question of whether the desired product was formed due to kinetic or thermodynamic reasons. We reasoned that the sterically encumbered nature of the system could cause the observed product to be more thermodynamically favored. For this reason, we turned to DFT calculations to shed light on the relative stabilities. Notably, while the unobserved *E* isomer had the highest energy both in the gas phase and considering a THF solvation model under all of the conditions applied (see SI for details), the observed *Z*-product was consistently higher energy than the unobserved conjugated product. On the basis of this, we propose that the β-hydride elimination occurs selectively, presumably due to a

https://doi.org/10.1021/jacs.1c04261
J. Am. Chem. Soc. 2021, 143, 10352−10360

kinetic preference, rather than being under thermodynamic control.

The selective formation of the less stable alkene intermediate **10** and subsequent less stable product **3a** could be due to the size of the catalyst; we had previously demonstrated the likelihood that Pd nanoparticles (Pd NPs) were formed when allylamines and Pd were combined in acidic solvents. Notably, the lack of deuterium incorporation at the γ'-position (Scheme 3a,d) suggested to us that β-hydride elimination might be irreversible under the reaction conditions, meaning that elimination from the less substituted site was kinetically favored after both aryl-insertions. To test if Pd NPs were formed in the current reaction, the filtered reaction mixtures were subjected to scanning electron microscopy and dynamic light scattering, and the formation of particles in the reaction mixture was clearly observed when Pd is added (see SI for details). However, this only proved that Pd NPs had formed and not that they were actually the active catalyst.

Previous work had demonstrated the formation of catalytically relevant Pd NPs in a similar mixture of TFA and an ethereal solvent.[82] An indirect test for the role of a NP catalyst is to perform a mercury drop test.[83] In this case, the addition of mercury prevented any product formation; when mercury was added midway through the reaction, no further product was formed. However, since the utility of the mercury drop test for cyclopalladated complexes has recently been called into question,[84] we also prepared Pd NPs by addition of $NaBH_4$ to an ethanolic solution of $Pd(OAc)_2$ and ran the reaction with these unstabilized Pd NPs. In this case, the product could still be found in 57% (Scheme 3g), which we believe provides further evidence for a Pd NP-catalyzed reaction, although we cannot rule out the potential for involvement of Ag NPs[85] or mixed Pd/Ag NPs.[86]

On the basis of these experiments and previous reports, we propose the following catalytic cycle (Figure 1): The amine will be protonated under the acidic conditions, allowing slow release of the amine. This is proposed to prevent rapid decomposition of the substrate. Some free amine reduces the palladium to form palladium nanoparticles, which are subsequently stabilized by additional amine substrate to form **I**.[87] While we envision that a Pd^0 nanoparticle is formed, Pd^{II} nanoparticles have also been used for Mizoroki-Heck reactions.[88] Free amine can also react with the Pd^{II} salt to give **I'**, although this is not expected to be a productive pathway. Conveniently, the insertion pathway is open to both the *cis* and *trans*. The palladium nanoparticles undergo oxidative addition to aryl iodide, driven by precipitation of AgI, to form **II**. Intermediate **II** undergoes γ-selective migratory insertion into the olefin to generate **III**. Although the formation of a mononuclear four-membered palladacycle is expected to be less favored than the five-membered palladacycle, the larger nanoparticle obviates this strain by allowing one Pd to bond with N and a second one to bond with C in the metallocycle. The insertion is then followed by regioselective β-hydride elimination to give intermediate **IV**. Subsequently, oxidative addition to a second equivalent of aryl iodide generates **V**, and the following selective insertion gives rise to intermediate **VI**. We propose that the exceptional steric bulk of the resulting intermediate coupled with the bulky nanoparticle catalyst drives the final stereoselective β-hydride elimination, which then furnishes the expected product and regenerates the active Pd nanoparticle catalyst.

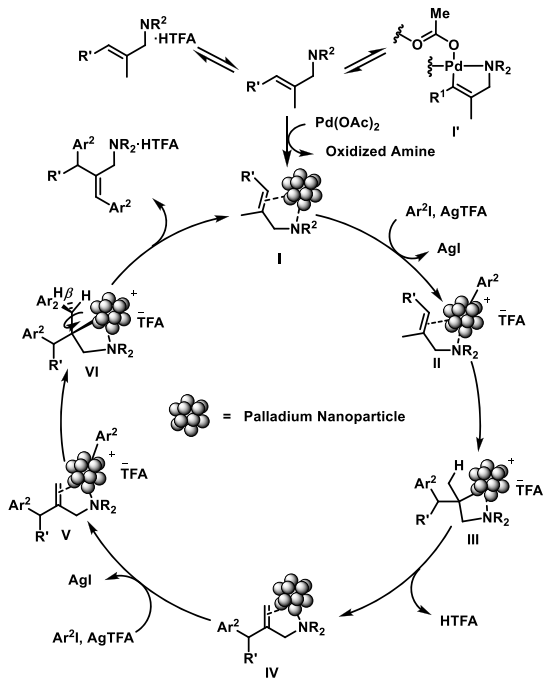


Figure 1. Proposed catalytic cycle.

CONCLUSION

In summary, we have developed a new γ,γ'-diarylation reaction of β-alkyl allylamines. The methodology works well for bulky 2° amines and can be extended to less bulky 2° amines and 3° amines simply by changing the silver salt used in the reaction. Aside from having broad substrate scope and being reasonably scalable, our mechanistic experiments provide what we consider to be a reasonably clear picture of how this 1,3-difunctionalization reaction occurs. Notably, we have demonstrated how the unprotected amine gives superior results under the present conditions when compared with some traditional, protected amine directing groups.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c04261.

Synthesis of amine substrates and iodoarenes, optimization and synthesis of γ,γ'-diarylated alkenylamines, mechanistic experiments, directing group experiments, ^1H and ^{13}C spectra of new compounds, X-ray, STEM, DLS, computational data (PDF)

Accession Codes

CCDC 2075997−2075999 and 2076000−2076002 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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https://doi.org/10.1021/jacs.1c04261
J. Am. Chem. Soc. 2021, 143, 10352−10360

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Author Contributions

The manuscript was written through contributions of all authors./All authors have given approval to the final version of the manuscript.

Funding

This work was supported in part through start-up funds from The University of Toledo, as well as a generous grant from the ACS Herman Frasch Foundation (830-HF17). A.J.G. and Y. F. were supported by funds from the University of Toledo − Office of Undergraduate Research. J. L. P. wishes to acknowledge Kenyon College's Individual Faculty Development Account for financial support.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors wish to acknowledge Dr. Ian Riddington, Dr. Kristin Suhr, Ms. Abby Gatmaitan, and Mr. Phuoc Ngo at The University of Austin's Mass Spectrometer Facility for collection of high resolution mass spectrometry data. Dr. Kristin Kirschbaum is acknowledged for advice with collection of x-ray diffraction data, and Dr. Jennifer Gadient is acknowledged for assistance collecting STEM and DLS data. J. L. P wishes to acknowledge computational resources from the Ohio Supercomputing Center (OSC).

■ REFERENCES

(1) Bai, Z.; Zhang, H.; Wang, H.; Yu, H.; Chen, G.; He, G. Enantioselective Alkylamination of Unactivated Alkenes under Copper Catalysis. *J. Am. Chem. Soc.* **2021**, *143*, 1195−1202.

(2) Patra, T.; Das, M.; Daniliuc, C. G.; Glorius, F. Metal-Free Photosensitized Oxyimination of Unactivated Alkenes with Bifunctional Oxime Carbonates. *Nature Catal.* **2021**, *4*, 54−61.

(3) Gembreska, N. R.; Vogel, A. K.; Ziegelmeyer, E. C.; Cheng, E.; Wu, F.; Roberts, L. P.; Vesoulis, M. M.; Li, W. Halonium Catalysis: An Underutilized and Underexplored Catalytic Concept in Olefin Functionalizations. *Synlett* **2021**, *32*, 539−544.

(4) Mondal, S.; Pinkert, T.; Daniliuc, C.; Glorius, F. Regioselective and Redox-Neutral Cp^*Ir^{III}-Catalyzed Allylic C−H Alkynylation. *Angew. Chem., Int. Ed.* **2021**, *60*, 5688−5692.

(5) Iovan, D. A.; Wilding, M. J. T.; Baek, Y.; Hennessy, E. T.; Betley, T. A. Diastereoselective C−H Bond Amination for Disubstituted Pyrrolidines. *Angew. Chem., Int. Ed.* **2017**, *56*, 15599−15602.

(6) Ammann, S. E.; Liu, W.; White, M. C. Enantioselective Allylic C−H Oxidation of Terminal Olefins to Isochromans by Palladium-(II)/Chiral Sulfoxide Catalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 9571−9575.

(7) Scamp, R. J.; Rigoli, J. W.; Schomaker, J. M. Chemoselective Silver-Catalyzed Nitrene Insertion Reactions. *Pure Appl. Chem.* **2014**, *86*, 381−393.

(8) Liu, C.; Yuan, J.; Zhang, Z.; Gridnev, I. D.; Zhang, W. Asymmetric Hydroacylation Involving Alkene Isomerization for the Construction of C_3-Chirogenic Center. *Angew. Chem., Int. Ed.* **2021**, *60*, 8997−9002.

(9) Shukla, R. K.; Chaturvedi, A. K.; Pal, S.; Volla, C. M. R. Catalytic, Regioselective Hydrocarbofunctionalization of Unactivated Alkenes Triggered by *trans*-Acetoxypalladation of Alkynes. *Org. Lett.* **2021**, *23*, 1440−1444.

(10) Diccianni, J.; Lin, Q.; Diao, T. Mechanisms of Nickel-Catalyzed Coupling Reactions and Applications in Alkene Functionalization. *Acc. Chem. Res.* **2020**, *53*, 906−919.

(11) Yang, X.-H.; Davison, R. T.; Nie, S.-Z.; Cruz, F. A.; McGinnis, T. M.; Dong, V. M. Catalytic Hydrothiolation: Counterion-Controlled Regioselectivity. *J. Am. Chem. Soc.* **2019**, *141*, 3006−3013.

(12) Zhang, W.; Lin, S. Electroreductive Carbfunctionalization of Alkenes with Alkyl Bromides via a Radical-Polar Crossover Mechanism. *J. Am. Chem. Soc.* **2020**, *142*, 20661−20670.

(13) Han, X.-W.; Daugulis, O.; Brookhart, M. Unsaturated Alcohols as Chain-Transfer Agents in Olefin Polymerization: Synthesis of Aldehyde End-Capped Oligomers and Polymers. *J. Am. Chem. Soc.* **2020**, *142*, 15431−15437.

(14) Lu, M.-Z.; Chen, X.-R.; Xu, H.; Dai, H.-X.; Yu, J.-Q. Ligand-Enabled ortho-C−H Olefination of Phenylacetic Amides with Unactivated Alkenes. *Chem. Sci.* **2018**, *9*, 1311−1316.15.

(15) Ma, S.; Hill, C. K.; Olen, C. L.; Hartwig, J. F. Ruthenium-Catalyzed Hydroamination of Unactivated Terminal Alkenes with Stoichiometric Amounts of Alkene and an Ammonia Surrogate by Sequential Oxidation and Reduction. *J. Am. Chem. Soc.* **2021**, *143*, 359−368.

(16) Tathe, A. K.; Urvashi; Yadav, A. K.; Chintawar, C. C.; Patil, N. T. Gold-Catalyzed 1,2-Aminoarylation of Alkenes with External Amines. *ACS Catal.* **2021**, *11*, 4576−4582.

(17) Rago, A. J.; Dong, G. Synthesis of C3,C4-Disubstituted Indoles via the Palladium/Norbornene-Catalyzed *ortho*-Amination/*ipso*-Heck Cyclization. *Org. Lett.* **2021**, *23*, 3755−3760.

(18) Wu, F.; Kaur, N.; Alom, N.-E.; Li, W. Chiral Hypervalent Iodine Catalysis Enables an Unusual Regiodivergent Intermolecular Olefin Aminooxygenation. *JACS Au* **2021**, DOI: 10.1021/jacsau.1c00103.

(19) Ma, S.; Hill, C. K.; Olen, C. L.; Hartwig, J. F. Ruthenium-Catalyzed Hydroamination of Unactivated Terminal Alkenes with Stoichiometric Amounts of Alkene and an Ammonia Surrogate by Sequential Oxidation and Reduction. *J. Am. Chem. Soc.* **2021**, *143*, 359−368.

(20) Dhungana, R. K.; Sapkota, R. R.; Wickham, L. M.; Niroula, D.; Giri, R. Ni-Catalyzed Regioselective 1,2-Dialkylation of Alkenes Enabled by the Formation of Two $C(sp^3)$−$C(sp^3)$ Bonds. *J. Am. Chem. Soc.* **2020**, *142*, 20930−20936.

(21) Ni, H.-Q.; Kevlishvili, I.; Bedekar, P. G.; Barber, J. S.; Yang, S.; Tran-Dubé, M.; Romine, A. M.; Lu, H.-H.; McAlpine, I. J.; Liu, P.; Engle, K. M. *Anti*-Selective [3 + 2] (Hetero)annulation of non-Conjugated Alkenes via Directed Nucleopalladation. *Nat. Commun.* **2020**, *11*, 6432.

(22) Kim, N.; Tran, V. T.; Apolinar, O.; Wisniewski, S. R.; Eastgate, M. D.; Engle, K. M. Ni(COD)(DMFU): A Heteroleptic 16-Electron Precatalyst for 1,2-Diarylation of Alkenes. *Synlett*, 2021, In Press, DOI: DOI: 10.1055/a-1344-6040.
(23) Liu, R. Y.; Buchwald, S. L. CuH-Catalyzed Olefin Functionalization: From Hydroamination to Carbonyl Addition. *Acc. Chem. Res.* **2020**, *53*, 1229−1243.
(24) Kraus, S. L.; Ross, S. P.; Sigman, M. S. Rate Profiling the Impact of Remote Functional Groups on the Redox-Relay Heck Reactions. *Org. Lett.* **2021**, *23*, 2505−2509.
(25) Ross, S. P.; Rahman, A. A.; Sigman, M. S. Development and Mechanistic Interrogation of Interrupted Chain-Walking in the Enantioselective Relay Heck Reaction. *J. Am. Chem. Soc.* **2020**, *142*, 10516−10525.
(26) Sommer, H.; Julá-Hernández, F.; Martin, R.; Marek, I. Walking Metals for Remote Functionalization. *ACS Cent. Sci.* **2018**, *4*, 153−165.
(27) Murphy, S. K.; Bruch, A.; Dong, V. M. Mechanistic Insights into Hydroacylaton with Non-Chelating Aldehydes. *Chem. Sci.* **2015**, *6*, 174−180.
(28) Xu, Y.; Young, M. C.; Dong, G. Catalytic Coupling Between Unactivated Aliphatic C−H Bonds and Alkynes via a Metal−Hydride Pathway. *J. Am. Chem. Soc.* **2017**, *139*, 5716−5719.
(29) Wu, Z.; Fatuzzo, N.; Dong, G. Distal Alkenyl C−H Functionalization via the Palladium/Norbornene Cooperative Catalysis. *J. Am. Chem. Soc.* **2020**, *142*, 2715−2720.
(30) Huffman, T. R.; Wu, Y.; Emmerich, A.; Shenvi, R. A. Intermolecular Heck Coupling with Hindered Alkenes Directed by Potassium Carboxylates. *Angew. Chem., Int. Ed.* **2019**, *58*, 2371−2376.
(31) Lv, L.; Zhu, D.; Li, C.-J. Direct Dehydrogenative Alkyl Heck-Couplings of Vinylarenes with Umpolung Aldehydes Catalyzed by Nickel. *Nat. Commun.* **2019**, *10*, 715.
(32) Tang, C.; Zhang, R.; Zhu, B.; Fu, J.; Deng, Y.; Tian, L.; Guan, W.; Bi, X. Directed Copper-Catalyzed Intermolecular Heck-Type Reaction of Unactivated Olefins and Alkyl Halides. *J. Am. Chem. Soc.* **2018**, *140*, 16929−16935.
(33) González, J.; Cendón, B.; Mascareñas, J. L.; Gulías, M. Kinetic Resolution of Allyltriflamides Through a Pd-Catalyzed C−H Functionalization with Allenes: Asymmetric Assembly of Tetrahydropyridines. *J. Am. Chem. Soc.* **2021**, *143*, 3747−3752.
(34) Marchese, A. D.; Adrianov, T.; Köllen, M. F.; Mirabi, B.; Lautens, M. Synthesis of Carbocyclic Compounds via a Nickel-Catalyzed Carboiodination Reaction. *ACS Catal.* **2021**, *11*, 925−931.
(35) White, D. R.; Hinds, E. M.; Bornowski, E. C.; Wolfe, J. P. Pd-Catalyzed Alkene Difunctionalization Reactions of Malonate Nucleophiles: Synthesis of Substituted Cyclopentanes via Alkene Aryl-Alkylation and Akenyl-Alkylation. *Org. Lett.* **2019**, *21*, 3813−3816.
(36) Li, W.; Boon, J. K.; Zhao, Y. Nickel-Catalyzed Difunctionalization of Allyl Moieties Using Organoboronic Acids and Halides with Divergent Regioselectivities. *Chem. Sci.* **2018**, *9*, 600−607.
(37) Gockel, S. N.; Buchanan, T. L.; Hull, K. L. Cu-Catalyzed Three-Component Carboamination of Alkenes. *J. Am. Chem. Soc.* **2018**, *140*, 58−61.
(38) Basnet, P.; Dhungana, R. K.; Thapa, S.; Shrestha, B.; KC, S.; Sears, J. M.; Giri, R. Ni-Catalyzed Regioselective β,δ-Diarylation of Unactivated Olefins in Ketimines via Ligand-Enabled Contraction of Transient Nickellacycles: Rapid Access to Remotely Diarylated Ketones. *J. Am. Chem. Soc.* **2018**, *140*, 7782−7786.
(39) 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.
(40) Thakuri, R. S.; Schmidt, J. A. R. Palladium-Based Hydroamination Catalysts Employing Sterically Demanding 3-Iminophosphines: Branched Kinetic Products by Prevention of Allylamine Isomerization. *Organometallics* **2019**, *38*, 1917−1927.
(41) Johns, A. M.; Liu, Z.; Hartwig, J. F. Primary *tert*- and *sec*-Allylamines via Palladium Catalyzed Hydroamination and Allylic Substitution with Hydrazine and Hydroxylamine Derivatives.
(42) Kaufmann, W.; Venanzi, L. M. The Wacker-Type Oxidation of Allylamine. *J. Organomet. Chem.* **1991**, *417*, 205−209.
(43) Li, M.-B.; Wang, Y.; Tian, S.-K. Regioselective and Stereospecific Cross-Coupling of Primary Allylic Amines with Boronic Acids and Boronates Through Palladium-Catalyzed C−N Bond Cleavage. *Angew. Chem., Int. Ed.* **2012**, *51*, 2968−2971.
(44) Ran, C.-K.; Huang, H.; Li, X.-H.; Wang, W.; Ye, J.-H.; Yan, S.-S.; Wang, B.-Q.; Feng, C.; Yu, D.-G. Cu-Catalyzed Selective Oxy-Cyanoalkylation of Allylamines with Cycloketone Oxime Esters and CO_2. *Chin. J. Chem.* **2020**, *38*, 69−76.
(45) Flodén, N. J.; Trowbridge, A.; Willcox, D.; Walton, S. M.; Kim, Y.; Gaunt, M. J. Streamlined Synthesis of C(sp^3)−Rich *N*-Heterospirocycles Enabled by Visible-Light-Mediated Photocatalysis. *J. Am. Chem. Soc.* **2019**, *141*, 8426−8430.
(46) Julian, L. D.; Hartwig, J. F. Intramolecular Hydroamination of Unbiased and Functionalized Primary Aminoalkenes Catalyzed by a Rhodium Aminophosphine Complex. *J. Am. Chem. Soc.* **2010**, *132*, 13813−13822.
(47) Lazareva, A.; Daugulis, O. Direct Palladium-Catalyzed *Ortho*-Arylation of Benzylamines. *Org. Lett.* **2006**, *8*, 5211−5213.
(48) Zhang, L.; Dong, C.; Ding, C.; Chen, J.; Tang, W.; Li, H.; Xu, L.; Xiao, J. Palladium-Catalyzed Regioselective and Stereoselective Oxidative Heck Arylation of Allylamines with Arylboronic Acids. *Adv. Synth. Catal.* **2013**, *355*, 1570−1578.
(49) Prediger, P.; Barbosa, L. F.; Génisson, Y.; Correia, C. R. D. Substrate-Directable Heck Reactions with Arenediazonium Salts. The Regio- and Stereoselective Arylation of Allylamine Derivatives and Applications in the Synthesis of Naftifine and Abamines. *J. Org. Chem.* **2011**, *76*, 7737−7749.
(50) Werner, E. W.; Sigman, M. S. A Highly Selective and General Palladium Catalyst for the Oxidative Heck Reaction of Electronically Nonbiased Olefins. *J. Am. Chem. Soc.* **2010**, *132*, 13981−13983.
(51) Delcamp, J. H.; Brucks, A. P.; White, M. C. A General and Highly Selective Chelate-Controlled Intermolecular Oxidative Heck Reaction. *J. Am. Chem. Soc.* **2008**, *130*, 11270−11271.
(52) He, Y.; Yang, Z.; Thornbury, R. T.; Toste, F. D. Palladium-Catalyzed Enantioselective 1,1-Fluoroarylation of Aminoalkenes. *J. Am. Chem. Soc.* **2015**, *137*, 12207−12210.
(53) Derosa, J.; Kleinmans, R.; Tran, V. T.; Karunananda, M. K.; Wisniewski, S. R.; Eastgate, M. D.; Engle, K. M. Nickel-Catalyzed 1,2-Diarylation of Simple Alkenyl Amines. *J. Am. Chem. Soc.* **2018**, *140*, 17878−17883.
(54) Kapoor, M.; Singh, A.; Sharma, K.; Hsu, M. H. Site-Selective C(sp^3)−H and C(sp^2)−H Functionalization of Amines Using a Directing-Group-Guided Strategy. *Adv. Synth. Catal.* **2020**, *362*, 4513−4542.
(55) Chen, Y.-Q.; Singh, S.; Wu, Y.; Wang, Z.; Hao, W.; Verma, P.; Qiao, J. X.; Sunoj, R. B.; Yu, J.-Q. Pd-Catalyzed γ-C(sp^3)−H Fluorination of Free Amines. *J. Am. Chem. Soc.* **2020**, *142*, 9966−9974.
(56) St John-Campbell, S.; Ou, A. K.; Bull, J. A. Palladium-Catalyzed C(sp^3)−H Arylation of Primary Amines Using a Catalytic Alkyl Acetal to Form a Transient Directing Group. *Chem. - Eur. J.* **2018**, *24*, 17838−17843.
(57) Lin, H.; Wang, C.; Bannister, T. D.; Kamenecka, T. M. Site-Selective gamma-C(sp^3)−H and gamma-C(sp^2)−H Arylation of Free Amino Esters Promoted by a Catalytic Transient Directing Group. *Chem. - Eur. J.* **2018**, *24*, 9535−9541.
(58) Xu, Y.; Young, M. C.; Wang, C.; Magness, D. M.; Dong, G. Catalytic C(sp^3)−H Arylation of Free Primary Amines with an *exo* Directing Group Generated In Situ. *Angew. Chem., Int. Ed.* **2016**, *55*, 9084−9087.
(59) Liu, Y.; Ge, H. Site-Selective C−H Arylation of Primary Aliphatic Amines Enabled by a Catalytic Transient Directing Group. *Nat. Chem.* **2017**, *9*, 26−32.

(60) Kapoor, M.; Liu, D.; Young, M. C. Carbon Dioxide-Mediated C(sp^3)−H Arylation of Amine Substrates. *J. Am. Chem. Soc.* **2018**, *140*, 6818−6822.
(61) Chand-Thakuri, P.; Landge, V. G.; Kapoor, M.; Young, M. C. One-Pot C−H Arylation/Lactamization Cascade Reaction of Free Benzylamines. *J. Org. Chem.* **2020**, *85*, 6626−6644.
(62) Landge, V. G.; Maxwell, J. M.; Thakuri, P. C.; Kapoor, M.; Diemler, E. T.; Young, M. C. Palladium-Catalyzed Regioselective Arylation of Unprotected Allylamines. *JACS Au* **2021**, *1*, 13−22.
(63) Badir, S. O. Developments in Photoredox/Nickel Dual-Catalyzed 1,2-Difunctionalizations. *Chem.* **2020**, *6*, 1327−1339.
(64) Derosa, J.; Apolinar, O.; Kang, T.; Tran, V. T.; Engle, K. M. Recent Developments in Nickel-Catalyzed Intermolecular Dicarbofunctionalization of Alkenes. *Chem. Sci.* **2020**, *11*, 4287−4296.
(65) Dhungana, R. K.; KC, S.; Basnet, P.; Giri, R. Transition Metal-Catalyzed Dicarbofunctionalization of Unactivated Olefins. *Chem. Rec.* **2018**, *18*, 1314−1340.
(66) Dhungana, R. K.; Sapkota, R. R.; Niroula, D.; Giri, R. Walking Metals: Catalytic Difunctionalization of Alkenes at Nonclassical Sites. *Chem. Sci.* **2020**, *11*, 9757−9774.
(67) Giri, R.; KC, S. Strategies Toward Dicarbofunctionalization of Unactivated Olefins by Combined Heck Carbometallation and Cross-Coupling. *J. Org. Chem.* **2018**, *83*, 3013−3022.
(68) Sun, S.-Z.; Talavera, L.; Spieß, P.; Day, C. S.; Martin, R. sp^3*Bis*-Organometallic Reagents via Catalytic 1,1-Difunctionalization of Unactivated Olefins. *Angew. Chem., Int. Ed.* **2021**, *60*, 11740−11744.
(69) Wang, W.; Ding, C.; Yin, G. Catalyst-Controlled Enantioselective 1,1-Arylboration of Unactivated Olefins. *Nature Catal.* **2020**, *3*, 951−958.
(70) Dhungana, R. K.; KC, S.; Basnet, P.; Aryal, V.; Chesley, L. J.; Giri, R. Ni(I)-Catalyzed β,δ-Vinylarylation of γ,δ-Alkenyl α-Cyanocarboxylic Esters via Contraction of Transient Nickellacycles. *ACS Catal.* **2019**, *9*, 10887−10893.
(71) Buettner, C. S.; Willcox, D.; Chappell, B. G. N.; Gaunt, M. J. Mechanistic Investigation into the C(sp^3)−H Acetoxylation of Morpholines. *Chem. Sci.* **2019**, *10*, 83−89.
(72) Hogg, K. F.; Trowbridge, A.; Alvarez-Pérez, A.; Gaunt, M. J. The α-Tertiary Amine Motif Drives Remarkable Selectivity for Pd-Catalyzed Carbonylation of β-Methylene C−H Bonds. *Chem. Sci.* **2017**, *8*, 8198−8203.
(73) Parella, R.; Babu, S. A. Pd(II)-Catalyzed, Picolinamide-Assisted, *Z*-Selective γ-Arylation of Allylamines to Construct *Z*-Cinnamylamines. *J. Org. Chem.* **2017**, *82*, 6550−6567.
(74) Bay, K. L.; Yang, Y.-F.; Houk, K. N. Multiple Roles of Silver Salts in Palladium-Catalyzed C−H Activations. *J. Organomet. Chem.* **2018**, *864*, 19−25.
(75) Lotz, M. D.; Camasso, N. M.; Canty, A. J.; Sanford, M. S. Role of Silver Salts in Palladium-Catalyzed Arene and Heteroarene C−H Functionalization Reactions. *Organometallics* **2017**, *36*, 165−171.
(76) Whitaker, D.; Burés, J.; Larrosa, I. Ag(I)-Catalyzed C−H Activation: The Role of the Ag(I) Salt in Pd/Ag-Mediated C−H Arylation of Electron-Deficient Arenes. *J. Am. Chem. Soc.* **2016**, *138*, 8384−8387.
(77) Mack, J. B.; Gipson, J. D.; Du Bois, J.; Sigman, M. S. Ruthenium-Catalyzed C−H Hydroxylation in Aqueous Acid Enables Selective Functionalization of Amine Derivatives. *J. Am. Chem. Soc.* **2017**, *139*, 9503−9506.
(78) Mbofana, C. T.; Chong, E.; Lawniczak, J.; Sanford, M. S. Iron-Catalyzed Oxyfunctionalization of Aliphatic Amines at Remove Benzylic C−H Sites. *Org. Lett.* **2016**, *18*, 4258−4261.
(79) Howell, J. M.; Feng, K.; Clark, J. R.; Trzepkowski, L. J.; White, M. C. Remote Oxidation of Aliphatic C−H Bonds in Nitrogen-Containing Molecules. *J. Am. Chem. Soc.* **2015**, *137*, 14590−14593.
(80) Matsuura, R.; Karunananda, M. K.; Liu, M.; Nguyen, N.; Blackmond, D. G.; Engle, K. M. Mechanistic Studies of Pd(II)-Catalyzed *E*/*Z* Isomerization of Unactivated Alkenes: Evidence for a Monometallic Nucleopalladation Pathway. *ACS Catal.* **2021**, *11*, 4239−4246.
(81) McNally, A.; Haffemayer, B.; Collins, B. S. L.; Gaunt, M. J. Palladium-Catalysed C−H Activation of Aliphatic Amines to give Strained Nitrogen Heterocycles. *Nature* **2014**, *510*, 129−133.
(82) Huang, Z.; Sam, Q. P.; Dong, G. Palladium-Catalyzed Direct β-Arylation of Ketones with Diaryliodonium Salts: a Stoichiometric Heavy Metal-Free and User-Friendly Approach. *Chem. Sci.* **2015**, *6*, 5491−5498.
(83) Crabtree, R. H. Resolving Heterogenieity Problems and Artifacts in Operationally Homogeneous Transition Metal Catalysts. *Chem. Rev.* **2012**, *112*, 1536−1554.
(84) Gorunova, O. N.; Novitskiy, I. M.; Grishin, Y. K.; Gloriozov, I. P.; Roznyatovsky, V. A.; Khrustalev, V. N.; Kochetkov, K. A.; Dunina, V. V. When Applying the Mercury Poisoning Test to Palladacycle-Catalyzed Reactions, One Should Not Consider the Common Misconception of Mercury(0) Selectivity. *Organometallics* **2018**, *37*, 2842−2858.
(85) Desireddy, A.; Conn, B. E.; Guo, J.; Yoon, B.; Barnett, R. N.; Monahan, B. M.; Kirschbaum, K.; Griffith, W. P.; Whetten, R. L.; Landman, U.; Bigioni, T. P. Ultrastable Silver Nanoparticles. *Nature* **2013**, *501*, 399−402.
(86) Tedsree, K.; Li, T.; Jones, S.; Chan, C. W. A.; Yu, K. M. K.; Bagot, P. A. J.; Marquis, E. A.; Smith, G. D. W.; Tsang, S. C. E. Hydrogen Production from Formic Acid Decomposition at Room Temperature using a Ag−Pd Core−Shell Nanocatalyst. *Nat. Nanotechnol.* **2011**, *6*, 302−307.
(87) Zhang, L.; Wang, L.; Jiang, Z.; Xie, Z. Synthesis of Size-Controlled Monodisperse Pd Nanoparticles via a non-Aqueous Seed-Mediated Growth. *Nanoscale Res. Lett.* **2012**, *7*, 312.
(88) Ansari, T. N.; Jasinski, J. B.; Leahy, D. K.; Handa, S. Metal−Micelle Cooperativity: Phosphine Ligand-Free Ultrasmall Palladium-(II) Nanoparticles for Oxidative Mizoroki−Heck-type Couplings in Water at Room Temperature. *JACS Au* **2021**, *1*, 308−315.

NOTE ADDED AFTER ASAP PUBLICATION

This paper was published on June 23, 2021. Tables 1 and 2 have been updated. The revised version re-posted on June 29, 2021.

https://doi.org/10.1021/jacs.1c04261
J. Am. Chem. Soc. 2021, 143, 10352−10360