OL | Organic Letters

Letter

Cite This: Org. Lett. 2019, 21, 4868–4872

pubs.acs.org/OrgLett

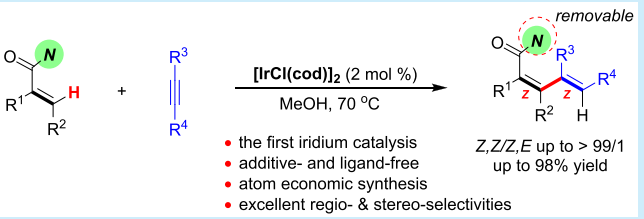
Additive- and Ligand-Free Cross-Coupling Reactions between Alkenes and Alkynes by Iridium Catalysis

Yaling Sun,[‡] Keke Meng,[‡] Jian Zhang,* Mengxin Jin, Nini Huang, and Guofu Zhong*

College of Materials, Chemistry and Chemical Engineering, Hangzhou Normal University, Hangzhou 310036, China

Supporting Information

ABSTRACT: Although a range of transition-metal-catalyzed cross-coupling reactions of alkenes and alkynes have been developed to produce valuable conjugated dienes, extension of these reactions to iridium catalysis has yet to be demonstrated. The first iridium-catalyzed alkene−alkyne cross-coupling reactions have been realized under ligand- and additive-free conditions. A wide range of acrylamides and alkynes could be used as coupling partners, providing branched (*Z*,*Z*)-butadiene skeletons with excellent site- and stereoselectivities. The utility of this approach is also demonstrated by preparative-scale and C−H functionalization of perillic and artemisic amides.



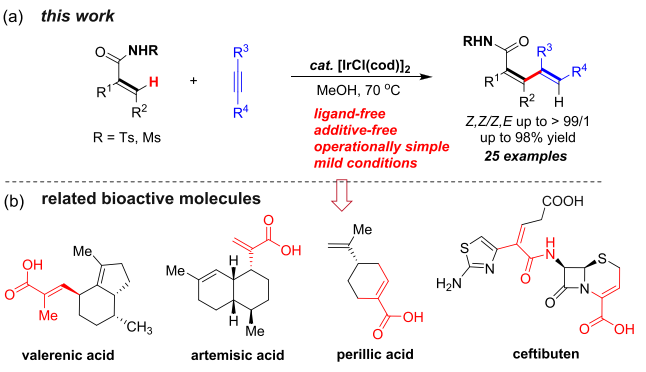
Cross-coupling reactions are highly sought after in pharmaceutical and materials chemistry, converting readily available raw feedstocks to useful, value-added commodity chemicals.[1] In particular, the formation of C(alkenyl)−C(alkenyl) bonds via oxidative C−H/C−H cross-coupling is highly desirable because conjugated diene skeletons are ubiquitous in natural products and drugs.[2]

The catalytic alkene−alkyne coupling reactions provided an attractive access from the standpoint of atomic economy, which has been achieved via metallacyclopentene,[3] chelation-assisted hydrovinylation of alkyne,[2i,4] or a Mizoroki−Heck-type mechanism,[5] usually leading to a *Z*,*E*-configuration. A central challenge in this area is the development of divergent methods to achieve highly regio- and stereoselective formation of either branched or linear butadienes. New catalytic protocols with additive-free, ligand-free, and/or oxidant-free conditions, broader substrate scope, better reactivity, as well as unique chemo- and stereoselectivity are still highly desirable. Transition metals of the fourth and fifth period, such as ruthenium, rhodium, palladium, nickel, and cobalt, have been utilized in alkene−alkyne cross-coupling reactions.[3−5] However, there is still no example catalyzed by transition metal of the sixth period such as iridium.[6]

In light of the rapid development of Ir-catalyzed C−H functionalizations,[7−9] it is highly desirable to extend the alkyne−alkene cross-couplings to iridium chemistry for a number of reasons. First, both the substrate scope and reaction type can be complementary to previous reactions or even with better reactivity and selectivity.[7] Second, the different ligands used for Ir-catalyzed C−H functionalization could offer new opportunities for developing ligand-controlled, chemo- and stereoselective cross-coupling reactions.[9] Despite remarkable progress on Ir-catalyzed aromatic and alkyl C−H functionalizations,[7,8] examples of alkenyl C−H functionalization by iridium catalysis continue to be scarce,[10] presumably due to lability of alkenes under highly active iridium catalysis. Moreover, competitive C(alkenyl)−H and C(allyl)−H cleavage sites, displaying ready olefin isomerization via π-allyliridium or iridium hydride intermediate,[7,10,11] can make reactivity and selectivity of cross-coupling reaction a significant challenge.

Using ubiquitous acrylic acids or their derivatives such as acrylamides as coupling partners is advantageous due to their low cost and widely occurring in natural products and drugs (Scheme 1b). In line with our ongoing interest in olefinic C−H activation and butadiene synthesis,[2g−i,4e] we herein disclose Ir-catalyzed regio- and stereoselective cross-couplings using structurally diverse acrylamides and alkynes, leading to branched *Z*,*Z*-configured butadienes (Scheme 1a). The utility

Scheme 1. Ir-Catalyzed Cross-Couplings of Alkenes and Alkynes



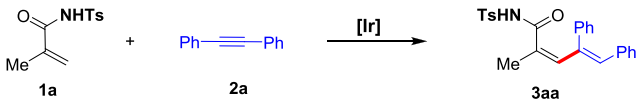
Received: May 20, 2019
Published: June 12, 2019

DOI: 10.1021/acs.orglett.9b01766
Org. Lett. 2019, 21, 4868–4872

of this approach is also demonstrated by preparative-scale and C−H functionalization of perillic and artemisic amides.

Due to the widely occurring and great importance of amide group, we examined the cross-coupling between different *N*-substituted acrylamides **1** and alkyne **2a**. Unfortunately, *N*-alkylamides led to poor reactivity/selectivity under a variety of catalytic conditions. In this context, we envisioned that high acidity of the N−H proton might be essential for the formation of the amidoiridium species via deprotonation to facilitate the C−H insertion.[7] We turned to examine the reaction of acrylamide bearing a *p*-toluenesulfonyl group. Although $[IrCp^*Cl_2]_2$ was inefficient, the cross-coupling reaction was found to take place in the presence of $[Ir(OMe)(cod)]_2$ (2 mol %), yielding product **3aa** in 74% yield (Table 1, entries 1

Table 1. Optimization of Catalytic Conditions[a]



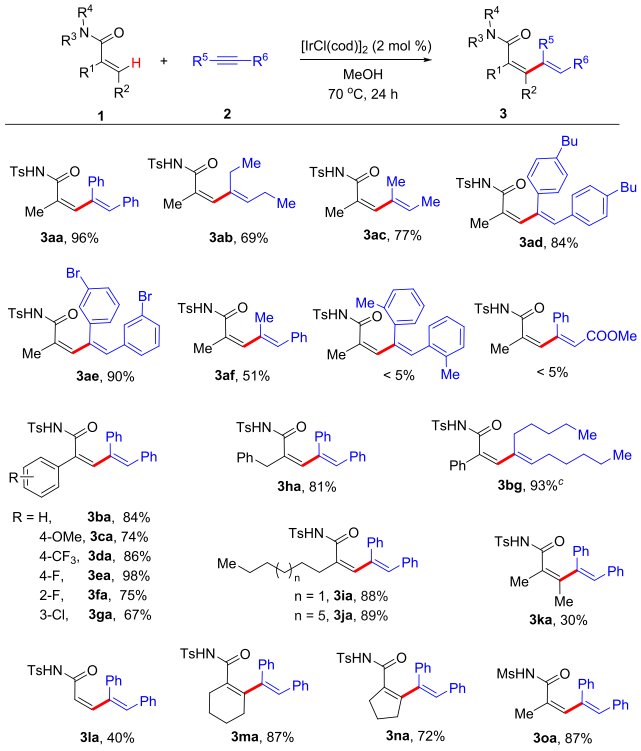
entry	catalyst	additive	solvent	yield[b] (%)
1	$[IrCp^*Cl_2]_2$		toluene	0
2	$[Ir(OMe)(cod)]_2$		toluene	74
3	$[IrCl(cod)]_2$		toluene	87
4	$[IrCl(cod)]_2$		dioxane	86
5	$[IrCl(cod)]_2$		DCE	83
6	$[IrCl(cod)]_2$		DME	71
7	**$[IrCl(cod)]_2$**		**MeOH**	**96**
8	$[IrCl(cod)]_2$		EtOH	72
9	$[IrCl(cod)]_2$		^{i}PrOH	76
10	$[IrCl(cod)]_2$		H_2O	73
11[c]	$[IrCl(cod)]_2$	$AgSbF_6$	MeOH	85
12[c]	$[IrCl(cod)]_2$	AgOTf	MeOH	87
13[d]	$[IrCl(cod)]_2$		MeOH	84

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), [Ir] (4 mol %), in solvent (1 mL) at 70 °C, 24 h. [b]Isolated yields. [c]Ag additive (4 mol %) added. [d]1 mol % of $[IrCl(cod)]_2$ used, 48 h. DME = 1,2-dimethoxyethane; DCE = 1,2-dichloroethane.

and 2). This prompted us to try another catalyst $[IrCl(cod)]_2$ also chelated by diene ligand, leading to 87% yield (entry 3). Replacing the toluene with dioxane, DCE, or DME did not improve the reaction (entries 4−6). To our delight, using of MeOH led to quantitative yield and excellent stereoselectivity (*Z*,*Z*/*Z*,*E* > 99/1) (entry 7). The *Z*,*Z*-configuration supported a directed oxidative addition of the olefinic C−H bond followed by a *syn*-insertion into the alkyne.[4] Other alcohols such as ethanol and 2-propanol led to decreased yields (entries 8 and 9). Interestingly, the reaction proceeded even in water, albeit with decreased efficacy (entry 10). Notably, addition of silver salts such as $AgSbF_6$ and AgOTf even retarded the reaction slightly (entries 11 and 12).[12] The alkenylation still proceeded well under lower catalyst loading (entry 13).

With the optimized reaction conditions in hand, we next examined the scope and limitation of alkenes **1** and alkynes **2** (Scheme 2). The reactions of dialkylacetylenes **2b** and **2c** also reacted well with acrylamide **1a** to give the *Z*,*Z*-configured products **3ab** and **3ac** in 69% and 77% yields, respectively. Diarylacetylenes bearing Br or alkyl substituents proceeded smoothly to give the products in excellent yields (**3ad** and **3ae**). In the reactions of unsymmetrically substituted alkynes such as 1-phenyl-1-propyne, C−C bond formation only

Scheme 2. Scope of Differently Substituted Substrates[a]



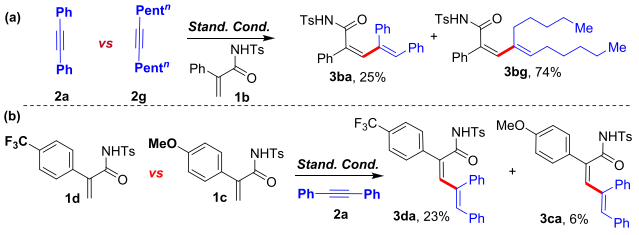
[a]Reaction conditions: **1** (0.2 mmol), **2** (0.3 mmol), $[IrCl(cod)]_2$ (2 mol %) in MeOH (1 mL) at 70 °C for 24 h. [b]Isolated yields. [c]*Z*,*Z*/*Z*,*E* = 87/13.

occurred at the C-2 position, indicating excellent regioselectivity governed by electronic and steric factors (**3af**). Unfortunately, both bis(2-methylphenyl) acetylene and phenylpropiolate failed to react even at elevated temperatures.[13a] Thereafter, we turned to the reactions of other representative aliphatic and aryl substituted acrylamides **1**. Aromatic F, Cl, CF_3, and OMe were also well tolerated and gave the corresponding products in 67−98% yields, thus showing good functionality compatibility (**3ba**−**3ga**). 6-Dodecyne also reacted well, leading to 93% yield (**3bg**). Notably, acrylamide bearing a sensitive benzyl group was also converted (**3ha**). Installation of longer alkyl chain at the *α*-position furnished the corresponding cross-coupling in excellent yields (**3ia** and **3ja**). Even angelic amide and plain acrylamide were converted, though both of them were totally inert or incompatible in previous directed C(alkenyl)−H functionalizations (**3ka** and **3la**).[2,4] Conformationally restricted acrylamide bearing a cyclohexenyl or a cyclopentene moiety converted smoothly (**3ma** and **3na**). All of these results exhibited a much broader substrate scope than the previous Ru-catalyzed protocol.[4e] Finally, *N*-methylsulfonyl acrylamide **1o** gave the cross-coupling product **3oa** in 87% yield.[13b]

Given the high catalytic efficacy of the iridium-catalyzed cross-couplings, we attempted to gain some preliminary understanding of the reaction mechanisms. Competition experiments between alkynes **2a** and **2g** highlighted alkylalkynes to be more reactive (Scheme 3a). Intermolecular competition experiments between acrylamides **1d** and **1c** revealed that electron-deficient acrylamide was converted preferentially, hence rendering an electrophilic C−H bond activation less likely to be operative (Scheme 3b).[2] These

DOI: 10.1021/acs.orglett.9b01766
Org. Lett. 2019, 21, 4868−4872

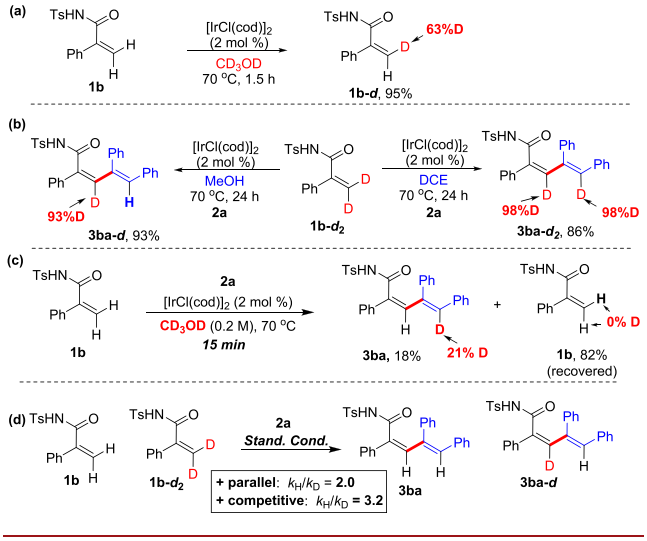
Scheme 3. Competitive Reactions



results are consistent with our prior observation in ruthenium-catalyzed alkene−alkyne coupling.[4e]

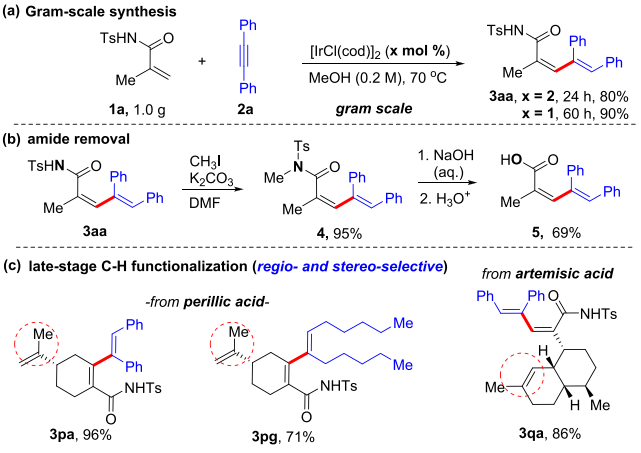
If acrylamide **1b** was subjected to the corresponding optimal conditions with CD_3OD, significant olefinic H/D exchanges were observed, thereby implicating a reversible cyclometalation mode (Scheme 4a). The excellent site- and stereoselective H/D exchanges excluded the possible alkyliridium mechanism by insertion.[7] Treatment of deuterium-labeling acrylamide **1b**-d_2 with acetylene **2a** in protic methanol led to a complete deuterium loss in the olefinic position of product **3ba**-*d*, while the *cis*-olefinic deuterium completely transferred to the product **3ba**-d_2 using DCE as a solvent (Scheme 4b). Although a number of deuteration of alkenes have been reported, extension to butadiene derivatives continued to be scarce, and such selective deuteration may find valuable utilization in mechanistic and metabolic studies.[14] We also performed the deuterium incorporation experiment under the optimal conditions in the presence of alkyne **2a**. The lack of D-incorporation to recovered acrylamide **1b** suggested that the alkenylation step is sufficiently fast to outcompete the reversibility of the C−H activation step, while 21% D-incorporation to the product **3ba** exhibited a fast H/D exchange on hydridoiridium intermediate (Scheme 4c). Finally, kinetic isotope effect (KIE) values determined via intermolecular competition experiments and parallel experiments using non- and deuterated acrylamides **1b** and **1b**-d_2 confirmed olefinic C−H cleavage to be the rate-determining step (Scheme 4d).[15]

Scheme 4. Deuterium-Labeled Experiments



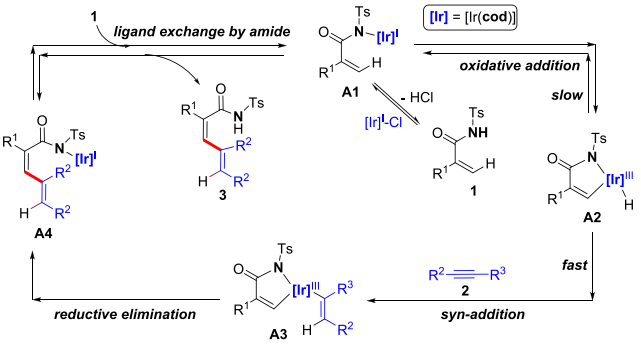
The gram-scale cross-coupling reaction also proceeded well even with 1 mol % catalyst loading, as illustrated by the preparation of **3aa** to demonstrate the robustness of the protocol (Scheme 5a). The amide group can be conveniently removed under methylation−hydrolysis conditions, providing carboxylic acid **5** without any erosion of the *Z*/*E* configuration (Scheme 5b). A particularly useful application of this method is in the late-stage C−H derivatization of bioactive molecules such as perillic and artemisic acid derived amides. All of them reacted smoothly, leading to alkenylation analogues **3pa**−**3qa** in 71−96% yields with excellent site- and stereoselectivities (Scheme 5c).[16] Given that many therapeutic agents contain acrylic acid/acrylamide moieties, we expect our methodology to provide valuable opportunities to accelerate structure−activity relationship studies in drug discovery.

Scheme 5. Synthetic Applications



Plausible catalytic cycles are shown in Scheme 6. First, [Ir]-Cl reacts with *N*-sulfonyl acrylamide **1** to give an amidoiridium species **A1**. Oxidative addition of olefinic C−H bond to the iridium produces a hydridoiridium intermediate **A2**, which reacts quickly with alkyne **2** by *syn*-addition to generate the intermediate **A3**. Reductive elimination and ligand exchange by amide **1** give the diene **3** and regenerate **A1** (Scheme 6).[7,14]

Scheme 6. Proposed Mechanism



In summary, we have presented the first cross-couplings of alkenes and alkynes by iridium catalysis, leading to stereoselective synthesis of a wide range of branched *Z*,*Z*-dienamide derivatives. By judicious choice of iridium complexes [IrCl(cod)]$_2$, the cross-couplings proceeded under metal additive- and ligand-free conditions, leading to good to excellent reactivity and selectivity. The operationally simple protocols displayed broad substrate classes, including mono-, di-, and trisubstituted acrylamides and enabled the gram-scale prepara-

DOI: 10.1021/acs.orglett.9b01766
Org. Lett. 2019, 21, 4868−4872

tion and C−H modification of perillic and artemisic amides, demonstrating their practicality and versatility. Furthermore, the *N*-Ts amide auxiliary could be smoothly removed under mild conditions. We anticipate that these divergent cross-coupling reactions will find broad applicability in multifarious synthetic endeavors.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01766.

Experimental procedures and spectral data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: zhangjian@hznu.edu.cn.
*E-mail: zgf@hznu.edu.cn.

ORCID

Jian Zhang: 0000-0001-8734-3003
Guofu Zhong: 0000-0001-9497-9069

Author Contributions

‡Y.S. and K.M. contributed equally

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge the National Natural Science Foundation of China (NSFC) (21502037 and 21672048), the Natural Science Foundation of Zhejiang Province (ZJNSF) (LY19B020006), and the Hangzhou Normal University for financial support. G.Z. acknowledges a Qianjiang Scholar award from Zhejiang Province, China.

■ REFERENCES

(1) (a) Stille, J. K. The Palladium-Catalyzed Cross-Coupling Reactions of Organotin Reagents with Organic Electrophiles. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Le Bras, J.; Muzart, J. Intermolecular Dehydrogenative Heck Reactions. *Chem. Rev.* **2011**, *111*, 1170. (c) Zheng, S.-C.; Wang, Q.; Zhu, J. Catalytic Atropenantioselective Heteroannulation between Isocyanoacetates and Alkynyl Ketones: Synthesis of Enantioenriched Axially Chiral 3-Arylpyrroles. *Angew. Chem., Int. Ed.* **2019**, *58*, 1494. (d) Luh, T. Y.; Wong, K. T. Silyl-Substituted Conjugated Dienes: Versatile Building Blocks in Organic Synthesis. *Synthesis* **1993**, *1993*, 349. (e) Negishi, E.-i.; Huang, Z.; Wang, G.; Mohan, S.; Wang, C.; Hattori, H. Recent Advances in Efficient and Selective Synthesis of Di-, Tri-, and Tetrasubstituted Alkenes via Pd-Catalyzed Alkenylation-Carbonyl. *Acc. Chem. Res.* **2008**, *41*, 1474. (f) Nakamura, I.; Ishida, Y.; Terada, M. Cu-Catalyzed Skeletal Rearrangement of *O*-Propargylic Electron-Rich Arylaldoximes into Amidodienes. *Org. Lett.* **2014**, *16*, 2562.

(2) (a) Shang, X.; Liu, Z.-Q. Transition Metal-Catalyzed C_{vinyl}-C_{vinyl} Bond Formation *via* Double C_{vinyl}-H Bond Activation. *Chem. Soc. Rev.* **2013**, *42*, 3253. (b) Wang, K.; Hu, F.; Zhang, Y.; Wang, J. Directing Group-Assisted Transition-Metal-Catalyzed Vinylic C-H Bond Functionalization. *Sci. China: Chem.* **2015**, *58*, 1252. (c) Hatamoto, Y.; Sakaguchi, S.; Ishii, Y. Oxidative Cross-Coupling of Acrylates with Vinyl Carboxylates Catalyzed by a $Pd(OAc)_2$/HPMoV/O_2 System. *Org. Lett.* **2004**, *6*, 4623. (d) Xu, Y. H.; Lu, J.; Loh, T. P. Direct Cross-Coupling Reaction of Simple Alkenes with Acrylates Catalyzed by Palladium Catalyst. *J. Am. Chem. Soc.* **2009**, *131*, 1372. (e) Liang, Q.-J.; Yang, C.; Meng, F.-F.; Jiang, B.; Xu, Y.-H.; Loh, T.-P. Chelation *versus* Non-Chelation Control in the Stereoselective Alkenyl sp^2 C−H Bond Functionalization Reaction. *Angew. Chem., Int. Ed.* **2017**, *56*, 5091. (f) Hu, X.-H.; Yang, X.-F.; Loh, T.-P. Selective Alkenylation and Hydroalkenylation of Enol Phosphates through Direct C-H Functionalization. *Angew. Chem., Int. Ed.* **2015**, *54*, 15535. (g) Li, F.; Yu, C.; Zhang, J.; Zhong, G. Olefination of Electron-Deficient Alkenes with Allyl Acetate: Stereo- and Regioselective Access to (2Z,4E)-Dienamides. *Org. Lett.* **2016**, *18*, 4582. (h) Yu, C.; Li, F.; Zhang, J.; Zhong, G. A direct Cross-Coupling Reaction of Electron-Deficient Alkenes Using An Oxidizing Directing Group. *Chem. Commun.* **2017**, *53*, 533. (i) Li, T.; Zhang, J.; Yu, C.; Lu, X.; Xu, L.; Zhong, G. Ruthenium-Catalyzed Olefinic C−H Alkenylation of Enol-carbamates: Highly Stereo-selective Synthesis of (*Z*,*Z*) and (*Z*,*E*)-Butadienes. *Chem. Commun.* **2017**, *53*, 12926. (j) Zhang, J.; Loh, T.-P. Ruthenium- and Rhodium-Catalyzed Cross-Coupling Reaction of Acrylamides with Alkenes: Efficient Access to (Z,E)-Dienamides. *Chem. Commun.* **2012**, *48*, 11232.

(3) (a) Mannathan, S.; Cheng, C.-H. Cobalt-Catalyzed Regio- and Stereoselective Intermolecular Enyne Coupling: An Efficient Route to 1,3-Diene Derivatives. *Chem. Commun.* **2010**, *46*, 1923. (b) Horie, H.; Koyama, I.; Kurahashi, T.; Matsubara, S. Nickel-Catalyzed Intermolecular Codimerization of Acrylates and Alkynes. *Chem. Commun.* **2011**, *47*, 2658. (c) Echeverria, P.-G.; Fürstner, A. An Iron-Catalyzed Bond-Making/Bond-Breaking Cascade Merges Cycloisomerization and Cross-Coupling Chemistry. *Angew. Chem., Int. Ed.* **2016**, *55*, 11188. (d) Saito, N.; Saito, K.; Shiro, M.; Sato, Y. Regio- and Stereoselective Synthesis of 2-Amino-1,3-diene Derivatives by Ruthenium-Catalyzed Coupling of Ynamides and Ethylene. *Org. Lett.* **2011**, *13*, 2718.

(4) (a) Neisius, N. M.; Plietker, B. The Ruthenium-Catalyzed Hydrovinylation of Internal Alkynes by Acrylates: An Atom Economic Approach to Highly Substituted 1,3-Dienes. *Angew. Chem., Int. Ed.* **2009**, *48*, 5752. (b) Azpíroz, R.; Rubio-Pérez, L.; Di Giuseppe, A.; Passarelli, V.; Lahoz, F. J.; Castarlenas, R.; Pérez-Torrente, J. J.; Oro, L. A. Rhodium(I)-N-Heterocyclic Carbene Catalyst for Selective Coupling of *N*-Vinylpyrazoles with Alkynes *via* C−H Activation. *ACS Catal.* **2014**, *4*, 4244. (c) Li, S.-S.; Xia, Y.-Q.; Liu, C.-F.; Zhang, G.-T.; Su, F.; Zhang, X.-M.; Dong, L. Diverse Reactivity in a Rhodium(III)-Catalyzed Vinylic sp^2 C-H Bond Functionalization: Synthesis of Fused Polycyclic Heteroarenes or Conjugated Dienes. *Adv. Synth. Catal.* **2016**, *358*, 3724. (d) Shibata, Y.; Otake, Y.; Hirano, M.; Tanaka, K. Amide-Directed Alkenylation of sp^2 C−H Bonds Catalyzed by a Cationic Rh(I)/BIPHEP Complex Under Mild Conditions: Dramatic Rate Acceleration by a 1-Pyrrolidinecarbonyl Group. *Org. Lett.* **2009**, *11*, 689. We have developed Ru-catalyzed alkene−alkyne coupling using Ag additive; see: (e) Meng, K.; Zhang, J.; Li, F.; Lin, Z.; Zhang, K.; Zhong, G. Amide Directed Cross-Coupling between Alkenes and Alkynes: A Regio- and Stereoselective Approach to Substituted (2Z,4Z)-Dienamides. *Org. Lett.* **2017**, *19*, 2498. See also ref 2i.

(5) Lindhardt, A. T.; Mantel, M. L. H.; Skrydstrup, T. Palladium-Catalyzed Intermolecular Ene-Yne Coupling: Development of an Atom-Efficient Mizoroki-Heck-Type Reaction. *Angew. Chem., Int. Ed.* **2008**, *47*, 2668.

(6) Iridium(I)-catalyzed intramolecular cycloisomerization of enynes: Fernández, D. F.; Rodrigues, C. A. B.; Calvelo, M.; Gulías, M.; Mascareñas, J. L.; López, F. Iridium(I)-Catalyzed Intramolecular Cycloisomerization of Enynes: Scope and Mechanistic Course. *ACS Catal.* **2018**, *8*, 7397.

(7) Ir-catalyzed aromatic C−H activation: (a) Pan, S.; Shibata, T. Recent Advances in Iridium-Catalyzed Alkylation of C−H and N−H Bonds. *ACS Catal.* **2013**, *3*, 704. (b) Kim, J.; Park, S.-W.; Baik, M.-H.; Chang, S. Complete Switch of Selectivity in the C−H Alkenylation and Hydroarylation Catalyzed by Iridium: The Role of Directing Groups. *J. Am. Chem. Soc.* **2015**, *137*, 13448. (c) Ebe, Y.; Nishimura, T. Iridium-Catalyzed Branch-Selective Hydroarylation of Vinyl Ethers *via* C−H Bond Activation. *J. Am. Chem. Soc.* **2015**, *137*, 5899. (d) Nagamoto, M.; Fukuda, J.; Hatano, M.; Yorimitsu, H.; Nishimura,

DOI: 10.1021/acs.orglett.9b01766
Org. Lett. 2019, 21, 4868−4872

T. Hydroxoiridium-Catalyzed Hydroarylation of Alkynes and Bicycloalkenes with *N*-Sulfonylbenzamides. *Org. Lett.* **2017**, *19*, 5952. (e) Xia, J.; Yang, X.; Li, Y.; Li, X. Iridium(III)-Catalyzed Synthesis of Benzimidazoles *via* C−H Activation and Amidation of Aniline Derivatives. *Org. Lett.* **2017**, *19*, 3243. (f) Becker, P.; Pirwerdjan, R.; Bolm, C. Acylsilanes in Iridium-Catalyzed Directed Amidation Reactions and Formation of Heterocycles *via* Siloxycarbenes. *Angew. Chem., Int. Ed.* **2015**, *54*, 15493. (g) Shin, K.; Park, Y.; Baik, M.-H.; Chang, S. Iridium-Catalysed Arylation of C−H Bonds Enabled by Oxidatively Induced Reductive Elimination. *Nat. Chem.* **2018**, *10*, 218. (h) Romanov-Michailidis, F.; Ravetz, B. D.; Paley, D. W.; Rovis, T. Ir(III)-Catalyzed Carbocarbation of Alkynes through Undirected Double C−H Bond Activation of Anisoles. *J. Am. Chem. Soc.* **2018**, *140*, 5370. (i) Li, H. L.; Kuninobu, Y.; Kanai, M. Lewis Acid-Base Interaction-Controlled *ortho*-Selective C-H Borylation of Aryl Sulfides. *Angew. Chem., Int. Ed.* **2017**, *56*, 1495. (j) Erbing, E.; Sanz-Marco, A.; Vázquez-Romero, A.; Malmberg, J.; Johansson, M. J.; Gómez-Bengoa, E.; Martín-Matute, B. Base- and Additive-Free Ir-Catalyzed *ortho*-Iodination of Benzoic Acids: Scope and Mechanistic Investigations. *ACS Catal.* **2018**, *8*, 920. (k) Tan, G.; You, Q.; You, J. Iridium-Catalyzed Oxidative Heteroarylation of Arenes and Alkenes: Overcoming the Restriction to Specific Substrates. *ACS Catal.* **2018**, *8*, 8709. (l) Yu, M.; Zhang, T.; Jalani, H. B.; Dong, X.; Lu, H.; Li, G. Iridium-Catalyzed Aryl C−H Sulfonamidation and Amide Formation Using a Bifunctional Nitrogen Source. *Org. Lett.* **2018**, *20*, 4828.

(8) Ir-catalyzed alkyl C−H activation: (a) Tran, A. T.; Yu, J.-Q. Practical Alkoxythiocarbonyl Auxiliaries for Iridium(I)-Catalyzed C−H Alkylation of Azacycles. *Angew. Chem., Int. Ed.* **2017**, *56*, 10530. (b) Bunescu, A.; Butcher, T. W.; Hartwig, J. F. Traceless Silylation of β-C(sp^3)−H Bonds of Alcohols *via* Perfluorinated Acetals. *J. Am. Chem. Soc.* **2018**, *140*, 1502. (c) Fukumoto, Y.; Hirano, M.; Chatani, N. Iridium-Catalyzed Regioselective C(sp^3)−H Silylation of 4-Alkylpyridines at the Benzylic Position with Hydrosilanes Leading to 4-(1-Silylalkyl) pyridines. *ACS Catal.* **2017**, *7*, 3152.

(9) Ligand-controlled selective C−H functionalization: (a) Chattopadhyay, B.; Dannatt, J. E.; Sanctis, I.L.A.-D.; Gore, K. A.; Maleczka, R. E.; Singleton, D. A.; Smith, M. R., III. Ir-Catalyzed *ortho*-Borylation of Phenols Directed by Substrate−Ligand Electrostatic Interactions: A Combined Experimental/in Silico Strategy for Optimizing Weak Interactions. *J. Am. Chem. Soc.* **2017**, *139*, 7864. (b) Serratore, N. A.; Anderson, C. B.; Frost, G. B.; Hoang, T.-G.; Underwood, S. J.; Gemmel, P. M.; Hardy, M. A.; Douglas, C. J. Integrating Metal-Catalyzed C−H and C−O Functionalization To Achieve Sterically Controlled Regioselectivity in Arene Acylation. *J. Am. Chem. Soc.* **2018**, *140*, 10025. (c) Grélaud, S.; Cooper, P.; Feron, L. J.; Bower, J. F. Branch-Selective and Enantioselective Iridium-Catalyzed Alkene Hydroarylation via Anilide-Directed C−H Oxidative Addition. *J. Am. Chem. Soc.* **2018**, *140*, 9351. (d) Su, B.; Hartwig, J. F. Ir-Catalyzed Enantioselective, Intramolecular Silylation of Methyl C−H Bonds. *J. Am. Chem. Soc.* **2017**, *139*, 12137. (e) Hoque, M. E.; Bisht, R.; Haldar, C.; Chattopadhyay, B. Noncovalent Interactions in Ir-Catalyzed C−H Activation: L-Shaped Ligand for *Para*-Selective Borylation of Aromatic Esters. *J. Am. Chem. Soc.* **2017**, *139*, 7745. (f) Wang, G.; Liu, L.; Wang, H.; Ding, Y.-S.; Zhou, J.; Mao, S.; Li, P. N. B-Bidentate Boryl Ligand-Supported Iridium Catalyst for Efficient Functional-Group-Directed C−H Borylation. *J. Am. Chem. Soc.* **2017**, *139*, 91. (g) Yang, L.; Semba, K.; Nakao, Y. *para*-Selective C−H Borylation of (Hetero)Arenes by Cooperative Iridium/Aluminum Catalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 4853. (h) Hamilton, J. Y.; Rössler, S. L.; Carreira, E. M. Enantio- and Diastereoselective Spiroketalization Catalyzed by Chiral Iridium Complex. *J. Am. Chem. Soc.* **2017**, *139*, 8082. (i) Petrone, D. A.; Isomura, M.; Franzoni, I.; Rössler, S. L.; Carreira, E. M. Allenylic Carbonates in Enantioselective Iridium-Catalyzed Alkylations. *J. Am. Chem. Soc.* **2018**, *140*, 4697.

(10) Amidation: (a) Kim, H.; Park, G.; Park, J.; Chang, S. A Facile Access to Primary Alkylamines and Anilines *via* Ir(III)-Catalyzed C−H Amidation Using Azidoformates. *ACS Catal.* **2016**, *6*, 5922. Borylation: (b) Sasaki, I.; Taguchi, J.; Doi, H.; Ito, H.; Ishiyama, T. Iridium(I)-catalyzed C−H Borylation of α,β-Unsaturated Esters with Bis(pinacolato)diboron. *Chem. - Asian J.* **2016**, *11*, 1400. Deuteration: (c) Zhou, J.; Hartwig, J. F. Iridium-Catalyzed H/D Exchange at Vinyl Groups without Olefin Isomerization. *Angew. Chem., Int. Ed.* **2008**, *47*, 5783.

(11) Ebe, Y.; Onoda, M.; Nishimura, T.; Yorimitsu, H. Iridium-Catalyzed Regio- and Enantioselective Hydroarylation of Alkenyl Ethers by Olefin Isomerization. *Angew. Chem., Int. Ed.* **2017**, *56*, 5607.

(12) For details, see the Supporting Information.

(13) (a) Terminal alkynes showed no reactivity toward acrylamide. (b) NH-Me acrylamide exhibited limited reactivity (~15% yield), while N-Me-N-Ts acrylamide exhibited no reactivity.

(14) (a) Soulard, V.; Villa, G.; Vollmar, D. P.; Renaud, P. Radical Deuteration with D_2O: Catalysis and Mechanistic Insights. *J. Am. Chem. Soc.* **2018**, *140*, 155. (b) Hatano, M.; Nishimura, T.; Yorimitsu, H. Selective H/D Exchange at Vinyl and Methylidene Groups with D_2O Catalyzed by an Iridium Complex. *Org. Lett.* **2016**, *18*, 3674. (c) Puleo, T. R.; Strong, A. J.; Bandar, J. S. Catalytic α-Selective Deuteration of Styrene Derivatives. *J. Am. Chem. Soc.* **2019**, *141*, 1467.

(15) Simmons, E. M.; Hartwig, J. F. On the Interpretation of Deuterium Kinetic Isotope Effects in C-H Bond Functionalizations by Transition-Metal Complexes. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066.

(16) These structurally complex molecules were unsuitable with previous coupling conditions (ref 4e) presumably due to the presence of silver salt.

DOI: 10.1021/acs.orglett.9b01766
Org. Lett. 2019, 21, 4868−4872