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Editorial

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Recent Advances in C−H Functionalization

INTRODUCTION

C−H functionalization represents a paradigm shift from the standard logic of organic synthesis. Instead of focusing on orchestration of selective reactions at functional groups, the new logic relies on the controlled functionalization of specific C−H bonds, even in the presence of supposedly more reactive functional groups.[1−5] The classic methods for achieving functionalization of nonactivated C−H bonds have been free-radical processes, in which site selectivity is controlled either by the relative strengths of the C−H bonds or by intramolecular hydrogen abstraction.[6,7] With the advances made in organometallic chemistry, new opportunities have become available for achieving site-selective C−H functionalization. The initial approaches tended to focus on developing methods for the functionalization of relatively simple hydrocarbons,[8] but in recent years, C−H functionalization has matured to the point where it can be contemplated as a viable strategy for the synthesis of complex targets. Hence, the focus has moved from primarily an organometallic challenge to the development of powerful new synthetic methods and their broad application in organic synthesis.[9−16] The field is experiencing explosive growth, and since 2014, over 400 papers have been published in *The Journal of Organic Chemistry*, *Organic Letters*, and *Journal of the American Chemical Society* on various aspects of C−H functionalization chemistry. This editorial will highlight 24 of these recent papers and illustrate their significance to the C−H functionalization endeavor.

DIRECTED C−H FUNCTIONALIZATION

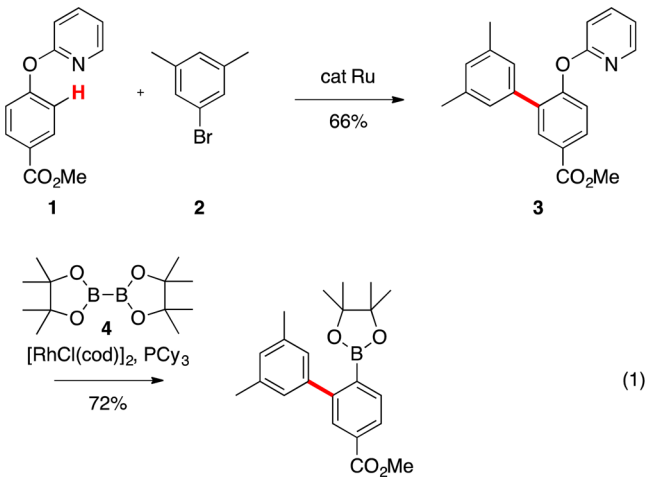
In order for C−H functionalization methods to be of broad utility, one of the critical requirements is control of site selectivity, especially as most compounds contain multiple types of C−H bonds and functional groups. The most successful approach has been to use a directing group strategy, popularized by Murai and Chatani.[17,18] Since their seminal work in the late 1990s, this area of chemistry has become extremely active, leading to a wide variety of solutions with broad utility in materials science and the pharmaceutical industry.

About a quarter of the recent C−H functionalization papers in *The Journal of Organic Chemistry*, *Organic Letters*, and *Journal of the American Chemical Society* use functionality within the substrate to bind to transition-metal catalysts to control site selectivity.[19−27] Some of the major current challenges covered in these papers are the following:

- Design of new directing groups that are readily removed or converted into useful functionality
- Broadening the scope from the more traditional functionalization of sp^2 C−H bonds to sp^3 C−H bonds[22,23]
- Application of the methodology so that a broader range of functionality can be introduced
- Modification of the directing influence away from just *ortho*-functionalization[21,27]
- Enhancement of the catalytic efficiency so that very low quantities of precious metal catalysts or earth-abundant catalysts are necessary[19,24]

Descriptions of some of the recent innovative advances that have been made in directed C−H functionalization are given in the next few paragraphs.

A considerable amount of work has been conducted in recent years to understand how modifications to the nature of the directing group impacts the efficiency of the overall chemistry. Yu has made considerable progress in using weakly coordinating directing groups which enable the overall catalytic cycle to proceed more efficiently and employs groups that are more synthetically versatile in subsequent transformations.[28,29] Another important advance would be the development of directing groups that are easily removed. This has driven significant work to develop "traceless" directing groups.[30] Tobisu and Chatani report their work on tackling this challenge, using an aryl 2-pyridyl ether, an extremely effective directing group to perform a selective directed C−H functionalization, and then performing a one-pot, catalytic borylative cleavage of the directing group, installing the versatile boryl functional group.[31] An illustrative example of this approach is the ruthenium-catalyzed arylation of the aryl 2-pyridyl ether **1** with the bromoaryl **2**, to form the arylated product **3** followed by a rhodium-catalyzed borylation with bis(pinacolato)diboron (**4**) to form the boryl derivative **5**, replacing the directing group (eq 1). This sequence demonstrates how an effective and



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readily available directing group can be converted to almost any desired functionality in a facile and concise fashion, significantly expanding the product scope of this class of directed C−H functionalization.

Classically, directed C−H functionalization leads to the introduction of groups at the *ortho* position of benzene rings because the transition-metal catalyst first coordinates to the directing group and is hence in close proximity to the *ortho* C−H bond. In recent years, there has been considerable interest in the extension of C−H functionalization to sp^3 C−H bonds.[32] Bull and co-workers[33] describe the palladium-catalyzed arylation

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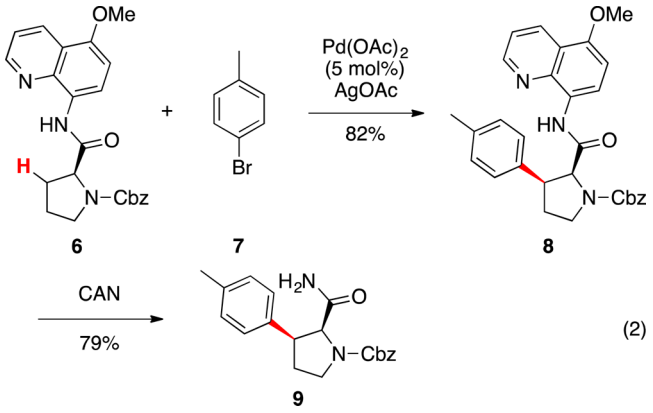
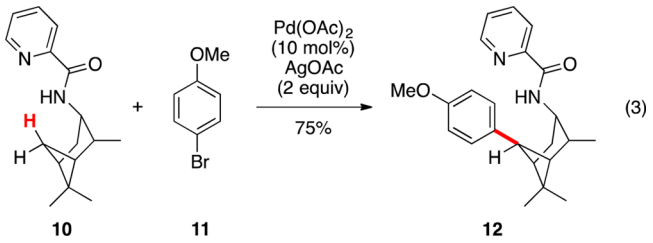
of the proline derivative **6** with the aryl bromide **7** to generate the 3-arylated pyrrolidine **8** in 82% yield (eq 2). The directing



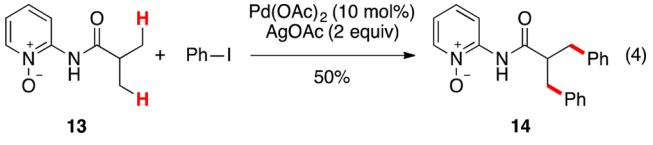
group not only controls the site selectivity of the reaction but also, through predefined stereochemistry in the substrate, ensures that the cis product **8** is exclusively formed. Most of the studies were conducted with the classic directing group, 8-amidoquinoline, but this group requires forcing conditions for removal. In the current study, the 5-methoxy-8-amidoquinoline directing group was also used, which offers the advantage of ready removal upon treatment with cerium(IV) ammonium nitrate (CAN), as seen in the conversion of **8** to the amide **9** in 79% yield.

Zhao, Hu, Wang, and co-workers[34] demonstrated that a palladium-catalyzed directed sp^3 C–H functionalization could be conducted on the bicylic system **10** with the aryl halide **11** to form the arylated derivative **12** (eq 3). Typically, directed



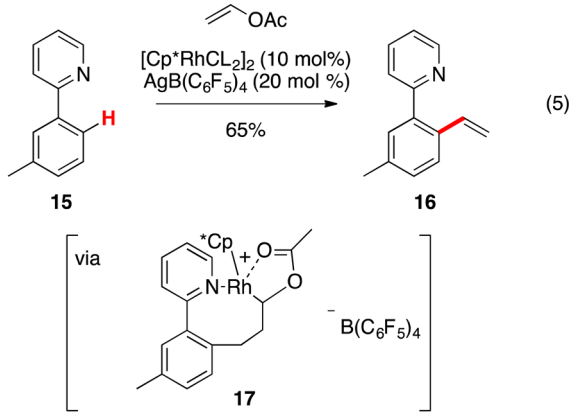
functionalization occurs at the β-sp^3 C–H bond because this will generate a favorable 5-membered metallacyclic intermediate. In this case, however, due to the steric and geometrical constraints of the system, the δ-C–H bond is selectively functionalized, leading to a useful scaffold with potential for further application in drug development.

Another useful directing group is pyridine *N*-oxide, originally developed by Fagnou and co-workers.[35] Zeng, Lu, and co-workers extended the use of this directing group for directed sp^3 C–H functionalization of acyclic systems, as illustrated in the palladium-catalyzed bis-arylation of **13** to form **14** (eq 4).[36]



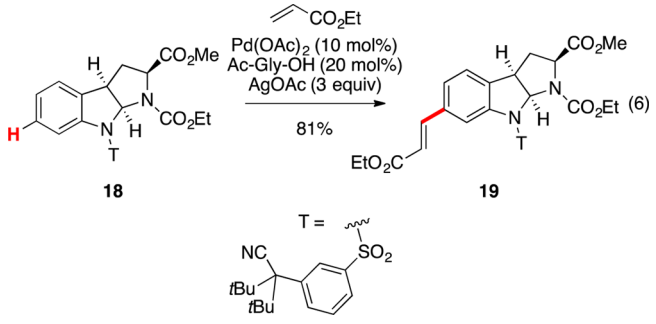
Depending on the steric demand of the substrate, either monoarylation or bis-arylation products are formed. In this system, the amide nitrogen and the *N*-oxide coordinate to the palladium and thus orientate the palladium in an ideal position for the site selective C–H functionalization.

Rhodium-catalyzed C–H functionalization has tended to use imine functionality, often as a component of a heterocycle, as the directing group.[37] Otley and Ellman have recently described a rhodium-catalyzed method for C–H vinylation.[38] In this case, either pyridine or an amide was used as the directing group, as illustrated in the conversion of the arylpyridine **15** to the styrene derivative **16** on treatment with vinyl acetate (eq 5).



The reaction was shown to proceed via the tricoordinated rhodium complex **17**, which then fragments to the styrene **16**.

The *ortho* C–H functionalization of aromatic compounds has matured to the stage where it has found wide application in the synthesis of pharmaceutically relevant compounds. A major current challenge has been to design new directing groups that will enable selective C–H functionalization at other positions. Yu and co-workers have designed new types of directing groups that will lead to *meta*-[39,40] and even *para*-[41] instead of *ortho*-C–H functionalization in palladium-catalyzed reactions. A collaborative project between the Yu and Movassaghi groups applied this strategy to the selective C-6 functionalization of 2,3-dihydroindoles, by using U-shaped templates that place the metal in close proximity to the *meta* C-6 position.[21] The method can be applied to complex substrates as illustrated in the C–H activation/Heck reaction with the dihydroindole **18** to form **19** (eq 6).



Dong[42] and Yu[43] have independently described an alternative palladium-catalyzed approach to achieve meta selective C–H functionalization. The foundation for this process is the Catellani reaction using norbornene as an organometallic relay, which has been extensively used by Catellani and Lautens for the derivatization of aromatic compounds.[44,45] Dong demonstrated that by combining the ortho-directed C–H functionalization with the norbornene-induced organometallic relay, the

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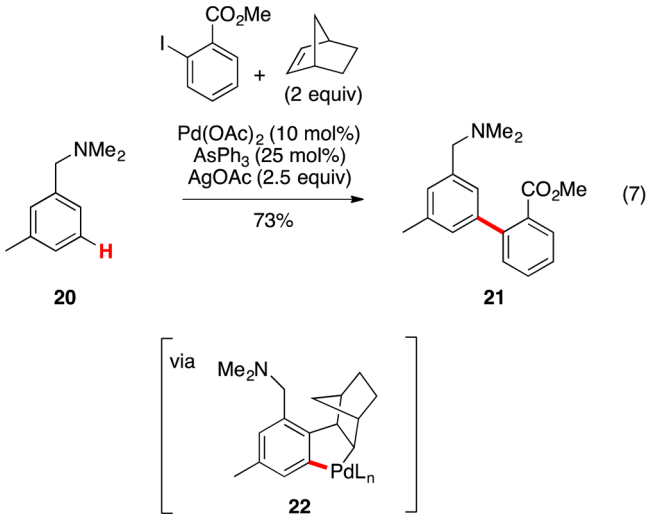
meta-substituted product could be generated, as illustrated in the arylation of **20** to form **21** (eq 7).[42] The reaction is



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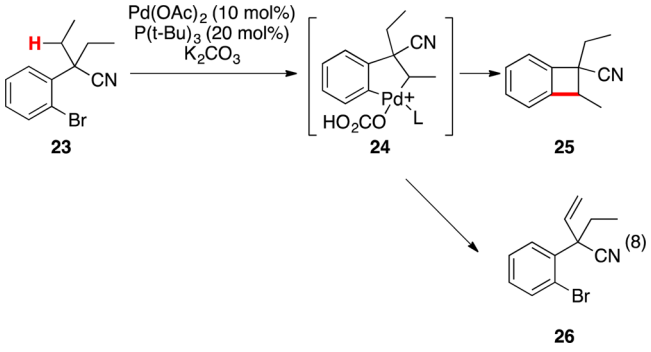
considered to proceed by a directed C−H functionalization followed by norbornene insertion and a second directed C−H functionalization to form intermediate **22**. This intermediate then undergoes a cross coupling with the aryl halide followed by β-hydride elimination of the norbornene to form **21**.

Baudoin and co-workers have conducted extensive studies on a C−H functionalization cascade in which the key step is an intramolecular C−H functionalization of an sp^3 C−H bond by an aryl palladium species.[46] The Baudoin and Clot groups have conducted a collaborative mechanistic study to determine the mechanistic details of this synthetic sequence.[47] The C−H functionalization on the model substrate **23** was shown to form the five-membered palladacycle **24**, which can undergo either decoordination of the protonated bicarbonate base and reductive elimination to give the benzocyclobutane **25** or go through proton transfer to the aryl ligand and base-mediated β-hydride elimination to give the olefin **26** (eq 8). Even though



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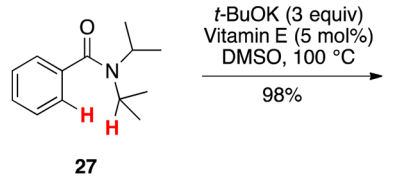
formation of the benzocyclobutane **25** is energetically slightly favored, product control can be achieved because the two reaction pathways are greatly influenced by whether or not the bicarbonate is dissociated from the complex.

Traditionally, the majority of the early metal-catalyzed C−H functionalization methods employ precious transition-metal catalysts based on rhodium, palladium, ruthenium, and iridium. With the current drive toward more sustainable methods, considerable interest has been directed toward emulating the established C−H functionalization transformations using first row transition-metal catalysts. In this regard, a particularly intriguing development is the use of nontransition metal catalysts to achieve selective C−H functionalization. Kumar and co-workers describe a potassium *tert*-butoxide induced C−H functionalization as a method for the conversion of the benzamide **27** to the isoindoline **28** (eq 9).[48] The reaction is reminiscent of the



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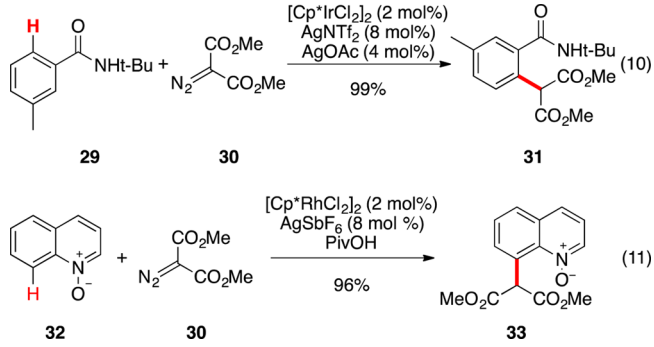
palladium-catalyzed transformation described by Baudoin, but in this case, the reaction is considered to proceed via a radical process. Other examples of potassium *tert*-butoxide-catalyzed C−H functionalization methods have been published in the last year, including a versatile method for the C−H silylation of heterocycles.[49]

Several examples have recently been published on the use of diazo compounds as coupling partners in directed C−H functionalization as this avoids the need for an external oxidation.[50] Two recent examples are shown in eqs 10 and 11. Wang and



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co-workers demonstrated that iridium-catalyzed reaction of the benzamide **29** with the diazomalonate **30** leads to the formation of the alkylated product **31**.[51] When azides are used as reagents, C−H amination can be achieved.[51,52] Likewise, Chang and co-workers have shown that rhodium-catalyzed reaction of the quinolone N-oxide **32** with diazomalonate **30** results in C-8 arylations to form **33** with good regiocontrol.[53]

FUNCTIONALIZATION OF HETEROCYCLES

The direct C−H functionalization of heterocycles is of considerable current interest for the synthesis of commercially relevant compounds in the pharmaceutical and agrochemical industry.[24] A highly significant paper, in this regard, is the study described by Larsen and Hartwig on the iridium-catalyzed C−H borylation of aromatic heterocycles.[54] Not only was the reaction demonstrated to be of broad scope, but generally useful selectivity rules were developed for a range of heterocyclic systems. As illustrated in the selective borylation of **34** to **35** (eq 12), sterically crowded sites are unfavorable, sites adjacent to an N−H are protected due to rapid reversible borylation of the N−H bond, and a C−H bond adjacent to an imine reacts slower than other C−H bonds, and the resulting products are unstable. Computational studies have shown that these reactions proceed through a late transition state, and the stability of the products play an important role in governing site selectivity.[55]

The direct conversion of a heterocyclic C−H bond to a trifluoromethyl group is of considerable current interest due to

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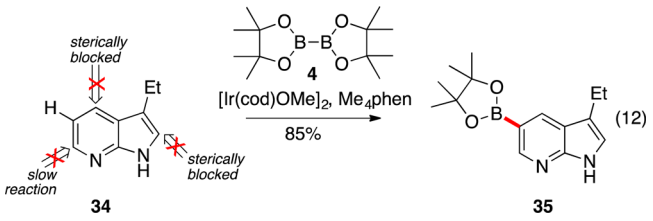
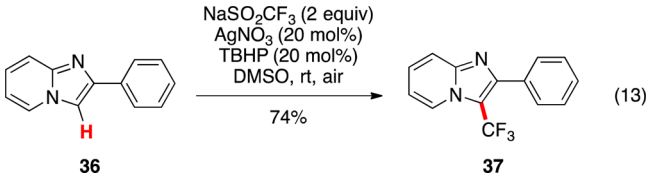
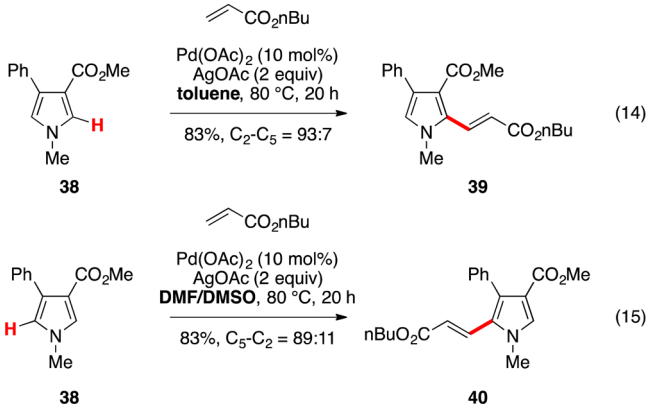


the importance of this group in the pharmaceutical sciences. Baran has recently published an effective oxidative trifluoromethylation using sodium trifluoromethanesulfonate,[56] commonly known as the Langlois reagent,[57] and this method has been extended to the introduction of a variety of different groups.[24,58,59] Hajra and co-workers illustrate the utility of the Langlois reagent in a silver-catalyzed oxidative trifluoromethylation for the conversion of the imidazopyridine **36** to the trifluoromethyl derivative **37** (eq 13).[60] The optimum oxidant



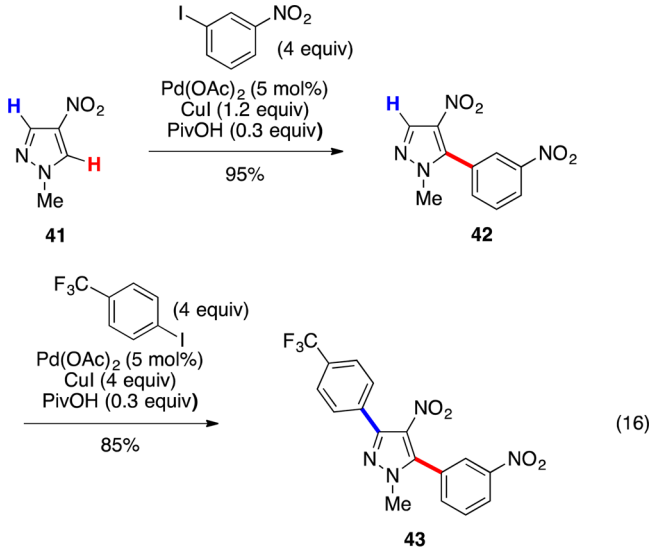
for the transformation was shown to be *tert*-butyl hydrogen peroxide, and the role of the silver was to generate the trifluoromethyl radical, which then reacts with the heterocyclic substrate. The introduction of a trifluoromethyl group to the imidazopyridine skeleton imparts a range of advantageous properties, including improved solubility, metabolic stability, and bioavailability.

A grand challenge associated with the C−H functionalization of heterocycles is to develop reagents and/or reaction conditions in which site selectivity is controlled at will. Lin, Yao, and co-workers demonstrate that in the palladium-catalyzed C−H alkenylation of 4-aryl-1*H*-pyrrole-3-carboxylate **38**, C-2 alkenylation to form **39** occurs in toluene (eq 14),



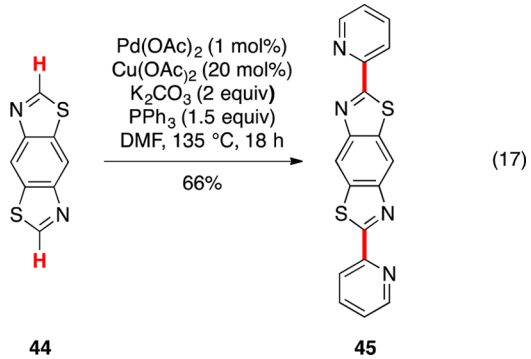
whereas C-4 alkenylation to form **40** occurs in DMF/DMSO (eq 15).[61] In the absence of a polar aprotic solvent, the ester group coordinates to the catalyst and directs the reaction to C-2. On the other hand, in a polar solvent, the reaction occurs at the site inherently more susceptible to electrophilic attack.

A number of impressive examples of sequential C−H functionalization of heterocycles have been reported, leading to the rapid generation of complex architectures.[62,63] Iaroshenko, Langer, and co-workers describe a good illustration of this concept in the regioselective functionalization of 4-nitropyrazoles.[64] Palladium- or nickel-catalyzed conditions were developed for the selective arylation at C-5, as illustrated for the conversion of the imidazole **41** to **42** (eq 16). Under more



forcing conditions with palladium or copper catalysis, a sequential second arylation was feasible to generate the triaryl derivative **43**.

Even though the vast majority of applications of heterocyclic C−H functionalization has been directed toward the synthesis of pharmaceutical and agrochemical targets, the potential also exists for the synthesis of compounds that will be of utility in materials science. A nice illustration of this is the recent work of Blakey, Marder, and co-workers that describes the palladium-catalyzed bis-arylation of benzobisthiazole derivatives as illustrated in the conversion of **44** to **45** (eq 17).[65] This results in



the generation of useful building blocks for further transformation into photonic materials through functionalization of a scaffold at a site that is orthogonal to its established reactivity.

CASCADE REACTIONS INCORPORATING C−H FUNCTIONALIZATION

An exciting development is the incorporation of C−H functionalization into complex cascade sequences. Reaction cascades involving gold(I)-catalyzed cyclization of 1,*n*-enynes have been demonstrated to rapidly generate molecular complexity. The Magauer group reports this gold-catalyzed

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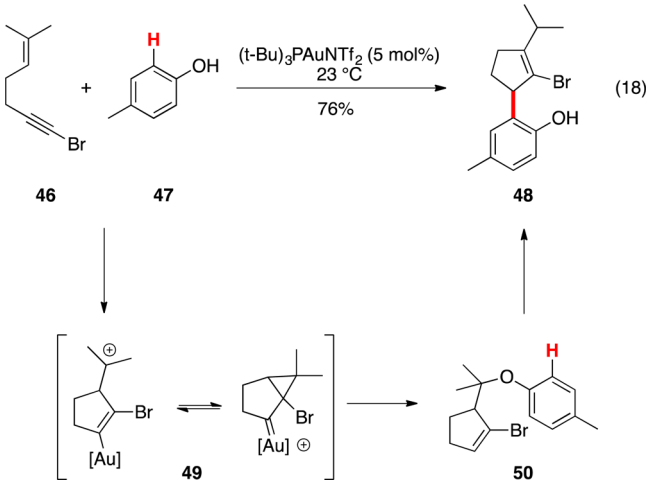
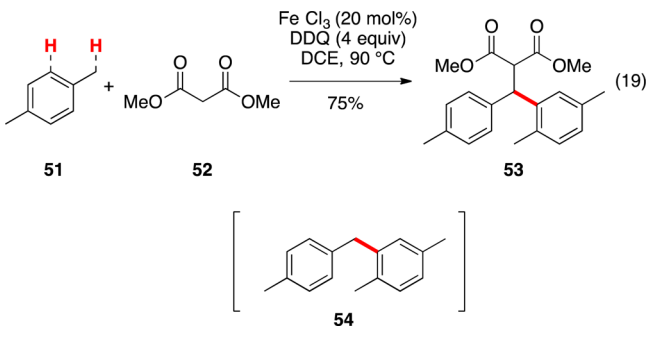
reaction cascade can be intercepted by a phenol, leading eventually to a product formally derived from *ortho* C−H functionalization of the phenol.[66] With optimized conditions, the cascade sequence was found to be broadly applicable across a range of sterically and electronically diverse phenols. An illustrative example is the conversion of enyne **46** and phenol **47** to form the (2-halocyclopent-2-en-1-yl)phenols **48** (eq 18).



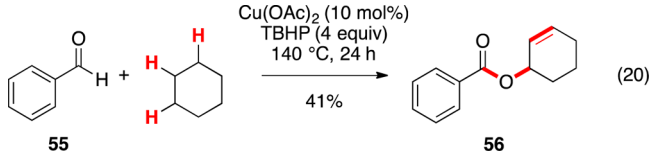
The intermediate **49** from the gold-catalyzed cyclization of the eneyne **46** is initially trapped to form the O-alkylated product **50**, which then isomerizes to **48** by either an acid- or gold-catalyzed elimination/addition sequence.

The development of C−H functionalization methods involving radical processes remains a vibrant area of current research.[67] Some notable achievements include Baran's development of a variety of reagents to broaden the scope of the classic Neminsci reaction for the free radical functionalization of aromatic systems,[56,58] as well as the metal-catalyzed dehydrogenative coupling reaction popularized by Li.[68] As is typical of radical reactions, these transformations can be expanded into complex cascade sequences. Recently, Yang and Song have shown that an iron-catalyzed double cross-dehydrogenative coupling between 1,3-dicarbonyl compounds and arylmethanes can be achieved.[69] An example of this is the three-component coupling between *p*-xylene **51** with diethyl malonate **52** to form **53** (eq 19). The first step is the



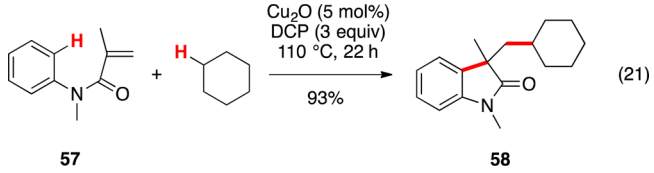
dehydrogenative coupling of the two aromatic compounds to generate **54**, which then undergoes further benzylic oxidation and coupling with the diethyl malonate to form **53**.

Catalytic dehydrogenation of alkanes to alkenes is an area of significant current interest and remarkable progress has been achieved, especially with Ir, Pt, and Re catalytic systems. The Han group describes an unusual Cu-catalyzed oxidation of cycloalkane with *tert*-butyl hydrogen peroxide (TBHP) in the presence of aromatic aldehydes to form cycloalkenyl benzoates as illustrated in the conversion of benzaldehyde (**55**) with cyclohexane to form **56** (eq 20).[70] The reaction is proposed to



proceed by four distinct C(sp^3)−H bond activation steps: (1) hydrogen abstraction from the cyclohexanes, (2) hydrogen abstraction from the cyclohexyl radical to form a cyclohexene, (3) hydrogen abstraction from the cyclohexene to generate an allylic radical which then forms a copper cyclohexyl oxide, and (4) hydrogen abstraction from the aromatic aldehyde to generate an acyl radical which combines with the copper cyclohexenyl oxide to form **56** as the final product.

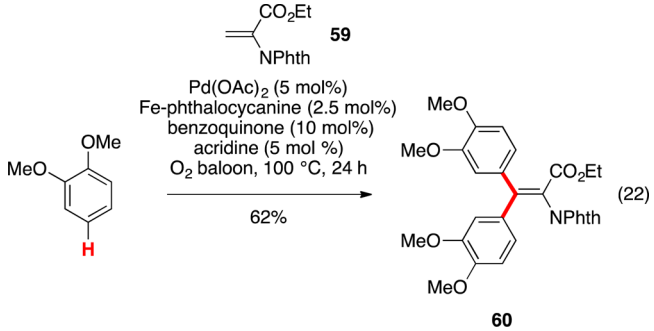
Another radical cascade process initiated by a C−H functionalization is the alkylarylation of alkenes with simple alkanes reported by Liu and co-workers.[71] In the presence of dicumyl peroxide and a catalytic amount of a copper salt, the unsaturated benzamide **57** reacts with alkanes, such as cyclohexane to form the oxindole **58** (eq 21). The initially formed



oxy radical abstracts a hydrogen from the alkane and the resulting alkyl radical adds to the unsaturated amide to generate a new radical that then reacts intramolecularly with the benzene ring to ultimately form **58**.

DEHYDROGENATIVE COUPLING

An attractive transformation is dehydrogenative coupling.[70,72] One example of this type is the dehydrogenative Heck coupling in which an aromatic substrate undergoes C−H activation followed by a Heck reaction under palladium-catalyzed conditions. One of the challenges associated with this type of the reaction is the requirement of strong oxidative conditions to regenerate the active palladium catalysts. The Bäckvall group has developed a more sustainable approach by using a bimetallic system, in which the second metal reoxidizes the palladium and is then in turn reoxidized by molecular oxygen. A recent publication describes the use of iron phthalocyanine combined with benzoquinone as the electron transfer mediators



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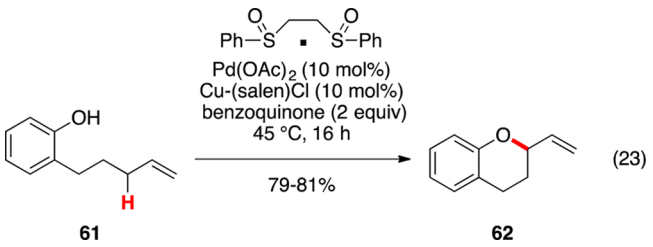
for the oxidative double dehydrogenative Heck reaction as illustrated in the conversion of the alkene **59** to the diarylated alkene **60** (eq 22).[73] The reaction to generate the monoarylated product is relatively fast, followed by a much slower second arylation, presumably due to steric hindrance, to ultimately form **60**.

■ ALLYLIC C−H OXIDATION

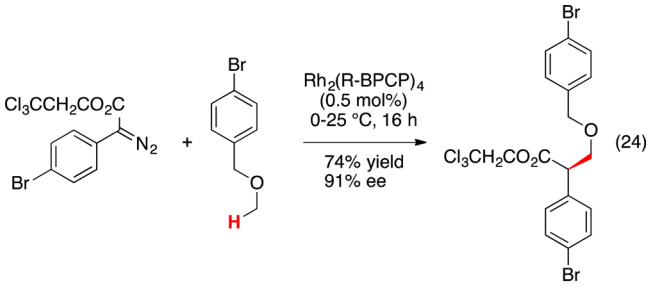
Another useful palladium catalyzed oxidation process is allylic C−H oxidation, which has been extensively developed by the White group using a palladium bis-sulfoxide catalyst.[74] A recent example of this work is the intramolecular C−H oxidation of terminal alkenes resulting in the formation of chromans, isochromans, and pyrans, as illustrated in the conversion of **61** to **62** (eq 23).[75] In this case, chromium salen was used as the

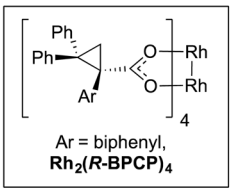


electron transfer mediator and benzoquinone was used as the terminal oxidant. The mechanism of the reaction was suggested to proceed via inner-sphere Pd coordination/activation of the oxygen nucleophile and subsequent reductive elimination. This novel strategy provides an operationally simple method for building oxygen-containing heterocycles and demonstrates broad applicability.

■ GROUP-TRANSFER REACTIONS

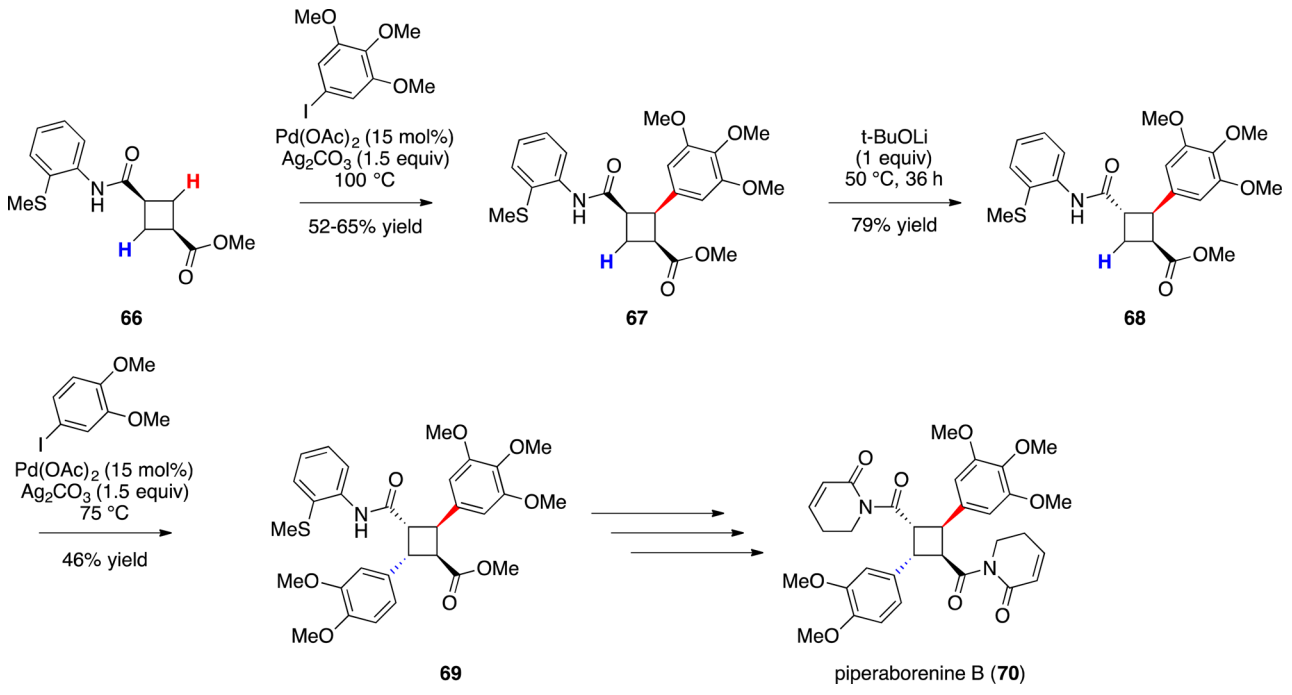
An alternative approach for achieving C−H functionalization is by using metal-catalyzed group transfer of metal-bound carbenes or nitrenes.[76,77] A particularly attractive feature of this approach is the ability to have considerable control of site selectivity depending on the nature of the catalyst.[78] A recent example of this concept is the dirhodium-catalyzed reactions of 2,2,2-trichloroethyl aryl- and heteroaryldiazoacetates from the Davies group.[79] The bulky dirhodium triarylcyclopropane carboxylate complex Rh_2(*R*-BPCP)$_4$ catalyzes the decomposition of this class of diazo reagents leading to the enantioselective intermolecular C−H functionalization of a range of methyl ethers with high levels of site selectivity and enantioselectivity. The trichloroethyl group plays an important role in enhancing site selectivity and the overall efficiency of the chemistry by inhibiting the carbene dimerization side reaction. The examples of the reaction of aryldiazoacetate **63** with the methyl ether **64** to form **65** (eq 24) illustrates how one can





consider C−H functionalization as being strategically equivalent to some of the classic reactions of organic synthesis.

Scheme 1



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In this case, it would be a surrogate to an asymmetric aldol reaction with formaldehyde, followed by alkylation.

SYNTHETIC STRATEGIES USING C−H FUNCTIONALIZATION

C−H functionalization is revolutionizing the way that organic chemists approach the synthesis of target molecules. Several reviews have been published discussing the potential of this new way of thinking for complex target synthesis.[1−4] Baran has been an influential contributor to the strategic analysis of C−H functionalization disconnections[80] and a recent paper from his group illustrates the effectiveness of the C−H functionalization logic when applied to the synthesis of highly functionalized cyclobutanes.[81] An illustration of the C−H functionalization strategy was given in the total synthesis of piperaborenine B (**70**) from the cyclobutyl amide **66** (Scheme 1). Palladium-catalyzed C−H arylation of **66** resulted in the introduction of the aryl group cis to the amide directing group to form **67** in 52−65% yield. Selective C-1 epimerization is possible using lithium *tert*-butoxide to form **68**. A second C−H arylation generated the 1,3-diarylcyclobutane **69**, which was then converted in three steps to piperaborenine B (**70**).

CONCLUSION

In summary, the selected papers illustrate the wide range of strategies that are being examined to achieve practical methods for C−H functionalization. The directed C−H functionalization has become an efficient method for the site-selective derivatization of C−H bonds and is now broadly used in synthesis. However, there are still major challenges associated with increasing the practicality of the chemistry. The catalyst performance still needs to be enhanced, cheaper and more sustainable catalysts are required, and broader application of oxygen as the terminal oxidant would be desirable. Rethinking how to use free-radical chemistry has led to many new advances in C−H functionalization, including elaborate cascade reactions. Group-transfer reactions have great promise for the development of catalyst-controlled site selective C−H functionalizations, leading to the possibility of having a "tool-box" of catalysts to control site selectivity at will. Several other emerging C−H functionalization methods have been reported, such as photoredox-induced radical reactions,[82−84] hydride-transfer-induced processes,[85−89] and enzyme-induced site selective C−H functionalization.[90,91] Considerable effort is also being expended to develop general strategies for synthesis that will illustrate the opportunities of using the C−H functionalization logic in complex target synthesis. We hope you enjoy reading the fine contributions highlighted in this ACS Select Virtual Issue.

Huw M. L. Davies
Daniel Morton
Department of Chemistry, Emory University

AUTHOR INFORMATION

Notes

Views expressed in this editorial are those of the author and not necessarily the views of the ACS.

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REFERENCES

(1) Brueckl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S. *Acc. Chem. Res.* **2012**, *45*, 826.
(2) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976.
(3) Newhouse, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362.
(4) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885.
(5) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960.
(6) Breslow, R.; Heyer, D. *J. Am. Chem. Soc.* **1982**, *104*, 2045.
(7) Wolff, M. E. *Chem. Rev.* **1963**, *63*, 55.
(8) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154.
(9) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879.
(10) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068.
(11) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890.
(12) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651.
(13) Wencel-Delord, J.; Droege, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740.
(14) Guo, X.-X.; Gu, D.-W.; Wu, Z.; Zhang, W. *Chem. Rev.* **2015**, *115*, 1622.
(15) Huang, Z.; Lim, H. N.; Mo, F.; Young, M. C.; Dong, G. *Chem. Soc. Rev.* **2015**, *44*, 7764.
(16) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.
(17) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 1698.
(18) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529.
(19) Shang, R.; Ilies, L.; Asako, S.; Nakamura, E. *J. Am. Chem. Soc.* **2014**, *136*, 14349.
(20) Hwang, H.; Kim, J.; Jeong, J.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 10770.
(21) Yang, G.; Lindovska, P.; Zhu, D.; Kim, J.; Wang, P.; Tang, R.-Y.; Movassaghi, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 10807.
(22) Xiao, K.-J.; Lin, D. W.; Miura, M.; Zhu, R.-Y.; Gong, W.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 8138.
(23) Li, S.; Chen, G.; Feng, C.-G.; Gong, W.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 5267.
(24) Foo, K.; Sella, E.; Thome, I.; Eastgate, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 5279.
(25) Kang, T.; Kim, Y.; Lee, D.; Wang, Z.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 4141.
(26) Kim, H. J.; Ajitha, M. J.; Lee, Y.; Ryu, J.; Kim, J.; Lee, Y.; Jung, Y.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 1132.
(27) Yang, Y.-F.; Cheng, G.-J.; Liu, P.; Leow, D.; Sun, T.-Y.; Chen, P.; Zhang, X.; Yu, J.-Q.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 344.
(28) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094.
(29) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788.
(30) Zhang, F.; Spring, D. R. *Chem. Soc. Rev.* **2014**, *43*, 6906.
(31) Kinuta, H.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2015**, *137*, 1593.
(32) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242.
(33) Affron, D. P.; Davis, O. A.; Bull, J. A. *Org. Lett.* **2014**, *16*, 4956.
(34) Cui, W.; Chen, S.; Wu, J.-Q.; Zhao, X.; Hu, W.; Wang, H. *Org. Lett.* **2014**, *16*, 4288.
(35) Campeau, L. C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020.
(36) Liu, J.; Xie, Y.; Zeng, W.; Lin, D.; Deng, Y.; Lu, X. *J. Org. Chem.* **2015**, *80*, 4618.

DOI: 10.1021/acs.joc.5b02818
J. Org. Chem. 2016, 81, 343−350

(37) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624.
(38) Otley, K. D.; Ellman, J. A. *Org. Lett.* **2015**, *17*, 1332.
(39) Deng, Y.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2015**, *54*, 888.
(40) Tang, R.-Y.; Li, G.; Yu, J.-Q. *Nature* **2014**, *507*, 215.
(41) Xu, H.; Shang, M.; Dai, H.-X.; Yu, J.-Q. *Org. Lett.* **2015**, *17*, 3830.
(42) Dong, Z.; Wang, J.; Dong, G. *J. Am. Chem. Soc.* **2015**, *137*, 5887.
(43) Wang, X.-C.; Gong, W.; Fang, L.-Z.; Zhu, R.-Y.; Li, S.; Engle, K. M.; Yu, J.-Q. *Nature* **2015**, *519*, 334.
(44) (a) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119. (b) Della Ca', N.; Maestri, G.; Malacria, M.; Derat, E.; Catellani, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 12257.
(45) (a) Martins, A.; Mariampillai, B.; Lautens, M. *Top. Curr. Chem.* **2009**, *292*, 1−33. (b) Ye, J.; Lautens, M. *Nat. Chem.* **2015**, *7*, 863.
(46) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem. - Eur. J.* **2010**, *16*, 2654.
(47) Kefalidis, C. E.; Davi, M.; Holstein, P. M.; Clot, E.; Baudoin, O. *J. Org. Chem.* **2014**, *79*, 11903.
(48) Bhakuni, B. S.; Yadav, A.; Kumar, S.; Patel, S.; Sharma, S.; Kumar, S. *J. Org. Chem.* **2014**, *79*, 2944.
(49) Toutov, A. A.; Liu, W.-B.; Betz, K. N.; Fedorov, A.; Stoltz, B. M.; Grubbs, R. H. *Nature* **2015**, *518*, 80.
(50) Yu, Z.; Ma, B.; Chen, M.; Wu, H.-H.; Liu, L.; Zhang, J. *J. Am. Chem. Soc.* **2014**, *136*, 6904.
(51) Xia, Y.; Liu, Z.; Feng, S.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2015**, *80*, 223.
(52) Park, S. H.; Kwak, J.; Shin, K.; Ryu, J.; Park, Y.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 2492.
(53) Jeong, J.; Patel, P.; Hwang, H.; Chang, S. *Org. Lett.* **2014**, *16*, 4598.
(54) Larsen, M. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 4287.
(55) Green, A. G.; Liu, P.; Merlic, C. A.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 4575.
(56) Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci. U. S. A.* **2011**, *108*, 14411.
(57) Langlois, B. R.; Laurent, E.; Roidot, N. *Tetrahedron Lett.* **1991**, *32*, 7525.
(58) Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494.
(59) Gui, J.; Zhou, Q.; Pan, C.-M.; Yabe, Y.; Burns, A. C.; Collins, M. R.; Ornelas, M. A.; Ishihara, Y.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 4853.
(60) Monir, K.; Bagdi, A. K.; Ghosh, M.; Hajra, A. *J. Org. Chem.* **2015**, *80*, 1332.
(61) Su, Y.; Zhou, H.; Chen, J.; Xu, J.; Wu, X.; Lin, A.; Yao, H. *Org. Lett.* **2014**, *16*, 4884.
(62) Mandal, D.; Yamaguchi, A. D.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2011**, *133*, 19660.
(63) Yamaguchi, A. D.; Chepiga, K. M.; Yamaguchi, J.; Itami, K.; Davies, H. M. L. *J. Am. Chem. Soc.* **2015**, *137*, 644.
(64) Iaroshenko, V. O.; Gevorgyan, A.; Davydova, O.; Villinger, A.; Langer, P. *J. Org. Chem.* **2014**, *79*, 2906.
(65) Bon, J. L.; Feng, D.; Marder, S. R.; Blakey, S. B. *J. Org. Chem.* **2014**, *79*, 7766.
(66) Speck, K.; Karaghiosoff, K.; Magauer, T. *Org. Lett.* **2015**, *17*, 1982.
(67) Muramatsu, W.; Nakano, K. *Org. Lett.* **2015**, *17*, 1549.
(68) (a) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74. (b) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335.
(69) Yang, K.; Song, Q. *Org. Lett.* **2015**, *17*, 548.
(70) Zhao, J.; Fang, H.; Han, J.; Pan, Y. *Org. Lett.* **2014**, *16*, 2530.
(71) Li, Z.; Zhang, Y.; Zhang, L.; Liu, Z.-Q. *Org. Lett.* **2014**, *16*, 382.
(72) Wang, D.; Izawa, Y.; Stahl, S. S. *J. Am. Chem. Soc.* **2014**, *136*, 9914.
(73) Gigant, N.; Quintin, F.; Bäckvall, J.-E. *J. Org. Chem.* **2015**, *80*, 2796.
(74) Osberger, T. J.; White, M. C. *J. Am. Chem. Soc.* **2014**, *136*, 11176.
(75) Ammann, S. E.; Rice, G. T.; White, M. C. *J. Am. Chem. Soc.* **2014**, *136*, 10834.
(76) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417.
(77) Davies, H. M. L.; Morton, D. *Chem. Soc. Rev.* **2011**, *40*, 1857.
(78) Qin, C.; Davies, H. M. L. *J. Am. Chem. Soc.* **2014**, *136*, 9792.
(79) Guptill, D. M.; Davies, H. M. L. *J. Am. Chem. Soc.* **2014**, *136*, 17718.
(80) Cherney, E. C.; Lopchuk, J. M.; Green, J. C.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 12592.
(81) Gutekunst, W. R.; Baran, P. S. *J. Org. Chem.* **2014**, *79*, 2430.
(82) Schmidt, V. A.; Quinn, R. K.; Brusoe, A. T.; Alexanian, E. J. *J. Am. Chem. Soc.* **2014**, *136*, 14389.
(83) Li, J.; Zhang, J.; Tan, H.; Wang, D. Z. *Org. Lett.* **2015**, *17*, 2522.
(84) Wang, L.; Wei, X.-J.; Jia, W.-L.; Zhong, J.-J.; Wu, L.-Z.; Liu, Q. *Org. Lett.* **2014**, *16*, 5842.
(85) Mori, K.; Kurihara, K.; Yabe, S.; Yamanaka, M.; Akiyama, T. *J. Am. Chem. Soc.* **2014**, *136*, 3744.
(86) Richers, M. T.; Breugst, M.; Platonova, A. Y.; Ullrich, A.; Dieckmann, A.; Houk, K. N.; Seidel, D. *J. Am. Chem. Soc.* **2014**, *136*, 6123.
(87) Douglas, J. J.; Cole, K. P.; Stephenson, C. R. J. *J. Org. Chem.* **2014**, *79*, 11631.
(88) Jin, J.; MacMillan, D. W. C. *Nature* **2015**, *525*, 87−90.
(89) Cuthbertson, J. D.; MacMillan, D. W. C. *Nature* **2015**, *519*, 74−77.
(90) Negretti, S.; Narayan, A. R. H.; Chiou, K. C.; Kells, P. M.; Stachowski, J. L.; Hansen, D. A.; Podust, L. M.; Montgomery, J.; Sherman, D. H. *J. Am. Chem. Soc.* **2014**, *136*, 4901.
(91) Zhang, W.; Liu, Y.; Yan, J.; Cao, S.; Bai, F.; Yang, Y.; Huang, S.; Yao, L.; Anzai, Y.; Kato, F.; Podust, L. M.; Sherman, D. H.; Li, S. *J. Am. Chem. Soc.* **2014**, *136*, 3640.

DOI: 10.1021/acs.joc.5b02818
J. Org. Chem. 2016, 81, 343−350