Regioselectivity and enantioselectivity in nickel-catalysed reductive coupling reactions of alkynes

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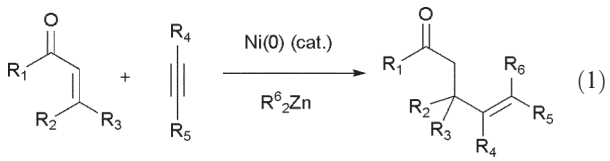
Nickel-catalysed reductive coupling reactions of alkynes have emerged as powerful synthetic tools for the selective preparation of functionalized alkenes. One of the greatest challenges associated with these transformations is control of regioselectivity. Recent work from our laboratory has provided an improved understanding of several of the factors governing regioselectivity in these reactions, and related studies have revealed that the reaction mechanism can differ substantially depending on the ligand employed. A discussion of stereoselective transformations and novel applications of nickel catalysis in coupling reactions of alkynes is also included.

1 Introduction

1.1 Addition reactions of alkynes

Alkynes are very useful functional groups in synthetic chemistry. They are stable to many common nucleophiles and electrophiles and generally resistant to mild acids, bases, and oxidants. Thus, the selective functionalization of alkynes *via* hydrometallation has proven to be a versatile tool in organic synthesis.[1] However, many of the common hydrometallations of alkynes require stoichiometric use of the metal reagent, and there has been growing interest in reactions of alkynes that are catalytic in transition metal.[2] Nickel has been associated with the catalytic reaction of alkynes since the seminal work of Wilke,[3] and has been shown to catalyse many of the transformations associated with alkyne functionalization[4,5] including the addition of alkynes to enones (eqn (1)).[6,7] The appearance in recent years of several excellent reviews on nickel-catalysed transformations is reflective of a growing interest in nickel catalysis.[8] This account will focus on advances in nickel-catalysed coupling reactions of alkynes made since 2004, with an emphasis on improvements made to control selectivity, increase reactivity, and expand the substrate scope of nickel-catalysed addition reactions of alkynes.



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1.2 Nickel-catalysed reductive and alkylative coupling reactions of alkynes to form allylic alcohols

Allylic alcohols are a found in a variety of natural products (Fig. 1).[9] While numerous methods for the synthesis of allylic alcohols have been reported,[10] routes that offer improved convergence and functional group compatibility continue to attract significant interest. For example, coupling reactions of alkynes and aldehydes that employ a stoichiometric reducing agent and a catalytic nickel source allow for single-step generation of this versatile functional group array.

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Ryan M. Moslin

Ryan Moslin was born in Grand Forks, Canada, and obtained his Bachelors degree from the University of British Columbia in 2001. He then moved to the Massachusetts Institute of Technology (MIT) where he completed his PhD under the tutelage of Professor Timothy F. Jamison in 2006. He currently is pursuing post-doctoral studies with Professor Timothy Swager, also at MIT.

Karen Miller-Moslin

Karen Miller-Moslin completed her undergraduate education at Dartmouth College in 2000. She then pursued graduate studies at the Massachusetts Institute of Technology under the supervision of Professor Timothy F. Jamison, with a focus on the development of nickel-catalysed, carbon–carbon bond-forming reactions of alkynes. She completed her PhD in 2005, and accepted a position as a Research Investigator in the Global Discovery Chemistry/Oncology division of the Novartis Institutes for Biomedical Research in Cambridge, MA, where she is currently employed.

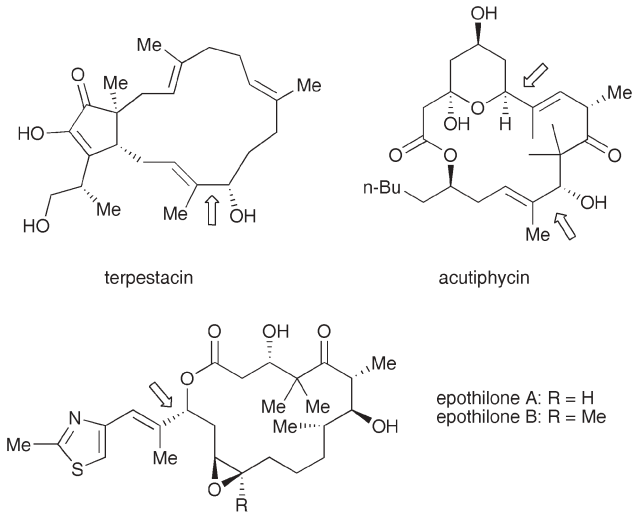
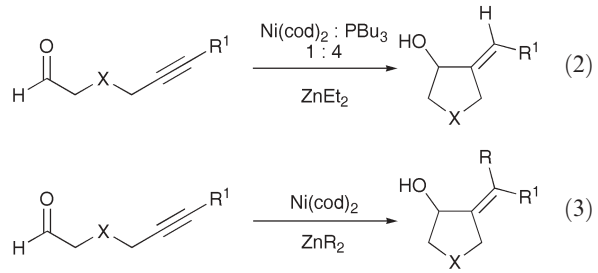


Fig. 1

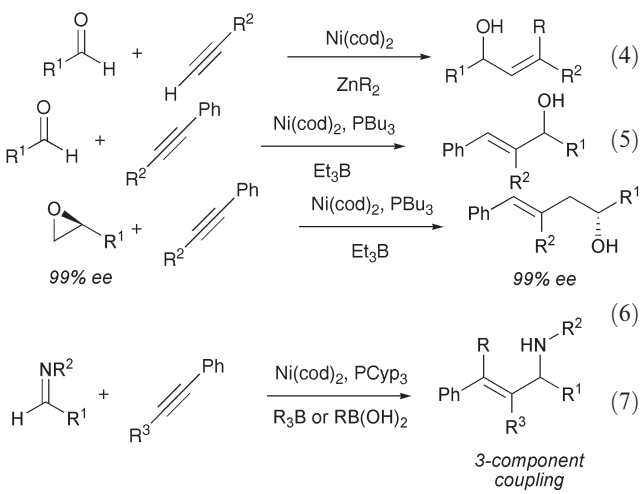
1.2.1 Intramolecular nickel-catalysed reductive and alkylative cyclization of α,ω-alkynals. In 1997, Montgomery and co-workers reported the first example of a nickel-catalysed reductive cyclization of an alkynal. In this transformation, diethylzinc served as the stoichiometric reducing agent, while the catalyst was composed of bis(1,5-cyclooctadiene)nickel(0) ($Ni(cod)_2$) and tributylphosphine (eqn (2)).[11] The authors observed that, in the absence of a catalytic phosphine additive, the alkylative cyclization product (*i.e.*, transfer of Et instead of H from diethylzinc) is observed (eqn (3)).[11] These cyclization strategies have been further developed and found several applications in total synthesis.[12]

Timothy F. Jamison

Tim Jamison was born in San Jose, CA and grew up in neighboring Los Gatos, CA. He received his undergraduate education at the University of California, Berkeley. A six-month research assistantship at ICI Americas in Richmond, CA under the mentorship of Dr William G. Haag was his first experience in chemistry research. Upon returning to Berkeley, he joined the laboratory of Prof. Henry Rapoport and conducted undergraduate research in his group for nearly three years, the majority of which was under the tutelage of William D. Lubell (now at the University of Montreal). A Fulbright Scholarship supported ten months of research in Prof. Steven A. Benner's laboratories at the ETH in Zürich, Switzerland, and thereafter he undertook his PhD studies at Harvard University with Prof. Stuart L. Schreiber. He then moved to the laboratory of Prof. Eric N. Jacobsen at Harvard University, where he was a Damon Runyon-Walter Winchell postdoctoral fellow. In July 1999, he began his independent career at MIT, where his research program focuses on the development of new methods of organic synthesis and their implementation in the total synthesis of natural products.



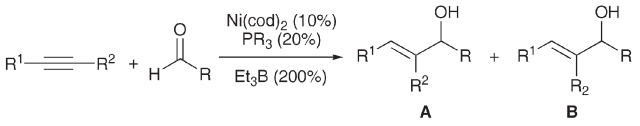
1.2.2 Intermolecular nickel-catalysed reductive and alkylative coupling of alkynes. The first report of an intermolecular nickel-catalysed coupling reaction of alkynes and aldehydes also employed diethylzinc as the stoichiometric reducing agent, and afforded the alkylative coupling product (*i.e.*, transfer of Et from diethylzinc) (eqn (4)).[11] To achieve intermolecular reductive coupling, our group examined a variety of reducing agents and catalytic ligand additives, eventually determining that use of triethylborane in the presence of catalytic $Ni(cod)_2$ and tributylphosphine provided the *E*-trisubstituted allylic alcohol with excellent yield and selectivity (eqn (5)).[13,14] We later found that a similar transformation was also possible using epoxides as coupling partners, which afforded homoallylic alcohol products (eqn (6)).[15,16] An intermolecular, nickel-catalysed three-component coupling of alkynes, imines, and organoborane reagents (either boronic acids or trialkylboranes) was also developed (eqn (7)).[17] These reactions all proceed with exclusive syn-addition across the alkyne, and often in excellent regioselectivity, making them attractive candidates for use in total synthesis. As such, nickel-catalysed coupling reactions of alkynes have been used in both fragment coupling reactions and macrocyclizations by ourselves[18] and others.[12]



2 Regioselectivity in nickel-catalysed reductive coupling reactions

Several classes of alkynes have previously been shown to afford excellent regioselectivity in nickel-catalyzed coupling reactions, including aryl-substituted alkynes (Ar–C≡C–alkyl), alkynyl silanes ($R–C≡C–SiR_3$), and terminal alkynes (R–C≡C–H) (Table 1).[14,18,29] However, alkynes substituted with two

Table 1 Nickel-catalysed reductive coupling of alkynes and aldehydes



Entry	R^1	R^2	**A** : **B**[a]
1	Ph	Me	92 : 8
2	*n*-Hexyl	H	96 : 4
3	*n*-Bu	$SiMe_3$	>98 : 2
4	*n*-Hexyl	Et	50 : 50

[a] Determined by ^{1}H NMR.

sterically and electronically similar groups, such as dialkyl alkynes (*i.e.*, alkyl–C≡C–alkyl′) typically afford poor regioselectivity (Table 1, entry 4).

2.1 1,3-Enynes

To address this deficiency and based on a hypothesis that the high regioselectivity observed with aryl-substituted alkynes is likely due to an electronic differentiation between the alkyl- and the aryl- substituents, we considered the possibility that another conjugating group would provide similar regiocontrol (Fig. 2). Of possible choices for such groups, a simple olefin seemed most intriguing as it might then be possible to convert this directing group into the corresponding saturated alkyl chain after the nickel-catalysed reductive coupling *via* site-selective hydrogenation.

We found that coupling reactions of 1,3-enynes are highly regioselective when trialkylphosphines are used as ligands (Scheme 1).[20] A variety of substitution patterns on the enyne are tolerated and both aldehydes and terminal epoxides can be employed as coupling partners. As terminal epoxides are readily available in highly enantiomerically-enriched form,[21] this method represents a convenient synthesis of enantiomerically-enriched homoallylic dienes.

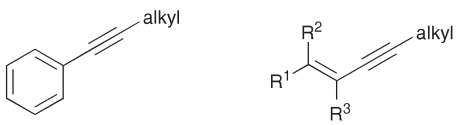
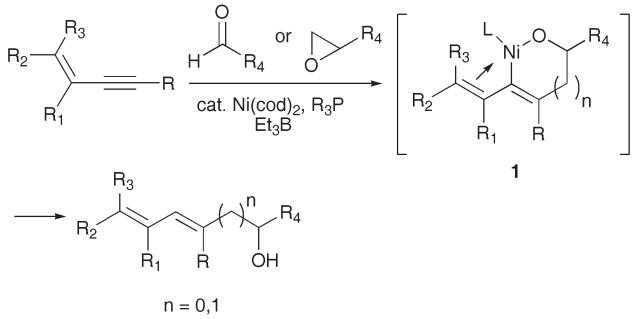
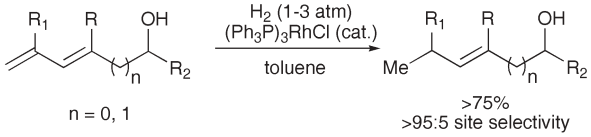


Fig. 2 1,3-Enynes as equivalents of aryl alkynes.



Scheme 1 1,3-Enynes as highly regioselective substrates in nickel-catalysed reductive coupling reactions.

We initially hypothesized that the high regioselectivity observed with 1,3-enynes was simply due to an electronic distinction between the two alkyne substituents; however, several results dispute this assertion. First, complete regioselectivity was observed in a reaction of 1-phenyl-3-butenyne, suggesting that a vinyl group is a significantly more potent directing group than a phenyl ring (Scheme 2). Second, coupling reactions of 5,5-dimethylhexenyne not only proceed efficiently, but in excellent regioselectivity to favour C–C bond formation at the more hindered alkyne carbon. The latter result is in stark contrast to other *tert*-alkyl-substituted alkynes, which either do not react at all under these conditions, or favour exclusive formation of the opposite, less-hindered regioisomer. Thus, the alkene substituent appears to strongly direct regioselectivity and also significantly increase reactivity. We believe that this unique effect is a result of the ability of the olefin to form a favourable bonding interaction with the nickel in a high-energy intermediate such as **1**, which serves to lower the energy of the transition state and thus influence regioselectivity.[22] A site-selective, rhodium-catalysed reduction of the less substituted olefin in the dienyl alcohols products obtained provides access to alkyl-substituted allylic and homoallylic alcohols not otherwise accessible in a regioselective fashion using nickel-catalysed reductive coupling chemistry (eqn (8)).



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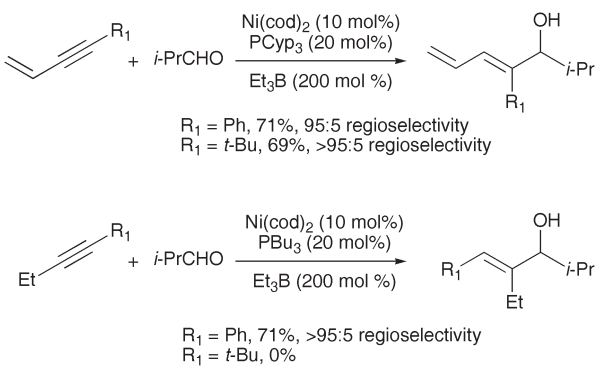
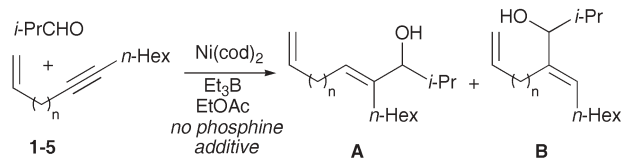
2.2 1,6-Enynes

In order to determine whether the directing effect of the olefin observed with 1,3-enynes could be extended to non-conjugated systems, a series of enynes was synthesized and evaluated in nickel-catalysed reductive couplings with isobutyraldehyde (Table 2).[23] Remarkably, in the absence of a phosphine additive, a marked difference in reactivity and selectivity was observed when the alkyne and alkene were separated by three methylene units (entry 4, Table 2). As it is very unlikely that enyne **4** is significantly different in a steric or electronic sense to alkynes **2**, **3** or **5**, it seems that direct involvement of the



Scheme 2 Highly regioselective Ni-catalysed reductive coupling reactions of 1,3-enynes and aldehydes.

Table 2 Directing effects of tethered alkenes[a]



Entry	Alkyne	*n*	Yield (%)	Regioselectivity[b] (**A** : **B**)
1	**1**	0	<5	n.d.
2	**2**	1	<5	n.d.
3	**3**	2	<5	n.d.
4	**4**	3	**53**	>**95** : **5**
5	**5**	4	<5	n.d.
6	*n*-C_5H_{11}–C≡C–*n*-C_6H_{13}	n.a.	28	50 : 50

[a] $Ni(cod)_2$ (10 mol%), Et_3B (200 mol%) in EtOAc (0.5 mL), 15 h at room temperature. [b] Determined by ^1H NMR and/or GC.

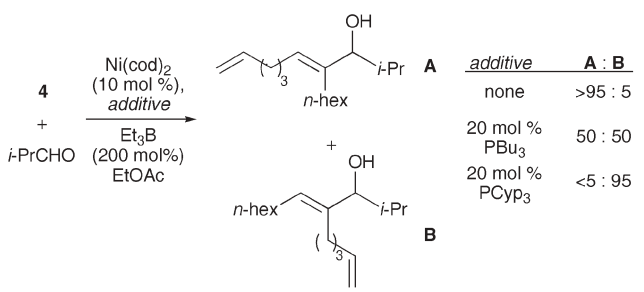
olefin in the reaction occurs uniquely in the case of the 1,6-enyne.

Considering that almost all other nickel-catalysed reductive coupling reactions previously reported required the addition of an external ligand,[24] the coupling reaction of 1,6-enynes and aldehydes proved remarkably general (Table 3). The presence of an olefin tether was sufficient to overcome an inherent steric preference for the **B** regioisomer (entry 4, Table 3).[25] Heteroatoms were also well tolerated and augment the versatility of this directed transformation (entries 6–8, Table 3).

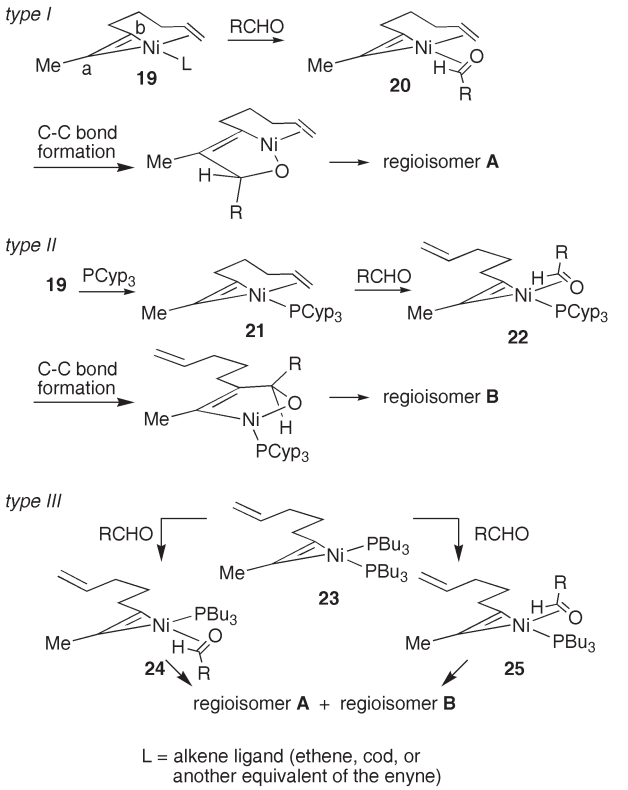
When conducted in the presence of an organophosphine additive ($PCyp_3$), the regioselectivity of the transformation showed a complete *reversal*, favouring regioisomer **B** (Scheme 3). The switch in regioselectivity upon the addition of a catalytic amount of an additive is highly unusual among tethered olefin-directed metal-mediated reactions.[26] The effect of the ligand additive seemed dependant upon the size of the phosphine, as smaller phosphines such as PBu_3 provided a mixture of regioisomers.[19]

We hypothesize that this pronounced ligand effect could be explained by considering a planar, three-coordinate nickel complex[27] that undergoes stereospecific ligand substitution with retention of stereochemistry (Scheme 4).[28,29] The olefin tether must bind 'cis' to carbon *b* to give **19**. A series of stereospecific ligand substitutions then conserve this initial bias, thus controlling regioselectivity even if the C–C bond is formed when the olefin is not coordinated to the nickel.[30]

In the absence of a phosphine, the olefin remains bound to the nickel and the aldehyde displaces a weakly bound ligand L



Scheme 3 Additive effects on regioselectivity.

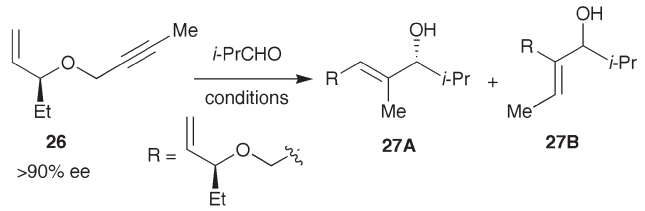


Scheme 4 Origin of regioselectivity in nickel-catalysed coupling reactions of 1,6-enynes and aldehydes. See eqn (6), Table 6.

to afford complex **20**. A phosphine ligand (*e.g.*, $PCyp_3$) binds strongly to the nickel center to give **21**. The olefin tether is displaced preferentially by the aldehyde to afford **22**, which undergoes C–C bond formation to give regioisomer **B**. Phosphines with smaller cone angles (*e.g.*, PBu_3) likely form 2 : 1 complexes with nickel, and thus will displace both L and the olefin. In this case, the aldehyde must displace either of two identical phosphine ligands, and a mixture of regioisomers results (**24** and **25**).

By incorporating a chiral stereocenter into the tether, we sought to probe the likelihood that the olefin remained bound, and hence imparted greater diastereoinduction, in the *type I* pathway, but not the *type II* and *type III* pathways (Table 4).[31] In the absence of a phosphine ligand, a single regioisomer was observed (as expected), and in excellent diastereoselectivity (95 : 5) (entry 1). This result is consistent with the olefin being bound to the nickel center during the C–C bond forming step. In the presence of $PCyp_3$, the opposite regioisomer is formed (>95 : 5) as approximately a 1 : 1 mixture of diastereomers (entry 2), suggesting that in this case the reaction proceeds through selective formation of complex **22**. With PBu_3, a mixture of regioisomers is observed, each of which is a mixture of diastereomers (entry 3), a result that is consistent with formation of a mixture of complexes **24** and **25**. The observation of stereochemical induction in the presence of a chiral phosphine ligand (entries 4 and 5) offers further support for the proposal that the phosphine is bound in the type III and, by extrapolation, the type II pathways.

Table 4 Coupling reactions of a chiral 1,6-enyne



Entry	Reaction conditions[a]	**A** : **B**[b]	dr **A** (*S* : *R*)[c]	dr **B**[c]
1	I	>95 : 5	95 : 5	—
2	II	<5 : 95	—	45 : 55
3	III	55 : 45	50 : 50	45 : 55
4	IV	48 : 52	30 : 70	28 : 72
5	V	55 : 45	66 : 34	68 : 32

[a] I: $Ni(cod)_2$ (10 mol%), Et_3B (200 mol%). II: Reaction conditions I + $PCyp_3$ (20 mol%). III: Reaction conditions I + PBu_3 (20 mol%). IV: Reaction conditions I + (*R*)-FcP(*o*-*i*-Pr)Ph (20 mol%). V: Reaction conditions I + (*S*)-FcP(*o*-*i*-Pr)Ph (20 mol%). [b] Based on isolated yields. [c] Determined by ^1H NMR.

All of these results are best explained *via* stereospecific ligand substitution on a trisubstituted planar nickel complex. Therefore, for nickel-catalysed reductive coupling reactions of alkynes and aldehydes using triethylborane as the reducing agent and organophosphine ligands we propose that the reaction proceeds through complex **22**. This potentially explains why bidentate phosphine ligands have not been successful,[19] since they would block or hinder the coordination of the aldehyde to the three-coordinate nickel center.

2.3 Effect of N-heterocyclic carbene ligands

N-Heterocyclic carbenes (NHC's) are sterically hindered, electron-rich ligands that have proven useful in a wide variety of metal-catalysed transformations (Fig. 3).[32] Recent applications in nickel-catalysed reductive coupling reactions have further illustrated the influence of the ligand on both reaction mechanism and regioselectivity.[33,34] Montgomery examined the macrocyclization of **28** and found that when R^1 is phenyl, both phosphine and NHC ligands afford product **30**; however, when R^1 is methyl, different regioselectivities were observed (Scheme 5).[32] Use of triethylborane as the reducing agent and PMe_3 as the ligand favoured formation of endocyclic product **29** (9 : 2 ratio), whereas a combination of IPr and triethylsilane led to predominant formation of the exocyclic double bond (5 : 1). The use of a larger phosphine (PBu_3) resulted in a reduced preference (3 : 1) for the endocyclic product and, similarly, a smaller NHC ligand (IMes) resulted in a 1 : 1 mixture of **29b** : **30b**. A study which compared the ratio of crossover products for the two sets of conditions revealed an inherent difference in their mechanisms (Table 5).[33] Very little crossover was

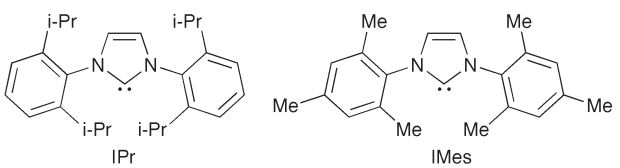
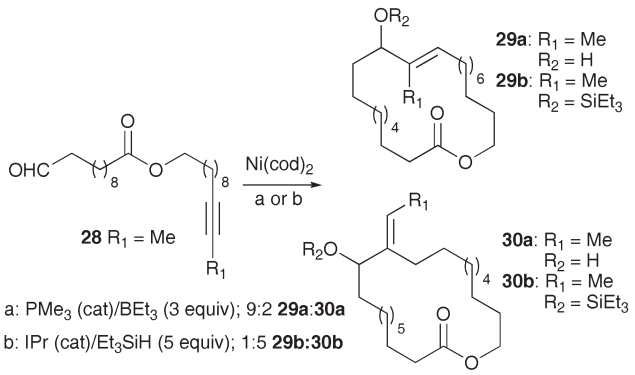


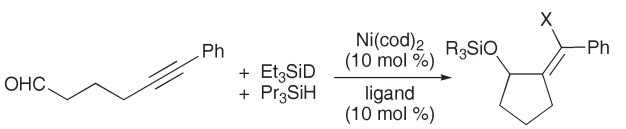
Fig. 3 Representative NHC ligands.



Scheme 5 Nickel-catalyzed reductive cyclizations.

observed when using the NHC ligand, as shown by the ratio (<4 : 96) of the crossover products (entries 1 and 4 combined) to the non-crossover products (entries 2 and 3 combined). The lack of crossover products suggests that the addition of the hydride and the silane occur simultaneously. However, in the presence of PBu_3 significant amounts of crossover products are formed, indicating that, in this case, the hydride and silane are added in separate steps (entries 2/3 : 1/4, 57 : 43). This same study revealed that, when NHC's are employed as ligands, it is possible to use trialkylsilanes as reducing agents in intermolecular, nickel-catalysed reductive coupling of alkynes and aldehydes (Table 6).[14b,35] This method generates silyl-protected allylic alcohols in excellent yield and regioselectivity when aryl-substituted alkynes (Ar–C≡C–R), terminal alkynes (R–C≡C–H), and 1,3-enynes are used (Table 6, entries 1–4).

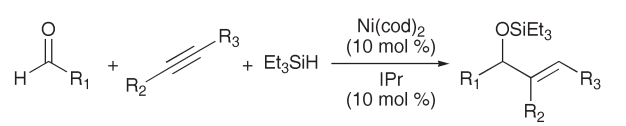
Table 5 Ligand dependence in the observation of crossover products



Entry	R	X	Relative (%) From IPr	Relative (%) From PBu_3
1[a]	Et	H	<2	25
2	Et	D	55	34
3	Pr	H	41	23
4[a]	Pr	D	<2	18

[a] Crossover product.

Table 6 Nickel-catalysed intermolecular reductive coupling reactions



Entry	R^1	R^2	R^3	Yield (%) (regioselectivity)
1	Ph	CH_3	Ph	84 (>98 : 2)
2	C_6H_{13}	CH_3	Ph	82 (>98 : 2)
3	Ph	H	C_6H_{13}	71 (>98 : 2)
4	Ph	Ph	$C(CH_3)=CH_2$	84 (>98 : 2)

3 Stereoselective nickel-catalysed reductive coupling reactions

Despite the success of nickel-catalysed coupling reactions of alkynes and aldehydes, until recently very few techniques existed for controlling the configuration of the allylic alcohol stereocenter generated during the reaction. There were only two, excluding our own work, examples of stereoselective intermolecular reductive coupling reactions of alkynes with carbonyls in the 2004 review on nickel-catalysed reductive coupling reactions by Montgomery.[12b] In the past few years, many methods for the control of stereochemistry in intermolecular nickel-catalysed coupling reactions have been developed.

3.1 Enantioselective reactions

In 2003, we reported the first examples of catalytic, enantioselective reductive couplings of alkynes and aldehydes, using two distinct classes of chiral organophosphines as ligands (Fig. 4). Superior results for alkynes containing one aromatic substituent (aryl–C≡C–alkyl) were achieved using neomenthyldiphenylphosphine ((+)-NMDPP) as a chiral ligand (Scheme 6).[14b] Alkynes substituted with two distinct alkyl groups (alkyl–C≡C–alkyl′) afforded reductive coupling products with modest enantioselectivities when *P*-chiral ferrocenyl phosphines **31/32** were employed.[26]

A ligand-controlled, stereoselective nickel-catalysed reductive coupling was used in the synthesis of terpestacin Scheme 7).[36] Fragments **33** and **34** were coupled to give the *E*-trisubstituted allylic alcohols **36** and **37** with good regioselectivity. The configuration of the allylic alcohol stereocenter was controlled by the configuration of the chiral phosphine. In

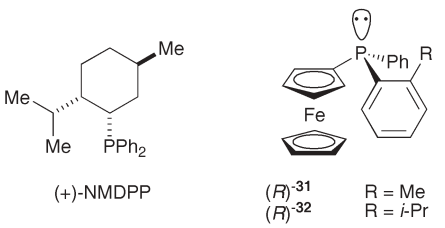
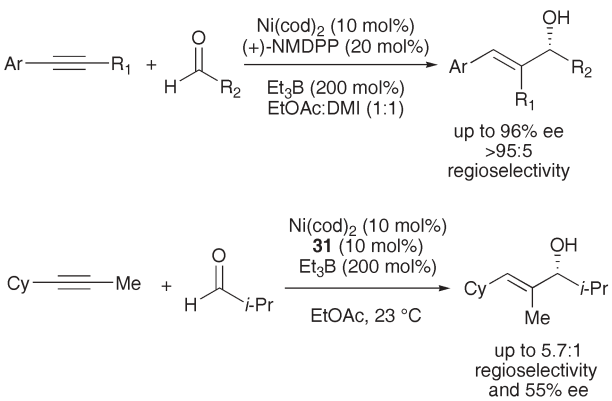
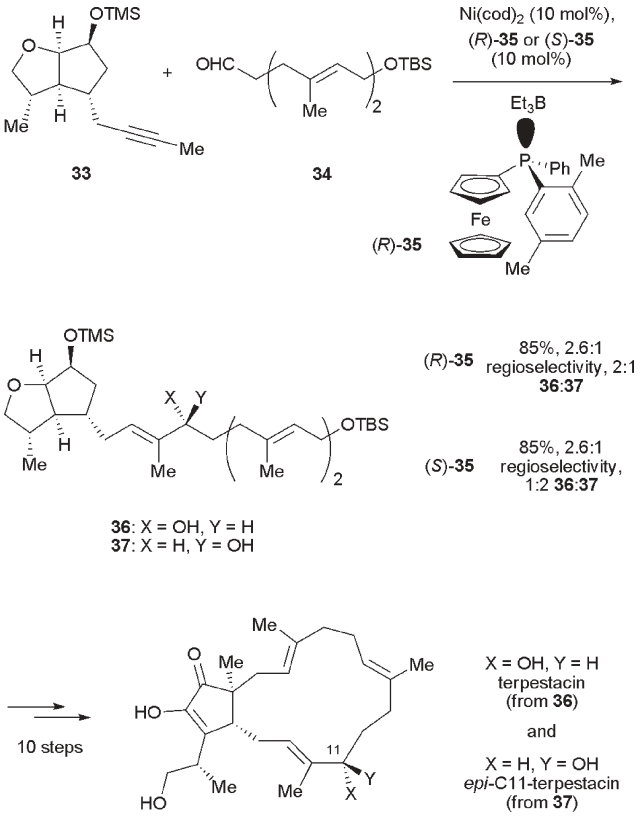


Fig. 4



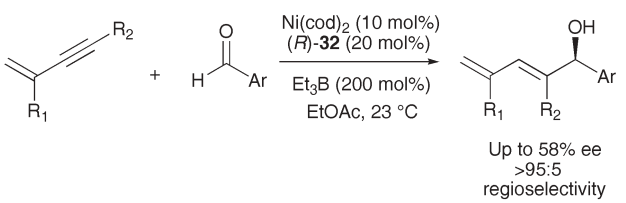
Scheme 6 Asymmetric induction.



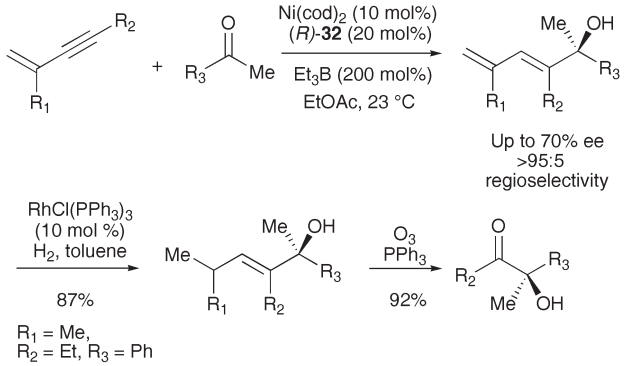
Scheme 7 Ligand control in the total synthesis of terpestacin.

comparison, the use of tributylphosphine gave a 1 : 1 mixture of **36** : **37** allowing for the synthesis of both terpestacin and *epi*-C11-terpestacin. It was originally believed that *epi*-C11-terpestacin was its own natural product, siccanol. However, when we obtained a sample of synthetic *epi*-C11-terpestacin it was determined that its spectra did not match that of isolated siccanol but rather that of terpestacin itself.[37] Macrocyclization *via* an intramolecular allylation, followed by methylation and α-oxidation led to the completed synthesis of terpestacin and *epi*-C11-terpestacin.

The *P*-chiral ferrocenyl phosphines developed in our laboratory have found use as ligands in several other asymmetric nickel-catalysed coupling reactions of alkynes. 1,3-Enynes underwent reductive coupling with a series of aromatic aldehydes in modest enantioselectivities in the presence of a ferrocenyl phosphine **32** (Scheme 8).[38] Although higher enantiomeric excesses are available in the coupling of aryl-alkynes and aliphatic aldehydes (Scheme 9), the enantiomerically enriched dienols afforded *via* 1,3-enyne couplings offer significant flexibility for further modification.



Scheme 8 Asymmetric induction with Ni-catalysed reductive coupling reactions of 1,3-enynes and aldehydes.



Scheme 9 Asymmetric induction with Ni-catalysed reductive coupling reactions of 1,3-enynes with ketones.

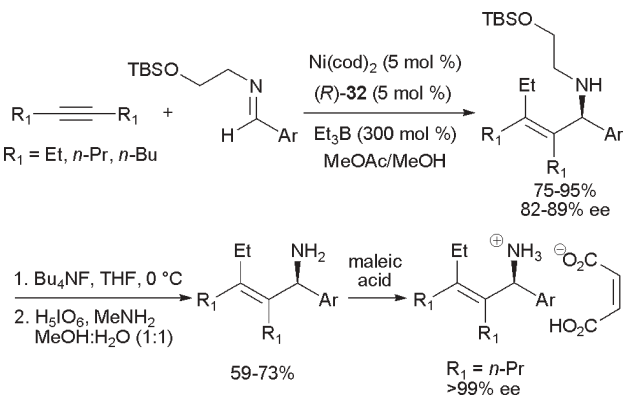
The enhanced reactivity of 1,3-enynes observed in nickel-catalyzed reductive coupling reactions also allowed for the use of ketones as electrophiles. Such couplings promoted by **32** afforded 1,3-dienes with an adjacent quaternary carbinol stereocenter in excellent regioselectivity and up to 70% ee (Scheme 9).[39] Site-selective reduction of the less-hindered olefin provides access to enantiomerically enriched tertiary allylic alcohols, and ozonolysis affords α-hydroxy ketones.

Enantioselective alkylative coupling reactions of alkynes and imines have been achieved using **32** to afford allylic amines in up to 89% ee (Scheme 10).[40] The use of a removable (trialkylsilyloxy)ethyl protecting group allows for facile generation of primary allylic amines, which can then be recrystallized to optical purity as their maleic acid salts.

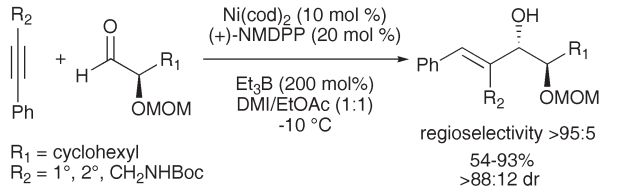
3.2 Diastereoselective reactions

We recently reported the diastereoselective addition of aryl-alkynes (Ar–C≡C–alkyl) to α-hydroxy aldehydes (Scheme 11).[41,42] High anti-selectivity is obtained regardless of protecting group on the α-hydroxy substituent. This is in sharp contrast to the syn-product typically observed when nucleophiles are added to aldehydes that possess an α-hydroxy group capable of coordination.[43]

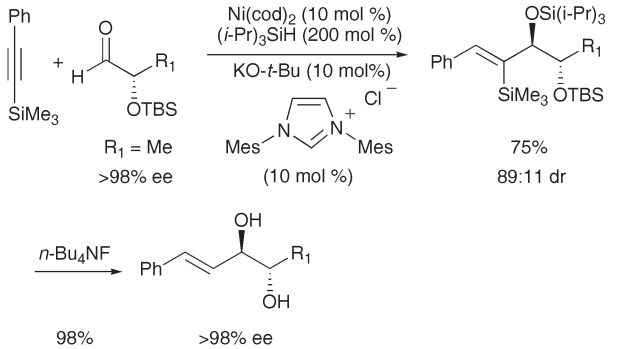
In a related report by Montgomery, high anti-selectivity (>98 : 2 for R^1 = *n*-pentyl or CH_2Bn) was again observed (Scheme 12).[44] In this case, a variety of silyl-substituted alkynes were employed (R_3Si–C≡C–R), including terminal and



Scheme 10 Asymmetric induction in the Ni-catalysed alkylative coupling of alkynes and imines.



Scheme 11 Diastereoselective reductive coupling reactions of aryl-alkynes.

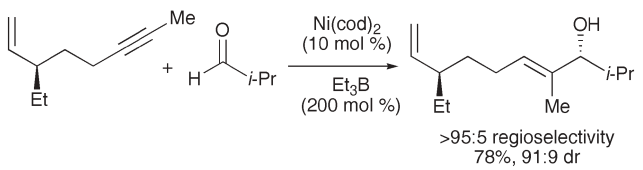


Scheme 12 Diastereoselective reductive coupling reactions of silyl-alkynes.

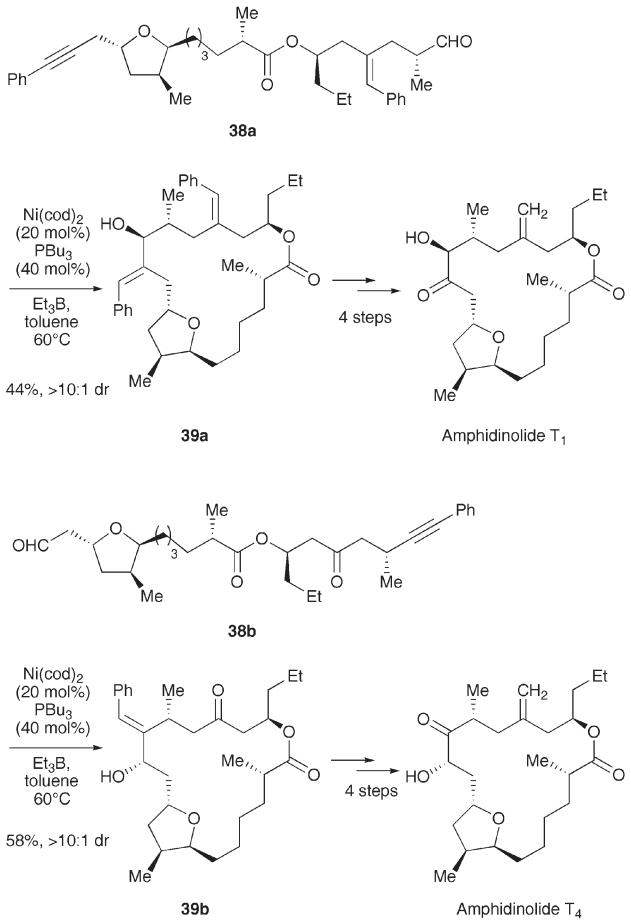
non-aromatic variants, and it was demonstrated that global deprotection of all three silyl groups was possible using TBAF. With respect to the aldehyde, the reaction was most effective when the R^1 substituent was unbranched; this was complimentary to our own work in which improved diastereoselectivities were obtained when R^1 was 3°.

The modes of diastereoinduction in these systems are unknown. Although the results are consistent with a Felkin model in the absence of chelation, the mechanistic considerations involved in this system are significantly more complex than a classical metalated nucleophile. That being said, the observation that identical senses of induction are obtained both in the absence and presence of a possible chelating group suggests that the α-alkoxy group does not interact with nickel during the C–C bond-forming step.

Diastereoselectivity can also be influenced by substitution on the alkyne, as was observed in our work on the reductive coupling of 1,6-enynes and aldehydes. Very high levels of diastereomeric induction could be obtained by placing a chiral centre within the enyne tether, even when the substituent was quite small (Scheme 13). Although the scope of the diastereoselective nickel-catalysed reductive coupling reactions of 1,6-enynes and aldehydes have not been fully explored, the high selectivities observed would suggest it as a viable strategy for the stereoselective formation of allylic alcohols.



Scheme 13 Diastereoselective phosphine-free nickel-catalysed coupling reaction.



Scheme 14 Diastereoselective nickel-catalysed reductive cyclization.

By using the allylic alcohols formed in stereoselective nickel-catalysed reductive macrocyclizations as masked α-hydroxy ketones, we have completed the total syntheses of amphidinolides T1 and T4 (Scheme 14).[45] In both natural products, the macrocyclization proceeds with excellent regioselectivity and diastereoselectivity. The regioselectivity is likely controlled by the phenyl substituent, while the diastereoselectivity may be a function of the cyclization since intermolecular variants were not as highly diastereoselective. Protection of the allylic alcohol followed by ozonolysis, selective methylenation and HF deprotection afforded the respective amphidinolides.

Conclusions

This review discusses recent developments in the area of nickel-catalysed coupling reactions of alkynes.[46,47] In the nickel-catalysed reductive coupling of alkynes and aldehydes, significant advances have been made in improving substrate scope, controlling regioselectivity, and understanding operative reaction mechanisms. Development of novel ligand systems has allowed for additional control of regio-, diastereo- and enantioselectivities. The use of both imines and weakly electrophilic ketones as coupling partners has been realized, and good to excellent enantioselectivities can be achieved in many cases.

It is clear that numerous challenges in the field remain, including, for example, better control of regioselectivity in couplings involving alkynes containing two distinct alkyl substituents (alkyl–C≡C–alkyl′). However, as understanding of these catalytic systems increases, enhancements in selectivity and generality may be obtained, thus supplementing the versatility of these selective transformations.

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