ACCOUNTS of chemical research

Article

pubs.acs.org/accounts

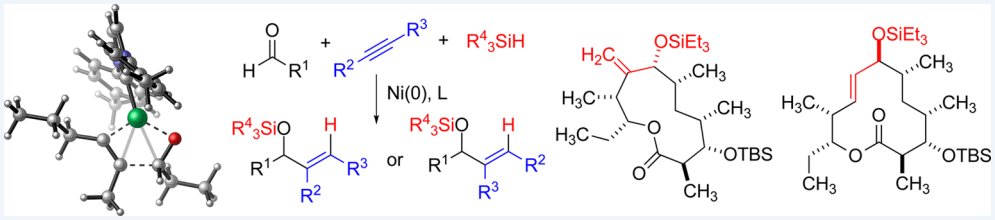
Mechanistic Basis for Regioselection and Regiodivergence in Nickel-Catalyzed Reductive Couplings

Published as part of the Accounts of Chemical Research special issue "Earth Abundant Metals in Homogeneous Catalysis".

Evan P. Jackson,[†] Hasnain A. Malik,[†,¶] Grant J. Sormunen,[†] Ryan D. Baxter,[†,#] Peng Liu,[‡,∥] Hengbin Wang,[†] Abdur-Rafay Shareef,[†,⊥] and John Montgomery*[,†]

[†]Department of Chemistry, University of Michigan, 930 N. University Avenue, Ann Arbor, Michigan 48109-1055, United States

[‡]Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, United States



CONSPECTUS: The control of regiochemistry is a considerable challenge in the development of a wide array of catalytic processes. Simple π-components such as alkenes, alkynes, 1,3-dienes, and allenes are among the many classes of substrates that present complexities in regioselective catalysis. Considering an internal alkyne as a representative example, when steric and electronic differences between the two substituents are minimal, differentiating among the two termini of the alkyne presents a great challenge. In cases where the differences between the alkyne substituents are substantial, overcoming those biases to access the regioisomer opposite that favored by substrate biases often presents an even greater challenge.

Nickel-catalyzed reductive couplings of unsymmetrical π-components make up a group of reactions where control of regiochemistry presents a challenging but important objective. In the course of our studies of aldehyde−alkyne reductive couplings, complementary solutions to challenges in regiocontrol have been developed. Through careful selection of the ligand and reductant, as well as the more subtle reaction variables such as temperature and concentration, effective protocols have been established that allow highly selective access to either regiosiomer of the allylic alcohol products using a wide range of unsymmetrical alkynes. Computational studies and an evaluation of reaction kinetics have provided an understanding of the origin of the regioselectivity control. Throughout the various procedures described, the development of ligand−substrate interactions plays an essential role, and the overall kinetic descriptions were found to differ between protocols. Rational alteration of the rate-determining step plays a key role in the regiochemistry reversal strategy, and in one instance, the two possible regioisomeric outcomes in a single reaction were found to operate by different kinetic descriptions. With this mechanistic information in hand, the empirical factors that influence regiochemistry can be readily understood, and more importantly, the insights suggest simple and predictable experimental variables to achieving a desired reaction outcome.

These studies thus present a detailed picture of the influences that control regioselectivity in a specific catalytic reaction, but they also delineate strategies for regiocontrol that may extend to numerous classes of reactions. The work provides an illustration of how insights into the kinetics and mechanism of a catalytic process can rationalize subtle empirical findings and suggest simple and rational modifications in procedure to access a desirable reaction outcome. Furthermore, these studies present an illustration of how important challenges in organic synthesis can be met by novel reactivity afforded by base metal catalysis. The use of nickel catalysis in this instance not only provides an inexpensive and sustainable method for catalysis but also enables unique reactivity patterns not accessible to other metals.

INTRODUCTION

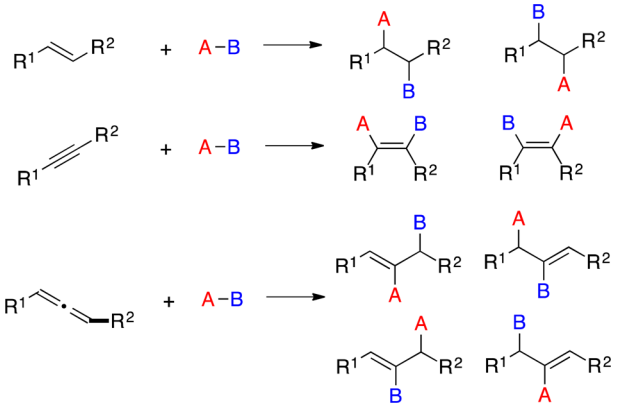
The control of selectivity in catalytic processes presents a considerable challenge in the development of new synthetic transformations. Different types of selectivity introduce unique challenges, including the control of enantioselectivity, regioselectivity, chemoselectivity, and site-selectivity.[1] Among these, the development of *regiodivergent* strategies in catalyzed additions to π-components utilizing first row transition metals has been a particular emphasis of several projects in our laboratory in recent years. A regioselective process is defined as one where one regioisomer can be accessed in preference to another, and a regiodivergent process is one where more than one regiochemical outcome can be selectively accessed for a

Received: February 22, 2015
Published: May 12, 2015

DOI: 10.1021/acs.accounts.5b00096
Acc. Chem. Res. 2015, 48, 1736−1745

single combination of substrates by tailoring the properties and behavior of the catalyst system. Developing regiodivergent processes presents considerably greater challenges than accessing a single regiochemical outcome. As depicted below (Scheme 1), catalytic additions to unsymmetrical alkenes and

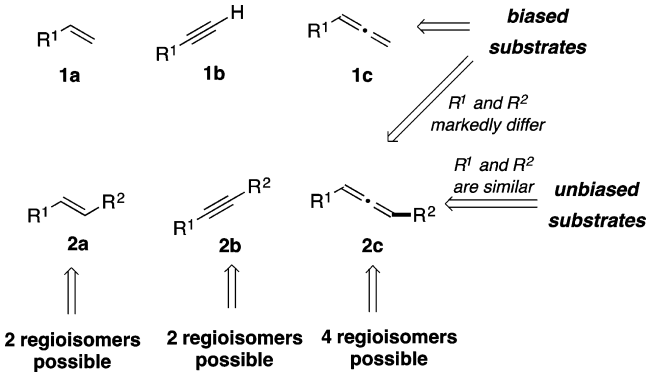
Scheme 1. Regioselectivity Outcomes in Additions to Alkenes, Alkynes, and Allenes



alkynes can afford two possible regioisomers, whereas additions to allenes can afford four possible regioisomeric outcomes. The various possible stereochemical relationships of the alkenes and stereogenic centers in the products add further to the number and types of isomers that may be obtained. Gaining access to all of the possible isomers in addition to unsymmetrical π-systems such as these presents a major challenge for nearly all classes of chemical reactions.[2−4]

One of the most widely employed strategies for control of catalytic, regioselective additions to π-components involves the use of directing groups on the alkyne.[5] Strategies of this type can be very effective in the control of regiochemistry, where a remote directing group can bind to a catalyst and favor one orientation of the substrate in the regiochemistry-determining step. Because installation and removal of the directing group can add additional steps to the overall synthetic operation, cases in which the directing group is either desired in the final product structure or easily converted to a desired functional group provide the most useful contexts for directed regiocontrol strategies. On the other hand, scenarios where directing groups are not easily installed or removed present a different set of challenges and require the development of nondirected approaches.[1,6−10] In these cases involving nondirected additions, π-components in regioselective and regiodivergent processes can typically be classified as biased or unbiased as illustrated for alkenes, alkynes, and allenes (Scheme 2). With biased substrates such as monosubstituted π-systems **1a−c** or alternatively disubstituted π-systems **2a−c** where R^1 and R^2 markedly differ in steric or electronic properties, structural features of the substrates influence the properties of the π-system. This bias often promotes a single operative mechanistic pathway, leading to a strong preference for the formation of one regioisomer over another. In cases where two different catalysts can promote the same net addition process by fundamentally different mechanisms, the inherent structural biases in the substrate can often allow a regiodivergent outcome for the two catalyst systems. A classic illustration of this type of regiodivergency is the copper- and ruthenium-catalyzed click reactions of azides and alkynes to

Scheme 2. Biased and Unbiased Substrates in Catalytic, Regioselective Operations



access either 1,4- or 1,5-triazole products.[11,12] Alternatively, accessing regiodivergent outcomes with biased substrates for a single catalyst type that operates by a single mechanism presents a considerable challenge. In these cases, either significant variation in ligand structure or fundamental changes in the kinetics (and thus identity of the regiochemistry-determining step) are typically required.

The development of regioselective or regiodivergent processes with unbiased substrates such as disubstituted π-systems **2a−c**, where the R^1 and R^2 groups possess similar steric and electronic properties, presents a different set of challenges (Scheme 2). In these cases, accessing any of the possible regioisomers selectively is typically quite challenging, since the contributing influence of the substrate is quite small and any substrate−ligand interactions would likely be similar for the two regioisomeric pathways. The ability to develop regioselective or regiodivergent catalytic processes of π-components that possess only negligible steric or electronic biases are extremely challenging in nearly all contexts.

In recent years, our laboratory has developed nickel-catalyzed processes that allow the production of allylic alcohols through the reductive coupling of aldehydes and alkynes.[13−15] With both biased and unbiased alkynes, highly selective regiodivergent pathways have been developed. Numerous factors, including structures of the reductant and ligand, concentration, temperature, and rate of addition, all have an important influence on the regiochemical outcomes with both biased and unbiased classes of alkynes. Through a series of kinetic and computational investigations, considerable insight into the origin of regiocontrol in several of the optimized protocols has been developed. This Account summarizes our insights to date on regiocontrol in this reaction class, with a focus on describing how mechanistic insights provided a rational and predictable path toward the development of highly effective synthetic procedures.

MECHANISMS OF NICKEL-CATALYZED ALDEHYDE−ALKYNE REDUCTIVE COUPLINGS

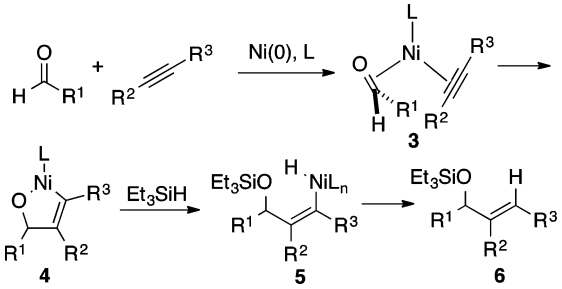
A number of effective protocols have been developed for the reductive coupling of aldehydes and alkynes. These methods involve either temporary conversion of the alkyne to a nucleophilic alkenyl metal through processes such as hydroboration or hydrozirconation followed by aldehyde addition[16,17] or alternatively through metallacyclic intermediates derived from oxidative cyclization of a low-valent metal with a bound aldehyde and alkyne to produce a five-membered

DOI: 10.1021/acs.accounts.5b00096
Acc. Chem. Res. 2015, 48, 1736−1745

metallacyclic intermediate. The latter pathway has been developed for metals across the periodic table, including methods involving titanium, rhodium, iridium, and nickel. The control of regiochemistry has seen significant advances, particularly in directed processes from Jamison with nickel,[18−20] Krische in iridium- and rhodium-catalyzed processes,[21,22] and Micalizio with titanium.[23,24] Additionally, related methods from Krische developing transfer hydrogenation methods are especially attractive in that the alcohol oxidation state may be directly employed as the source of the electrophilic partner.[25] The specific variant of aldehyde−alkyne reductive couplings that has been most extensively developed and studied in our laboratory involves silane reductants paired with phosphine or *N*-heterocyclic carbene (NHC) complexes of nickel(0), with NHCs being the most effective in addressing challenging problems in regiocontrol.[26−28] A brief perspective on the phosphine-promoted intramolecular addition studies from our laboratory will first be described, since this process was the focus of our initial evaluation of kinetics in this reaction class. More recent mechanistic insights in the NHC-promoted versions, which provide the highest degree of regiodivergency, will then be discussed.

The simplest framework for considering the metallacycle-based mechanism of aldehyde−alkyne reductive couplings involves coordination of the aldehyde and alkyne to Ni(0) to generate π-complex **3**, followed by oxidative cyclization to metallacycle **4**, σ-bond metathesis of **4** with the silane reductant to produce **5**, and finally reductive elimination to form the C−H bond of product **6** (Scheme 3). The initial proposal of this

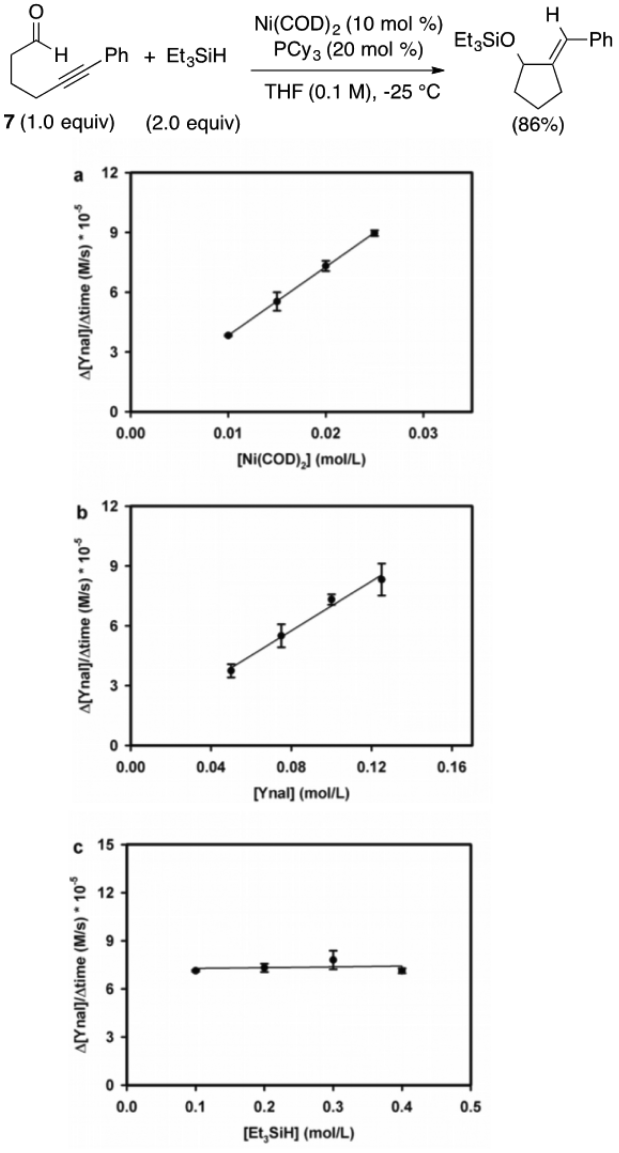
Scheme 3. Metallacycle Pathway for Aldehyde−Alkyne Reductive Couplings



mechanistic pathway[29] was based on related metallacycle-forming processes involving nickel, and a dimeric nickel metallacycle directly obtained from an aldehyde−alkyne complex was subsequently reported by Ogoshi.[30] Additionally, a number of theoretical studies have examined different combinations of metals, ligands, and reductants, with metallacycle formation uniformly being found as a key component of the operative pathway.[31−35]

The kinetics of this process was first studied on the reductive cyclization of ynal **7** using Et_3SiH as reductant and a catalyst derived from $Ni(COD)_2$ and PCy_3 (Scheme 4).[36] In reactions conducted at −25 °C and monitored by *in situ* IR, the kinetics displayed a clear first-order dependence on both the ynal and the nickel catalyst, and a zero order dependence on silane. Most notably, plots of reaction progression across a 4-fold increase in silane concentration nearly perfectly overlaid, illustrating the absence of a rate dependence on silane concentration. Further study illustrated that silane addition to the nickel catalyst was extremely slow in the presence of either aldehyde or alkyne,

Scheme 4. Initial Rate Analysis of an Intramolecular Process



ruling out the possibility that an initial burst of Ni(0) oxidative addition to the silane followed by rate-determining addition of a nickel hydride intermediate to the aldehyde or alkyne could be operative. On this basis, the metallacycle-based mechanism, where oxidative cyclization is rate determining, is fully consistent with the observed kinetic profile.

The initial computational studies of Et_3B-mediated intermolecular aldehyde−alkyne reductive couplings from Houk and Jamison found that metallacycle formation was rate-limiting,[31,32] followed by a fast borane-mediated step involving cleavage of the Ni−O bond of the metallacycle. Houk and Montgomery also conducted a computational study of the intermolecular process involving NHC ligands and silane reductants, and similarly found that the rate-determining step was again metallacycle formation, followed by a fast σ-bond metathesis reaction of the silane.[33] Most recently, post rate-limiting dimerization of a metallacycle derived from an intramolecular process using silanes with a nickel(0)-phosphine catalyst was found to be competitive with the simple mononuclear pathway depicted above (Scheme 3); however, in this study as well, metallacycle formation was proposed to be

DOI: 10.1021/acs.accounts.5b00096
Acc. Chem. Res. 2015, 48, 1736−1745

the rate-determining step.[35] In summary, across a broad range of combinations of substrate classes, including inter- and intramolecular processes, phosphine and NHC-derived catalyst systems, and silane and borane reductants, evidence from kinetics and computational studies of the most widely used protocols all pointed toward a metallacycle-based pathway involving a rate-determining oxidative cyclization to produce metallacycle **4** followed by a fast process involving metallacycle consumption by the reductant.

In our most recent efforts, we made a surprising empirical observation that the regiochemical outcome of intermolecular couplings varies according to silane structure if a bulky silane and bulky NHC ligand are *simultaneously* employed.[37] The effect is not observed if only one of the two structural changes (ligand or silane) is made. The influence on regiochemistry is most pronounced at high temperature and when the reaction is conducted at high dilution or with low silane concentrations. Against the backdrop described above of extensive evidence that the silane involvement strictly occurs after the rate- and regiochemistry-determining step, this result was entirely unexpected. However, since this new protocol presented considerable preparative advantages in regiocontrol (*vide infra*), we conducted a mechanistic study to elucidate the observed effects.

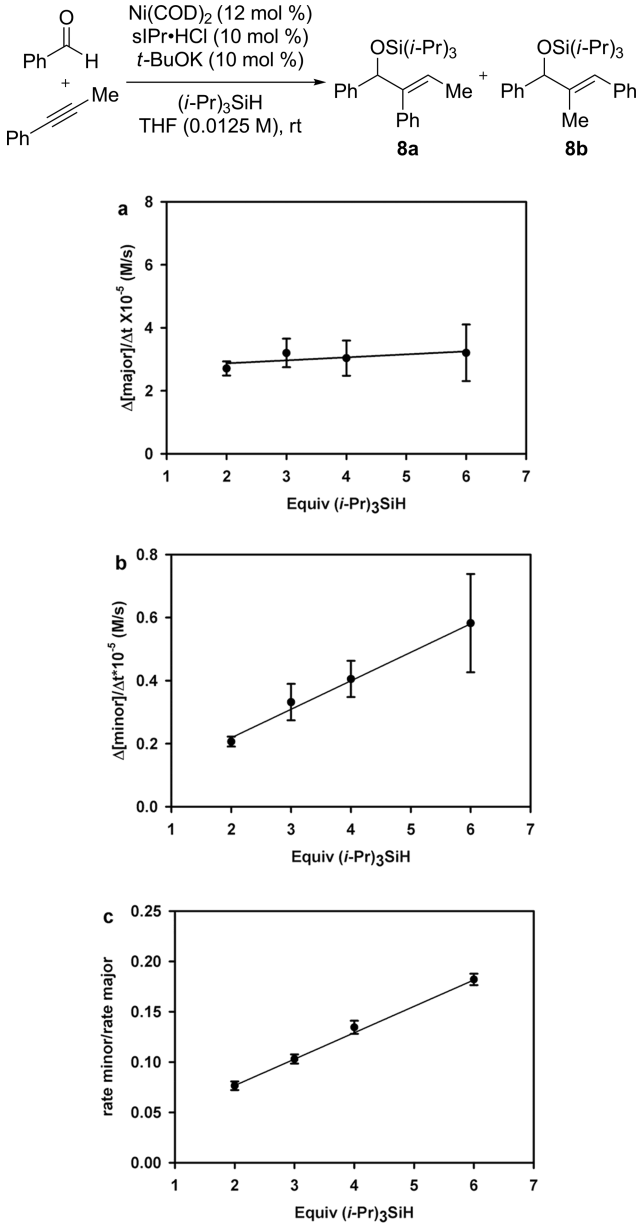
In studying the reductive coupling of benzaldehyde with phenylpropyne, using $(i\text{-Pr})_3SiH$ as reductant and the hindered NHC sIPr as ligand at rt, only a slight rate dependence on silane concentration was observed for the consumption of starting material. However, upon measuring the rate dependence for the two regioisomeric products separately, we observed that the rate of formation of the major regioisomer **8a** was independent of silane concentration, whereas the rate of formation of the minor regioisomer **8b** was strongly influenced by silane concentration (Scheme 5, panels a and b). By plotting the initials rates of the formation of the major and minor regioisomers as a ratio (Scheme 5, panel c), we can easily visualize the markedly different dependence of the two regioisomeric pathways on silane concentration.

The origin of this unusual affect appears to involve the reversible formation of the metallacycle **10b** that leads to the minor regioisomer **8b** and the irreversible formation of the metallacyle **10a** that leads to the major regioisomer **8a** (Scheme 6). The highly hindered nature of structure **10b**, in particular the steric repulsions between the proximal phenyl group and the bulky ligand, slows the addition of the bulky silane, leading to the reversibility of its formation. The entropic penalty for the **10b** to **11b** conversion is maximized at elevated temperature, and the rate of the **10b** to **11b** conversion (and thus the rate of formation of **8b**) is further slowed by maintaining a low concentration of silane. While changes between reversible and irreversible pathways are commonly invoked in discussions of regiodivergent processes, we are unaware of another case such as this where the kinetic profiles leading to two regioisomeric products in a single reaction are shown to differ to this clear extent.

MECHANISTIC INSIGHTS INFORM REGIODIVERGENT STRATEGIES IN NICKEL-CATALYZED ALDEHYDE–ALKYNE COUPLINGS

The above mechanistic studies illustrate a number of opportunities for effecting regiocontrol and regiodivergency

Scheme 5. Initial Rate Analysis of a Large NHC–Large Silane Protocol

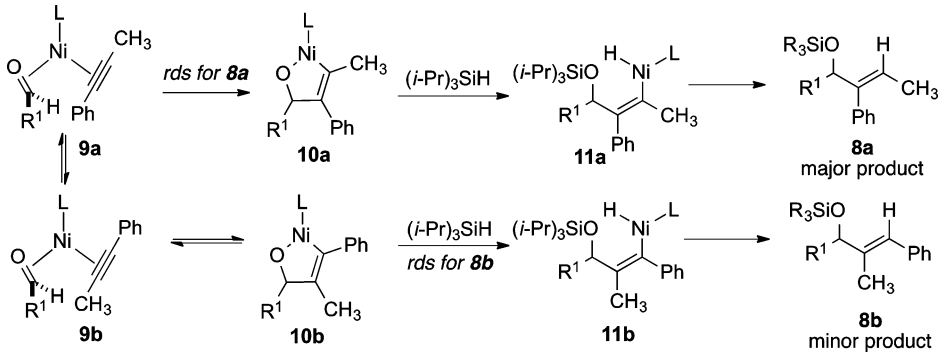


in aldehyde–alkyne reductive couplings. In considering the generality of regiocontrol strategies, it is instructive to consider not only the empirical observations that led to the development of effective strategies but also the underlying mechanistic basis for why the strategies are effective. Such mechanistic insights can lead to rapid and rational optimization of reaction conditions when a new combination of substrates is encountered. While several scenarios of reaction kinetics were documented in the studies outlined above, the underlying goal was to be able to use these insights in the development of highly selective, regiodivergent procedures for the formation of either product **12a** or **12b** across a range of substrates (Scheme 7).

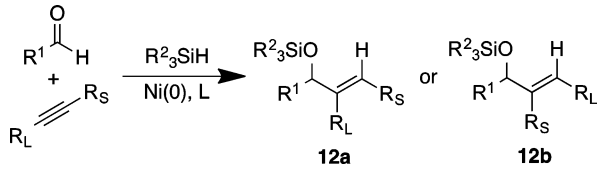
As the above kinetic studies demonstrated, most of the above-mentioned protocols involve the irreversible formation of metallacycles **14a** and **14b**.[28,33] These strategies, summarized in the upper portion of Scheme 8, involve metallacycle

DOI: 10.1021/acs.accounts.5b00096
Acc. Chem. Res. 2015, 48, 1736–1745

Scheme 6. Mechanism of the Large NHC−Large Silane Protocol



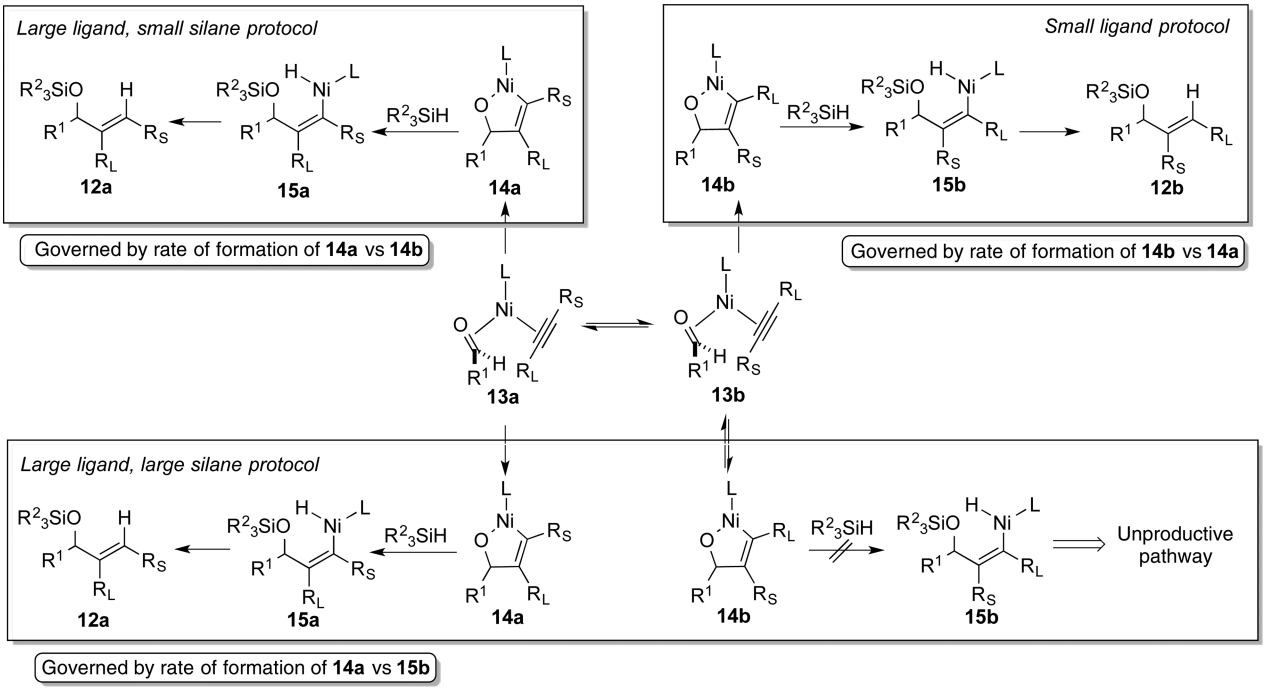
Scheme 7. Desired Regiodivergent Outcome in Aldehyde−Alkyne Couplings



formation as the rate- and regiochemistry-determining steps, where regioselectivity is determined by the relative rates of the **13a** to **14a** and the **13b** to **14b** conversions. The identity and concentration of the silane within this manifold is of no consequence, since the σ-bond metathesis steps involving silane (i.e., the formation of **15a** and **15b**) occur after the rate- and regiochemistry-determining steps. This manifold can generally be favored by using unhindered silanes. With small NHC ligands, even bulky silanes such as $(i\text{-Pr})_3\text{SiH}$ undergo fast additions, rendering metallacycle formation irreversible.

In contrast, a very specialized protocol can lead to the reversible formation of the more hindered metallacycle **14b**, while the formation of metallacycle **14a** under these conditions is irreversible (at least in the nonsyringe drive protocols where the kinetics studies were conducted).[37] This strategy, summarized in the lower portion of Scheme 8, is governed by the relative rates of the formation of metallacycle **14a** and the formation of intermediate **15b** produced by σ-bond metathesis reaction of **14b** with the silane. The change in silane order for the formation of the major and minor regioisomers noted above (Scheme 5) provides evidence for this conclusion. The more hindered metal−carbon bond of metallacycle **14b** (nickel proximal to R^L) compared with the less hindered environment of metallacycle **14a** (nickel proximal to R^S) is the origin of this change in kinetic description. The protocol that favors this outcome requires bulky silanes and bulky NHC ligands and is favored by low concentration of silane and elevated temperature. The temperature influence likely derives from the significant entropic penalty of the bimolecular addition required in the **14b** to **15b** conversion compared with unimolecular conversion of **13a** to **14a**. Notably, this protocol is only useful in accessing the more hindered regioisomer **12a**.

Scheme 8. Implications of Observed Mechanisms in Regiocontrol Strategies

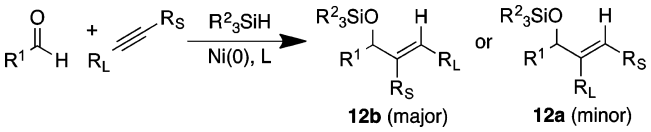


DOI: 10.1021/acs.accounts.5b00096
Acc. Chem. Res. 2015, 48, 1736−1745

Small Ligand Protocol

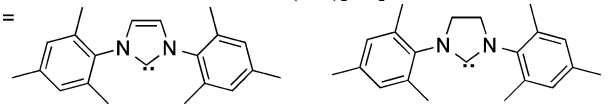
The identification of small ligands that are effective in accessing regioisomer **12b** was conducted using 2-hexyne as a prototypical unbiased alkyne.[28] With more biased alkynes such as terminal alkynes, aromatic alkynes, and conjugated enynes, the alkyne electronic and steric biases naturally favor regioisomer **12b**, so simple ligands routinely employed such as IMes[38−40] are entirely satisfactory for achieving high regioselectivity in these cases (Table 1, entries 1−3). However,

Table 1. Regioselectivity of the Small Ligand Protocol

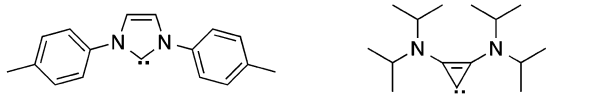


entry	R^1	R^S	R^L	$R^2{}_3SiH$	L	% yield	12b/12a
1	*n*-Hex	H	*i*-Pr	$(i\text{-Pr})_3SiH$	**16**	74	>98:2
2	Ph	Me	Ph	$(i\text{-Pr})_3SiH$	**16**	74	>98:2
3	*n*-Hex	Me	*c*-hexenyl	$(i\text{-Pr})_3SiH$	**16**	99	97:3
4	*n*-Hex	Me	*n*-Pr	$(i\text{-Pr})_3SiH$	**16**	83	67:33
5	*n*-Hex	Me	*n*-Pr	$(i\text{-Pr})_3SiH$	**17**	73	61:39
6	*n*-Hex	Me	*n*-Pr	$(i\text{-Pr})_3SiH$	**18**	18	87:13
7	*n*-Hex	Me	*n*-Pr	$(t\text{-Bu})_2SiH_2$	**19**	78	88:12

L =



IMes (16) sIMes (17)

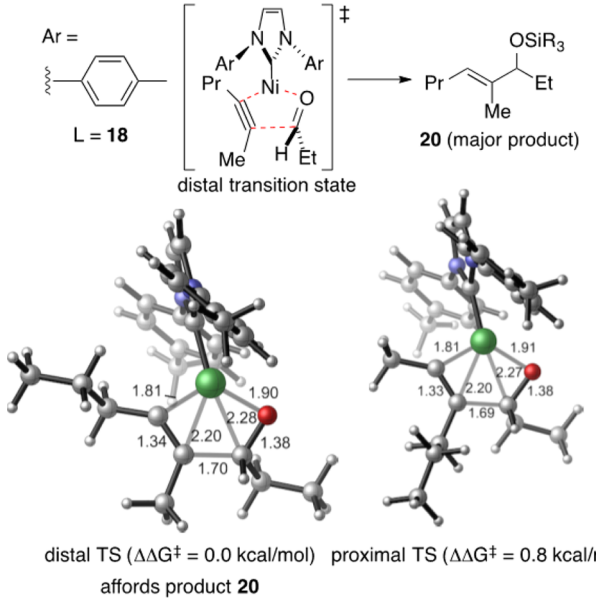


ITol (18) IPr-BAC (19)

with 2-hexyne, more specialized ligands such as ITol and IPr-BAC were found to be essential for the regioselective production of isomer **12b**. For example, in comparing the additions of 2-hexyne, regioselectivities with IMes (**16**) or sIMes (**17**) were a modest 67:33 and 61:39 ratio, whereas ITol (**18**) and IPr-BAC (**19**) achieved a synthetically useful regioisomeric ratio of 87:13 to 88:12 (Table 1, entries 4−7), respectively. Of these ligands, IPr-BAC[41] generally afforded the highest yield favoring the production of desired product **12b**. While regioselectivities are unaffected by silane structure, with small ligand classes, bulky silanes effectively diminish the amount of aldehyde or alkyne hydrosilylation that can sometimes become competitive.

Computational studies provided considerable insight into the origin of the regioselectivities with small ligands such as ITol (**18**) and IPr-BAC (**19**).[33] These unhindered ligands were examined in the coupling of 2-hexyne with propionaldehyde to evaluate the features that impact regioselectivity in the rate-determining metallacycle formation (Scheme 9). In this case, few steric interactions between the ligand and alkyne substituents are observed for either of the regioisomeric pathways, given the small ligand size and flexibility of the *N*-aryl orientation. However, strong steric repulsions experienced in the forming C−C bond in the proximal TS leading to the generation of the minor regioisomer **12a** ultimately favor the formation of the major regioisomer **20**. The difference in steric

Scheme 9. Oxidative Cyclization Transition State Energies for the Small Ligand Pathway with ITol as Ligand[a]



[a]Calculations were performed at the M06/SDD-6-311+G(d,p)//B3LYP/LANL2DZ-6-31G(d) level of theory. Here distal refers to the TS structure in which the bulkier alkyne substituent (*n*-Pr) is distal to the forming C−C bond.

repulsions with the similarly sized Me and *n*-Pr groups is sufficiently large to afford the high level of regioselectivity, due to the relatively short forming C−C bond distances (c.a. 1.7 Å) in the oxidative cyclization transition states. In summary, as these studies illustrate, IMes serves as an effective ligand in cases where the substrate biases favor the formation of regioisomer **12b**, but with more unbiased classes of alkynes, the IPr-BAC ligand effectively differentiates similar groups (such as Me vs *n*-Pr) and allows highly regioselective production of regioisomer **12b** through subtle substrate−ligand interactions.

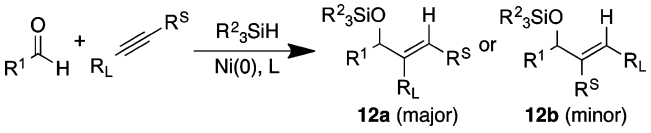
Large Ligand/Small Silane Protocol

With the above advances in accessing the regioisomer that involves formation of the least-crowded C−C bond, the sensitivity of the regioselectivity to small changes in NHC structure suggested that the opposite regioisomeric outcome could potentially be accessed. Toward this objective, an exploration of bulky ligand structures was conducted in the benchmark case of additions of phenylpropyne to heptaldehyde.[28] In progressing from IMes to IPr to sIPr to DP-IPr, the regiochemistry steadily improved to 94:6, now favoring the more hindered regioisomer **12a** (Table 2, entries 1−4). For the relatively unbiased alkyne 2-hexyne, the combination of IPr-BAC (**19**) as a small ligand and either sIPr (**22**) or DP-IPr (**23**) as a large ligand thus provides access to a highly regiodivergent outcome, with regioselectivities from 12:88 with IPr-BAC favoring **12b** to 94:6 with DP-IPr favoring **12a**. Avoiding undesired aldehyde or alkyne hydrosilylation was the primary motivation for the use of bulkier silanes in these initial studies. However, additional implications of the silane structural change are described in the development of a large ligand−large silane discussed in the final section of this Account.

These successes then raised the possibility of accessing regiodivergent outcomes with highly biased alkynes such as

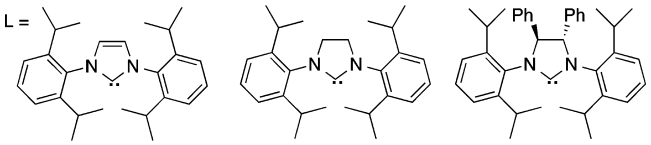
DOI: 10.1021/acs.accounts.5b00096
Acc. Chem. Res. 2015, 48, 1736−1745

Table 2. Initial Explorations with Large Ligand



entry	R^1	R^L	R^S	$R^2{}_3SiH$	L	% yield	12a/12b
1	*n*-Hex	*n*-Pr	Me	$(i\text{-Pr})_3SiH$	**16**	83	67:33
2	*n*-Hex	*n*-Pr	Me	$(i\text{-Pr})_3SiH$	**21**	84	80:20
3	*n*-Hex	*n*-Pr	Me	$(i\text{-Pr})_3SiH$	**22**	85	93:7
4	*n*-Hex	*n*-Pr	Me	Et_3SiH	**23**	94	94:6
5	*n*-Hex	*i*-Pr	H	$(i\text{-Pr})_3SiH$	**22**	40	41:59[a]
6	*n*-Hex	*i*-Pr	H	Et_3SiH	**23**	76	95:5
7	Ph	Ph	Me	Et_3SiH	**22**	65	58:42
8	Ph	Ph	Me	Et_3SiH	**23**	96	69:31[a]

[a]Data from H. A. Malik thesis, University of Michigan.

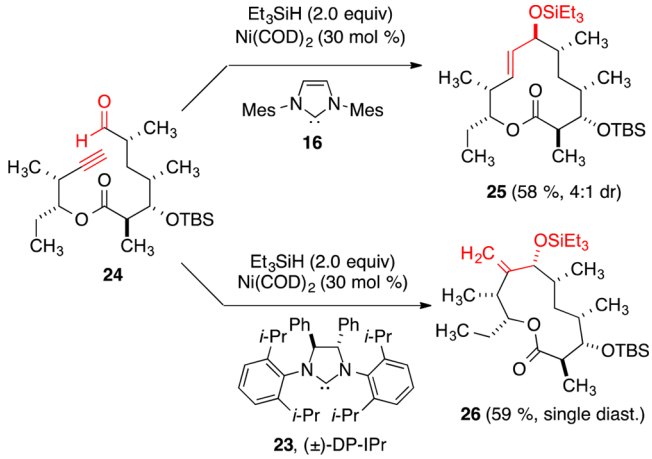


terminal alkynes and aromatic alkynes. In these cases, sIPr and DP-IPr were the most effective in reversing the regiochemistry outcome that is naturally favored by substrate biases. In the case of a terminal alkyne (Table 2, entries 5−6), the use of sIPr was ineffective, leading to a 41:59 ratio favoring the same regioisomer **12b** favored by IMes (**16**). However, the use of DP-IPr, which possesses the same *N*-aryl substituents as sIPr but also incorporates a C2-disubstituted ligand backbone, results in a dramatic improvement, providing the more hindered regioisomer **12a** with 95:5 regioselectivity. Bulkier silanes generally diminished the observation of aldehyde or alkyne hydrosilylation minor byproducts; however, the steric demand of ligand **23** typically required the use of a small silane such as Et_3SiH. With phenyl propyne, DP-IPr was slightly more effective than sIPr using Et_3SiH, but even DP-IPr resulted in only a modest regioselectivity of 69:31 (Table 2, entries 7−8).

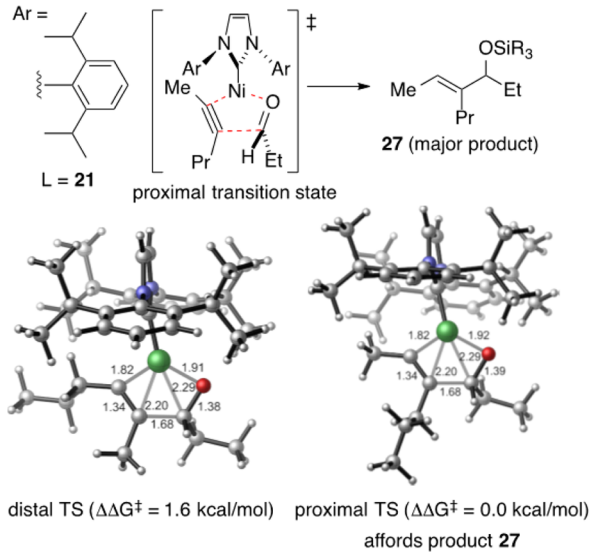
The unique characteristics of DP-IPr paired with Et_3SiH in reversing the regiochemistry of terminal alkyne couplings were explored in a challenging macrocyclization process in the course of developing a total synthesis of the macrolide 10-deoxymethynolide.[42] Utilizing the inherent substrate biases of the terminal alkyne of **24**, the use of IMes ligand proved satisfactory in an endocyclization process to access product **25** in 58% yield as a 4:1 mixture of diastereomers with only endocyclization products being observed (Scheme 10). Alternatively, the unique properties of DP-IPr with terminal alkynes are illustrated by the highly selective exocyclization of the same substrate to afford **26** in 59% yield as a single regio- and stereoisomer. Recent efforts have further developed this promising macrocyclization method across a broader range of substrates and with more readily available ligand motifs.[43]

Computational studies also provided considerable insight into the origin of the regioselectivities using large ligands such as IPr (**21**) (Scheme 11).[33] With this ligand, steric repulsions between the alkyne substituent and the ligand become significant during the formation of the metallacycle, and these effects override the aldehyde−alkyne steric interactions that govern the regiochemical outcome with smaller ligands. Additionally, 2D contour maps of the ligand van der Waals

Scheme 10. Regiodivergent Reductive Macrocyclizations



Scheme 11. Oxidative Cyclization Transition State Energies for Large Ligand/Small Silane Pathway with IPr as Ligand[a]

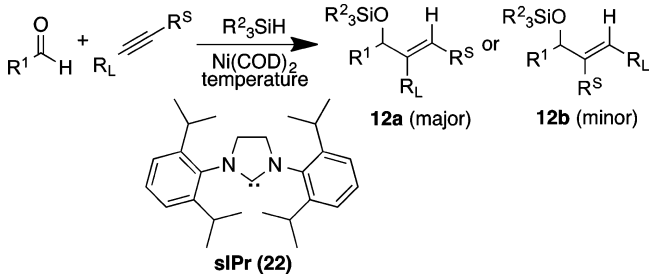


[a]Calculations were performed at the M06/SDD-6-311+G(d,p)//B3LYP/LANL2DZ-6-31G(d) level of theory. Here proximal refers to the TS structure in which the bulkier alkyne substituent (*n*-Pr) is proximal to the forming C−C bond.

surface in these metal complexes revealed the precise positioning where ligand sterics can most effectively influence regiocontrol through interaction with the alkyne. The 2- and 6-positions of *N*-aryl NHC motifs were found to be especially effective in exerting steric control, explaining the special role of this NHC class compared with bulky but ineffective ligands such as *N*-adamantyl derivatives. In comparing ligands **21** and **22**, computational studies found that the shorter Ni−C(carbene) bond distance (and the resulting greater effective steric bulk at the nickel center) with the saturated ligand **22** compared with the unsaturated ligand **21** was the origin of the improved large-ligand selectivity from ligand **22**. In summary, as the above examples demonstrate, regiodivergent outcomes are thus possible for a number of unbiased (i.e., 2-hexyne) and strongly biased (i.e., terminal alkynes, aromatic alkynes, and conjugated enynes) substrates using the combination of the complementary small ligand−small silane and large ligand−small silane pathways.

DOI: 10.1021/acs.accounts.5b00096
Acc. Chem. Res. 2015, 48, 1736−1745

Table 3. Regioselectivity of the Large Ligand/Large Silane Protocol



entry	R^1	R^L	R^S	$R^2{}_3SiH$	temp (°C)	% yield	**12a/12b**
1	Ph	Ph	Me	$(i\text{-Pr})_3SiH$	25	82	>98:2
2	*n*-Hept	Ph	Me	$(i\text{-Pr})_3SiH$	50	77	>98:2
3	*n*-Hept	*i*-Bu	Et	$(i\text{-Pr})_3SiH$	50	66	93:7
4	Ph	*i*-Pr	Me	$(i\text{-Pr})_3SiH$	50	78	>98:2
5	Ph	*n*-Pr	Et	$(i\text{-Pr})_3SiH$	50	56	68:32
6	*n*-Hex	*c*-hexenyl	Me	$(i\text{-Pr})_3SiH$	25	77	91:9
7	Ph	*i*-Pr	H	$(t\text{-Bu})_2MeSiH$	25	61	>98:2
8	Ph	*n*-Hex	H	$(t\text{-Bu})_2MeSiH$	25	69	95:5

Large Ligand/Large Silane Protocol

In our most recent work, an unusual influence of the silane structure on regiochemistry was noted when large ligands such as sIPr and large silanes such as $(i\text{-Pr})_3SiH$ were simultaneously employed.[37] An evaluation of kinetics suggested that the mechanism depicted earlier (Scheme 6), involving the reversibility of the metallacycle formation in the minor regioisomer pathway, was responsible for the effect. Several notable features were observed for this modified protocol, namely, much improved regioselectivity for the production of regioisomer **12a** with some substrate combinations compared with the large ligand−small silane protocol described above. For example, improved regiochemistry reversals could be accessed for a number of alkynes with a protocol optimized for internal alkynes, using $(i\text{-Pr})_3SiH$ at 50 °C. In reversing the normal bias of phenyl propyne, the more hindered regioisomer **12a** could be accessed in exceptional (>98:2) regioselectivities using either aromatic or aliphatic aldehydes (Table 3, entries 1−2). Very high regioselectivities favoring **12a** could also be accessed with unbiased alkynes. For example, *i*-Bu and Et groups or *i*-Pr and Me substituents could be easily differentiated (Table 3, entries 3−4), whereas the very challenging case of 3-heptyne (Et vs Pr) proceeded to give a 68:32 mixture of regioisomers, thus defining the limits of the method (Table 3, entry 5). With a conjugated enyne, excellent regioselectivities were observed for the more hindered isomer **12a** using sIPr even at rt to provide the desired isomer in 91:9 regioselectivity (Table 3, entry 6), thus reversing the regioselectivity normally accessed by this biased alkyne class (Table 1, entry 3). The elevated temperature protocol led to lower yields with terminal alkynes, and a procedure specifically used for terminal alkynes (rt, higher dilution, and $(t\text{-Bu})_2MeSiH$ as reductant) provided good yields of **12a** with excellent regiocontrol (Table 3, entries 7−8).

CONCLUSIONS

In summary, a series of complementary protocols have been developed that allow highly selective access to either regioisomer in nickel-catalyzed reductive couplings. The strategy does not require directing groups but rather relies upon precise control of the operative kinetic behavior of couplings and the development of ligand−substrate interactions to govern the regiochemical outcome. Regiodivergent outcomes are possible for unbiased internal alkynes as well as highly biased alkyne classes such as aromatic and terminal alkynes and conjugated enynes. By careful selection of ligand and reductant, modifications in the rate-determining step of the process can be engineered as a key component in the development of regiodivergent outcomes. The observation of different kinetic descriptions for the formation of two regioisomers in a single reaction is an underappreciated but highly effective strategy in accessing regiodivergent outcomes in catalytic processes.

AUTHOR INFORMATION

Corresponding Author

*E-mail: jmontg@umich.edu.

Present Addresses

[¶]H.A.M.: Department of Global Discovery Chemistry, Novartis Institutes for BioMedical Research, Inc., Cambridge, Massachusetts 02139, United States.
[#]R.D.B.: Department of Chemistry, University of California at Merced, 5200 N. Lake Rd., Merced, CA 95343, United States.
[‖]P.L.: Department of Chemistry, University of Pittsburgh, 219 Parkman Ave., Pittsburgh, PA 15260, United States.
[⊥]A.R.S.: US Food and Drug Administration, 109 Holton Street, Winchester, MA 01890, United States.

Author Contributions

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

Notes

The authors declare no competing financial interest.

Biographies

Evan P. Jackson, born in Portland, OR, obtained a B.A. degree from Willamette University in 2010 working with Sarah Kirk. He is currently completing his Ph.D. at the University of Michigan under the direction of John Montgomery studying nickel-catalyzed reductive coupling reactions.

DOI: 10.1021/acs.accounts.5b00096
Acc. Chem. Res. 2015, 48, 1736−1745

Hasnain A. Malik obtained his B.S. degree from Lehigh University in 2005, where he conducted his undergraduate research with Professor Ned D. Heindel. In 2010, he earned his Ph.D. from the University of Michigan, Ann Arbor, under the direction of Professor John Montgomery, working on strategies for regio- and enantiocontrol in Ni-catalyzed reductive couplings. Following postdoctoral studies with Professor Mark Lautens at the University of Toronto, he moved to the Department of Global Discovery Chemistry at the Novartis Institutes for BioMedical Research, Inc. (NIBRI) in Cambridge, Massachusetts where he is currently a Research Investigator.

Grant J. Sormunen, born in Duluth, MN, obtained a B.S. degree from the University of Wisconsin—Eau Claire in 2005 working with David Lewis. He received his Ph.D. degree at the University of Michigan in 2010 working with John Montgomery. In 2011, he became a Research Scientist at Promiliad Biopharma Inc.

Ryan D. Baxter obtained a B.Sc. degree from the University of Wisconsin—Madison in 2005 working with Samuel H. Gellman and received his M.Sc. (2007) and Ph.D. (2010) degrees at the University of Michigan working with John Montgomery. He then conducted postdoctoral research at the Scripps Research Institute as a National Institute of Health Postdoctoral Fellow with Donna Blackmond and Phil Baran before joining the faculty at UC Merced in 2014, where he is currently an Assistant Professor of Chemistry and Chemical Biology.

Peng Liu obtained his B.S. degree from the Peking University in 2003 and M.S. degree from the University of Guelph in 2006. He received his Ph.D. degree in 2010 and then performed postdoctoral studies with K. N. Houk at the University of California, Los Angeles. He joined the faculty at the University of Pittsburgh as an Assistant Professor of Chemistry in 2014.

Hengbin Wang, born in China, obtained a B.S. degree from Nankai University in 2001, and he received his Ph.D. degree at Emory University in 2012 working with Huw M. L. Daives. He then joined the Montgomery group at the University of Michigan as a postdoctoral researcher.

Abdur-Rafay Shareef, born in Richland, WA, obtained a B.S. and M.S. degree from Georgia State University working with David Boykin, and he received his Ph.D. degree at the University of Michigan working with David Sherman and John Montgomery. He is currently a chemist at the US Food and Drug Administration, where he develops surface-enhanced Raman spectroscopy (SERS) and mass spectroscopy methods.

John Montgomery, born in Concord, NC, obtained an A.B. degree from the University of North Carolina in 1987 working with Maurice Brookhart and Joe Templeton, and he received his Ph.D. degree at Colorado State University in 1991 working with Lou Hegedus. He then conducted postdoctoral research at the University of California at Irvine as an American Cancer Society Postdoctoral Fellow with Larry Overman before joining the faculty at Wayne State University at 1993. He joined the faculty at the University of Michigan in 2005, where he is currently the Margaret and Herman Sokol Professor in Medicinal or Synthetic Chemistry.

■ ACKNOWLEDGMENTS

Professor Ken Houk of UCLA is thanked for many helpful discussions during the course of this work. This work was funded by NIH (Grant GM-57014 to J.M., which supports the design of NHC ligands for regioselective transformations) and NSF (Grant CHE-1265491 to J.M., which supports the development of sustainable methods in catalysis, and Grant CHE-1361104 to K. N. Houk). G.J.S. acknowledges training grant support from NIH Grant GM-007767. R.D.B. acknowledges a U.S. Department of Education GAANN Fellowship; A.R.S. acknowledges receipt of a Rackham Merit Fellowship and a Fred W. Lyons Fellowship.

■ REFERENCES

(1) Mahatthananchai, J.; Dumas, A. M.; Bode, J. W. Catalytic Selective Synthesis. *Angew. Chem., Int. Ed.* **2012**, *51*, 10954−10990.
(2) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. Catalytic Markovnikov and Anti-Markovnikov Functionalization of Alkenes and Alkynes: Recent Developments and Trends. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368−3398.
(3) Chopade, P. R.; Louie, J. 2+2+2 Cycloaddition Reactions Catalyzed by Transition Metal Complexes. *Adv. Synth, Catal.* **2006**, *348*, 2307−2327.
(4) Saito, S.; Yamamoto, Y. Recent Advances in the Transition-Metal-Catalyzed Regioselective Approaches to Polysubstituted Benzene Derivatives. *Chem. Rev.* **2000**, *100*, 2901−2915.
(5) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. Substrate-Directable Chemical Reactions. *Chem. Rev.* **1993**, *93*, 1307−1370.
(6) Ohmura, T.; Oshima, K.; Taniguchi, H.; Suginome, M. Switch of Regioselectivity in Palladium-Catalyzed Silaboration of Terminal Alkynes by Ligand-Dependent Control of Reductive Elimination. *J. Am. Chem. Soc.* **2010**, *132*, 12194−12196.
(7) Gao, F.; Hoveyda, A. H. α-Selective Ni-Catalyzed Hydroalumination of Aryl- and Alkyl-Substituted Terminal Alkynes: Practical Syntheses of Internal Vinyl Aluminums, Halides, or Boronates. *J. Am. Chem. Soc.* **2010**, *132*, 10961−10963.
(8) Wu, J. Y.; Moreau, B.; Ritter, T. Iron-Catalyzed 1,4-Hydroboration of 1,3-Dienes. *J. Am. Chem. Soc.* **2009**, *131*, 12915−12917.
(9) Michel, B. W.; McCombs, J. R.; Winkler, A.; Sigman, M. S. Catalyst-Controlled Wacker-Type Oxidation of Protected Allylic Amines. *Angew. Chem., Int. Ed.* **2010**, *49*, 7312−7315.
(10) Miller, Z. D.; Li, W.; Belderrain, T. R.; Montgomery, J. Regioselective Allene Hydrosilylation Catalyzed by N-Heterocyclic Carbene Complexes of Nickel and Palladium. *J. Am. Chem. Soc.* **2013**, *135*, 15282−15285.
(11) Hein, J. E.; Fokin, V. V. Copper-Catalyzed Azide-Alkyne Cycloaddition (CuAAC) and Beyond: New Reactivity of Copper(I) Acetylides. *Chem. Soc. Rev.* **2010**, *39*, 1302−1315.
(12) Boren, B. C.; Narayan, S.; Rasmussen, L. K.; Zhang, L.; Zhao, H. T.; Lin, Z. Y.; Jia, G. C.; Fokin, V. V. Ruthenium-Catalyzed Azide-Alkyne Cycloaddition: Scope and Mechanism. *J. Am. Chem. Soc.* **2008**, *130*, 8923−8930.
(13) Montgomery, J. Organonickel Chemistry. In *Organometallics in Synthesis*; Lipshutz, B. H., Ed.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2013; p 319−428.
(14) Montgomery, J. Nickel-Catalyzed Reductive Cyclizations and Couplings. *Angew. Chem., Int. Ed.* **2004**, *43*, 3890−3908.
(15) Moslin, R. M.; Miller-Moslin, K.; Jamison, T. F. Regioselectivity and Enantioselectivity in Nickel-Catalysed Reductive Coupling Reactions of Alkynes. *Chem. Commun.* **2007**, 4441−4449.
(16) Oppolzer, W.; Radinov, R. N. Catalytic Asymmetric Synthesis of Secondary (E)-Allyl Alcohols from Acetylenes and Aldehydes via (1-Alkenylzinc) Intermediates. *Helv. Chim. Acta* **1992**, *75*, 170−173.
(17) Wipf, P.; Xu, W. J. Preparation of Allylic Alcohols by Alkene Transfer from Zirconium to Zinc. *Tetrahedron Lett.* **1994**, *35*, 5197−5200.
(18) Miller, K. M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T. F. Alkene-Directed, Nickel-Catalyzed Alkyne Coupling Reactions. *J. Am. Chem. Soc.* **2004**, *126*, 4130−4131.
(19) Miller, K. M.; Jamison, T. F. Ligand-Switchable Directing Effects of Tethered Alkenes in Nickel-Catalyzed Additions to Alkynes. *J. Am. Chem. Soc.* **2004**, *126*, 15342−15343.
(20) Moslin, R. A.; Miller, K. M.; Jamison, T. F. Directing Effects of Tethered Alkenes in Nickel-Catalyzed Coupling Reactions of 1,6-Enynes and Aldehydes. *Tetrahedron* **2006**, *62*, 7598−7610.

DOI: 10.1021/acs.accounts.5b00096
Acc. Chem. Res. 2015, 48, 1736−1745

(21) Jang, H. Y.; Krische, M. J. Catalytic C−C Bond Formation via Capture of Hydrogenation Intermediates. *Acc. Chem. Res.* **2004**, *37*, 653−661.
(22) Ngai, M. Y.; Kong, J. R.; Krische, M. J. Hydrogen-Mediated C−C Bond Formation: A Broad New Concept in Catalytic C−C Coupling. *J. Org. Chem.* **2007**, *72*, 1063−1072.
(23) Reichard, H. A.; McLaughlin, M.; Chen, M. Z.; Micalizio, G. C. Regioselective Reductive Cross-Coupling Reactions of Unsymmetrical Alkynes. *Eur. J. Org. Chem.* **2010**, 391−409.
(24) Bahadoor, A. B.; Flyer, A.; Micalizio, G. C. A Pentenyl Dianion-Based Strategy for Convergent Synthesis of Ene-1,5-diols. *J. Am. Chem. Soc.* **2005**, *127*, 3694−3695.
(25) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. Catalytic Carbonyl Addition through Transfer Hydrogenation: A Departure from Preformed Organometallic Reagents. *Angew. Chem., Int. Ed.* **2009**, *48*, 34−46.
(26) Tang, X. Q.; Montgomery, J. Nickel-Catalyzed Preparation of Bicyclic Heterocycles: Total Synthesis of (+)-Allopumiliotoxin 267A, (+)-Allopumiliotoxin 339A, and (+)-Allopumiliotoxin 339B. *J. Am. Chem. Soc.* **2000**, *122*, 6950−6954.
(27) Mahandru, G. M.; Liu, G.; Montgomery, J. Ligand-Dependent Scope and Divergent Mechanistic Behavior in Nickel-Catalyzed Reductive Couplings of Aldehydes and Alkynes. *J. Am. Chem. Soc.* **2004**, *126*, 3698−3699.
(28) Malik, H. A.; Sormunen, G. J.; Montgomery, J. A General Strategy for Regiocontrol in Nickel-Catalyzed Reductive Couplings of Aldehydes and Alkynes. *J. Am. Chem. Soc.* **2010**, *132*, 6304−6305.
(29) Oblinger, E.; Montgomery, J. A New Stereoselective Method for the Preparation of Allylic Alcohols. *J. Am. Chem. Soc.* **1997**, *119*, 9065−9066.
(30) Ogoshi, S.; Arai, T.; Ohashi, M.; Kurosawa, H. Nickel-adihydrofuran. Key Intermediate for Nickel-Catalyzed Reaction of Alkyne and Aldehyde. *Chem. Commun.* **2008**, 1347−1349.
(31) McCarren, P. R.; Liu, P.; Cheong, P. H. Y.; Jamison, T. F.; Houk, K. N. Mechanism and Transition-State Structures for Nickel-Catalyzed Reductive Alkyne-Aldehyde Coupling Reactions. *J. Am. Chem. Soc.* **2009**, *131*, 6654−6655.
(32) Liu, P.; McCarren, P.; Cheong, P. H. Y.; Jamison, T. F.; Houk, K. N. Origins of Regioselectivity and Alkene-Directing Effects in Nickel-Catalyzed Reductive Couplings of Alkynes and Aldehydes. *J. Am. Chem. Soc.* **2010**, *132*, 2050−2057.
(33) Liu, P.; Montgomery, J.; Houk, K. N. Ligand Steric Contours To Understand the Effects of N-Heterocyclic Carbene Ligands on the Reversal of Regioselectivity in Ni-Catalyzed Reductive Couplings of Alkynes and Aldehydes. *J. Am. Chem. Soc.* **2011**, *133*, 6956−6959.
(34) Liu, P.; Krische, M. J.; Houk, K. N. Mechanism and Origins of Regio- and Enantioselectivities in Rh-I-Catalyzed Hydrogenative Couplings of 1,3-Diynes and Activated Carbonyl Partners: Intervention of a Cumulene Intermediate. *Chem.—Eur. J.* **2011**, *17*, 4021−4029.
(35) Haynes, M. T., II; Liu, P.; Baxter, R. D.; Nett, A. J.; Houk, K. N.; Montgomery, J. Dimer Involvement and Origin of Crossover in Nickel-Catalyzed Aldehyde-Alkyne Reductive Couplings. *J. Am. Chem. Soc.* **2014**, *136*, 17495−17504.
(36) Baxter, R. D.; Montgomery, J. Mechanistic Study of Nickel-Catalyzed Ynal Reductive Cyclizations through Kinetic Analysis. *J. Am. Chem. Soc.* **2011**, *133*, 5728−5731.
(37) Jackson, E. P.; Montgomery, J. Regiocontrol in Catalytic Reductive Couplings through Alterations of Silane Rate Dependence. *J. Am. Chem. Soc.* **2015**, *137*, 958−963.
(38) Arduengo, A. J.; Gamper, S. F.; Calabrese, J. C.; Davidson, F. Low-Valent Coordinate Carbene Complexes of Nickel(0) and Platinum(0). *J. Am. Chem. Soc.* **1994**, *116*, 4391−4394.
(39) Herrmann, W. A. N-Heterocyclic Carbenes: A New Concept in Organometallic Catalysis. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290−1309.
(40) Haynes, M. T.; Jackson, E. P.; Montgomery, J. Nickel Complexes of *N*-Heterocyclic Carbenes. In *N-Heterocyclic Carbenes: Effective Tools for Organometallic Synthesis*; Nolan, S. P., Ed.; Wiley-VCH: Weinheim, Germany, 2014, 371−396.
(41) Lavallo, V.; Canac, Y.; Donnadieu, B.; Schoeller, W. W.; Bertrand, G. Cyclopropenylidenes: From Interstellar Space to an Isolated Derivative in the Laboratory. *Science* **2006**, *312*, 722−724.
(42) Shareef, A. R.; Sherman, D. H.; Montgomery, J. Nickel-Catalyzed Regiodivergent Approach to Macrolide Motifs. *Chem. Sci.* **2012**, *3*, 892−895.
(43) Wang, H.; Negretti, S.; Knauff, A. R.; Montgomery, J. Exo-Selective Reductive Macrocyclization of Ynals. *Org. Lett.* **2015**, *17*, 1493−1496.

DOI: 10.1021/acs.accounts.5b00096
Acc. Chem. Res. 2015, 48, 1736−1745