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Ni(I) Catalyzes the Regioselective Cross-Coupling of Alkylzinc Halides and Propargyl Bromides to Allenes

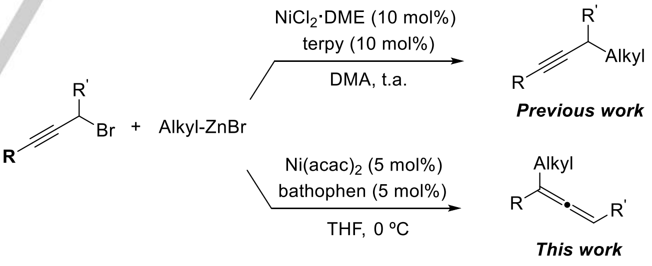
Rita Soler-Yanes, Iván Arribas-Álvarez, Manuel Guisán-Ceinos, Elena Buñuel, and Diego J. Cárdenas*[a]

Abstract: We describe the unprecedented formation of allenes by Ni-catalyzed cross-coupling of propargyl bromides with alkylzinc halides. The reaction regioselectivity is complementary with the previously reported formation of propargyl coupled compounds. Experiments support the formation of Ni(I) complexes as the active species, as well as the participation of radical intermediates. Kinetic studies provided the following information: the reaction is first order in the electrophile, zero-order in the nucleophile (fast transmetalation), and one-half order relative to the metal catalyst. Mechanistic studies support a bimetallic Ni(I)-based pathway involving fast homolytic cleavage of the C-Br bond by an alkyl-Ni(I) complex followed by radical coordination to Ni(I) which determines the observed regioselectivity.

Introduction

Preparation of allenes by metal-catalyzed reactions involving propargyl derivatives containing a good leaving-group constitutes one of the most convenient methods, since it involves the concomitant formation of the allene and a new carbon-carbon bond.[1] Pd,[2] Cu,[3] Rh,[4] Fe,[5] and Ni[6] derivatives have been used as catalysts in these reactions for the activation of propargyl halides, esters, carbonates and phosphonates. For cross-coupling reactions, nucleophiles can be derived from a wide variety of main group elements (Mg, Zn, In, B, Ti, Cu), and allow to install different kinds of fragments (alkyl, aryl, alkenyl, etc). Preparation of chiral allenes has been achieved by both transfer of stereochemical information from optically pure propargyl derivatives, or by using chiral ligands.[7] We are especially interested in the development of novel cross-coupling reactions involving first-row transition metals for economic and environmental reasons, and especially for the different activation mechanisms that are being discovered during the last years, involving radical intermediates and different oxidation states. In this respect, we have recently reported alkyl-alkyl,[8] and alkyl-aryl[9] Ni-catalyzed cross-coupling reactions using alkylmagnesium reagents and highly compatible alkylzinc halides. Intermediacy of radicals has made possible to develop cascade reactions involving the formation of two C-C bonds within the same synthetic operation. Interestingly, in some cases the use of first row transition metal catalysts allow the use of Grignard reagents as nucleophiles even in the presence of formerly incompatible functional groups, due to the high reactivity of certain catalytic systems.[10] Nevertheless, the use of organozinc compounds is more convenient due to the lower reactivity and higher compatibility of these nucleophiles with a wide variety of functionalities. Fu has developed the Ni-catalyzed cross coupling of propargyl halides with R_2Zn or RZnX reagents which afford the corresponding propargyl coupled compounds.[11]

In this work, we report a detailed study on the Ni-catalyzed cross-coupling reaction of propargyl halides with alkylzinc reagents for the formation of allenes. This constitutes the first Ni-catalyzed reaction for the formation of cumulenes from propargyl electrophiles involving this metal. In addition to the study of the reaction scope, which has resulted to be very broad, mechanistic studies both experimental and computational, have been performed in order to get insight into the mechanism of this reaction. This process is complementary of the above mentioned Fu's reaction for the alkyl-propargyl cross-coupling, that affords alkynes instead.[11,12]



Scheme 1. Ni-catalyzed coupling reactions from propargyl bromides and alkylzinc halides.

Results and Discussion

We initially explored the reaction between propargyl substrate **1a** and (1,3-dioxolan-2-yl)ethylzinc bromide (**2**) in the presence of $Ni(Py)_4Cl_2$ as precatalyst.[9b] Two possible cross-coupling products can be obtained: allene **3a** and the product exerting from the alkylation of the carbon containing the bromide (**4a**). The model reaction was performed using 3 equiv of nucleophile, 10 mol% of precatalyst, and 10 mol% of a variety of NHC, phosphine and nitrogen-based ligands, which afforded different yields and regioselectivities (see Supporting Information). The best results were obtained with bipyridine and phenanthroline derivatives. Thus, bipyridine (**L1**) and phenanthroline (**L2**)

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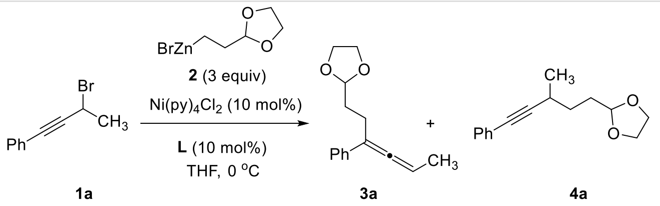
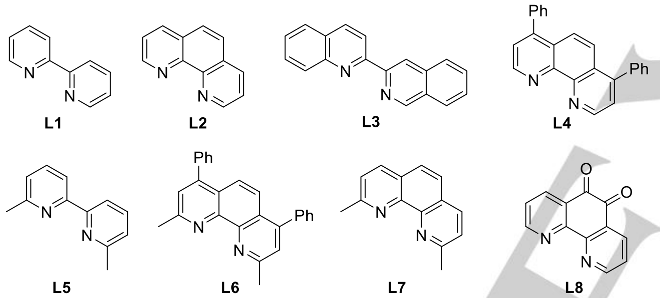
provided exclusively the allene (Table 1, entries 1-2) while the reaction was not fully regioselective for 2,2'-biquinoline (**L3**, entry 3). The best result in terms of both yield and regioselectivity was observed for bathophenanthroline (**L4**). Substitution next to the N atoms gave reasonable yields, lower regioselectivity, and even favored the formation of the propargyl coupling product as the major isomer. This is the case for 6,6'-dimethylbipyridine (**L5**), bathocuproine (**L6**), and neocuproine (**L7**). Diketone **L8** was totally ineffective. The use of just 5 mol% of Ni(acac)$_2$ provided similar yields, cleaner reactions and more reproducible results. On the other hand, the use of 2:1 ligand to metal ratio did not improve the results, and was also the case when increasing the reaction temperature to 23 °C.

Table 1. Reaction outcome for bipy- and phen-type ligands.

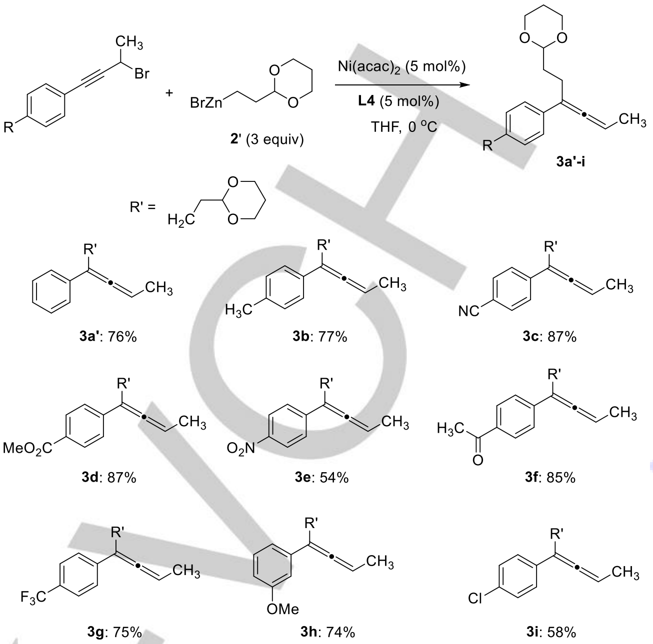




Entry	Ligand	**3a**:**4a**[a]	Yield (%)[b]
1	**L1**	99:1	65
2	**L2**	99:1	43
3	**L3**	87:13	50
4	**L4**	99:1	82
5	**L5**	40:60	78
6	**L6**	29:71	63
7	**L7**	42:58	67
8	**L8**	-	0

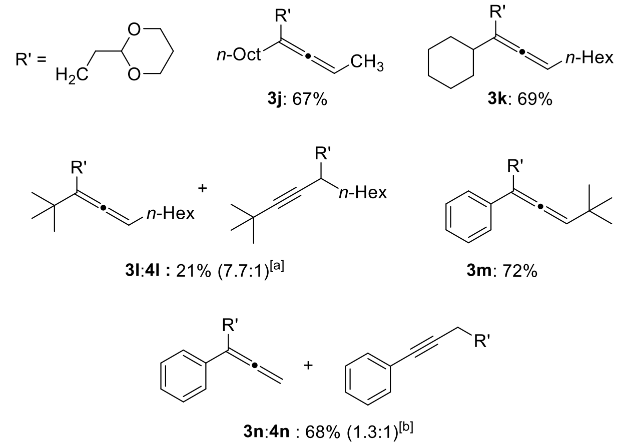
[a] Calculated by ^{1}H-NMR. [b] Combined isolated yields.

Therefore, we fixed 5 mol% of Ni(acac)$_2$, 5 mol% of **L4** (bathophenanthroline), and 0 °C as the optimized conditions to study the reaction scope.[13] All reactions were monitored by TLC and most of them get completed within 40 to 240 min.[14]



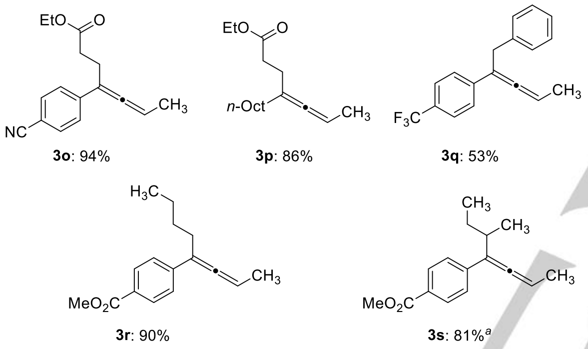
Scheme 2. Reaction scope for different substituted aryl electrophiles.

We initially studied how the substitution of the aromatic ring of the electrophile could affect the reaction outcome (Scheme 2). The reaction works in the presence of a whole variety substituents, in moderate to excellent yields to afford allene compounds **3a'**-**3i**. Formation of alkyne is not observed in any case. Especially relevant are the cross-coupling of the nitro derivative (**3e**) which is not usually compatible in Ni-catalyzed coupling reactions involving radical species, and the compatibility of the arylchloride (**3i**). Alkyl-substituted alkynes also gave the allene as the major products (Scheme 3) in contrast to that observed in the previously reported conditions.[10a]



Scheme 3. Reaction outcome for alkyl-substituted alkynes. [a] Product ratio determined by GC.[b] Product ratio determined by ^{1}H-NMR.

Interestingly, *t*-butyl substituted alkyne afforded some propargylic coupling derivative as a minor product (**3l**:**4l**; 7.7:1) in contrast to that observed for octyl or cyclohexyl compounds. In addition, homocoupling of the electrophile took place leading to a significantly lower overall yield (21%).[15] On the other hand, primary propargyl bromide shows very low selectivity, giving rise to a 1.3:1 mixture of **3n** and **4n**. It can be concluded that allene is strongly preferred unless the electrophile is a primary propargyl bromide or it bears a *t*-butyl substituted alkyne. Finally, some other alkylzinc bromides could be coupled with a variety of alkyl- and aryl-substituted propargyl bromides in moderate to excellent yields (**3o**-**3s**, Scheme 4). Interestingly, *n*-butylzinc bromide and *s*-butylzinc bromide afforded the corresponding derivatives **3r** and **3s**, respectively, without isomerisation of the butyl moiety, in contrast to that observed in our previous work on Ni-catalyzed cyclization-coupling reactions with Grignard reagents.[8a] Such isomerisation requires a relatively fast β–elimination of hydrogen that does not take place in the current process, according to the reaction outcome.

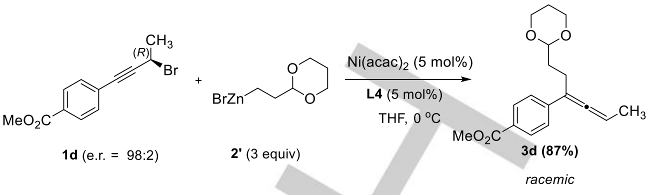


Scheme 4. Reaction scope with different nucleophiles ([a]: two diastereoisomers obtained as a 1:1 mixture, as shown by 1 H NMR, could not be separated).

Mechanistic studies

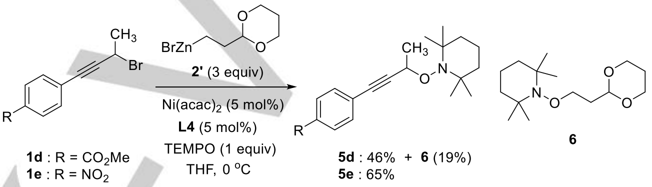
Several reports on cross-couplings support the formation of alkyl-Ni(I) derivatives that are able to activate primary and secondary alkyl halides by homolytic C-X cleavage leading to radicals and alkyl-Ni(II)-X species. Formation of Ni(I) seems to proceed through comproportionation of Ni(II) precursors and Ni(0) complexes formed upon reduction of the precatalyst by the organometallic nucleophile.[8,16] In order to probe the possible existence of intermediate radicals, enantiomerically enriched **1d** (*er* = 98:2) was submitted to cross-coupling with **2'**. The expected allene **3d** was obtained as a racemic mixture, with a complete loss of stereochemical information, suggesting the intermediacy of a propargyl radical (Scheme 5). Recovery of **1d** when running the reaction at 75% conversion showed no racemization of the starting halide.

On the other hand, when the reactions of **1d** and **1e** were performed in the presence of TEMPO, the main products were those resulting from the coupling of propargyl radicals to TEMPO (**5d** and **5e**, respectively, Scheme 6).



Scheme 5. Reaction of enantio-enriched electrophile **1d**.

In addition, the product exerting from the coupling of the nucleophile to TEMPO (**6**, 19% yield) was also observed for the reaction of **1d**. It may result from the reaction of an alkyl-Ni(I) complex with TEMPO followed by reductive elimination.[8b]



Scheme 6. Coupling reaction in the presence of TEMPO

Experiments were conducted with the aim of determining the oxidation state of the active species. Reaction of Ni(II) precatalysts with alkylzinc halides leads to an overall reduction of the metal along with the formation of formally oxidized organic derivatives, such as alkyl homocoupling and/or the alkene resulting from β-elimination. Homocoupling compound **7** (Figure 1) was the only organic product observed when the reaction was performed at 0 °C. No β–elimination or alkane formation took place.

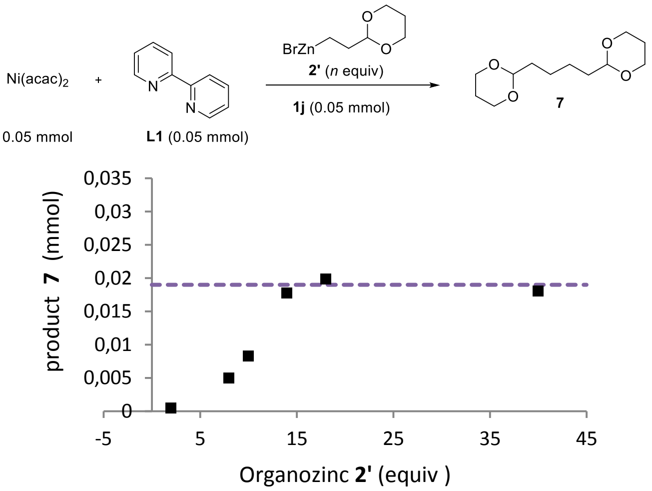
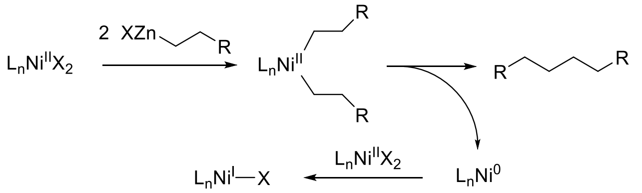


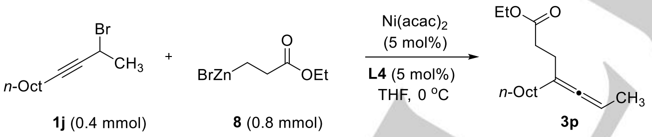
Figure 1. Determination of the oxidation state of Ni in the catalytic system by GC monitoring.

Thus, different vials containing the same amount on Ni(acac)$_2$ and bipy (**L1**) were treated with increasing amounts of **2’**, in the presence of **1j** to mimic the actual reaction conditions. After completion of the reactions, mixtures were analysed by GC. As it can be seen in Figure 1, the amount of homocoupling product **7** increases upon addition of increasing amounts of organozinc compound **2’**, and stabilizes at half of the starting amount of Ni, even after adding 40 equiv of nucleophile. These data indicate that one-half of the starting Ni(II) gets reduced to Ni(0), which implies formal to reduction to Ni(I). Double transmetalation from **2’** to Ni(acac)$_2$, followed by reductive elimination to give Ni(0) and **7**, and subsequent fast comproportionation of Ni(0) with remaining Ni(II) species would explain the formation of Ni(I) (Scheme 7).[16c] This mechanism accounts for the formation of sole organic oxidized compound formed in this reaction.



Scheme 7. Plausible pathway for Ni(I) complex generation involving comproportionation

Surprisingly, in contrast to that observed in our previous studies on Fe catalysis,[17] the catalytically active Ni(I) solution was EPR silent, suggesting that no paramagnetic species were actually present. Kinetic and computational studies provided an explanation (see below). We performed a kinetic study on model reaction involving 2-bromo-3-dodecine (**1j**) and ethoxycarbonylethylzinc bromide (**8**) (Scheme 8).



Scheme 8. Conversion *vs* t for this model coupling reaction shows an overall first order kinetics.

The integral method was employed, by fitting the variation of the concentration along the whole reaction period. Overall first order kinetics was observed (See Supporting Information). In subsequent experiments, variation of the concentration of **1j** while keeping constant the concentration of nucleophile **8** and catalyst, allowed determining a *first order reaction with respect to the electrophile*.

On the other hand, performing the reaction under different concentrations of the organozinc halide, the reaction coherently showed *zero order with respect to the concentration of the nucleophile*. Interestingly, the overall constant rate for the first order reaction is dependent on the Ni concentration, and taking into account the rate equation:

$$v = k\,[Ni]^a\,[R\text{-}Br] = k'\,[R\text{-}Br]\ ;\ k' = k\,[Ni]^a \qquad (1)$$

$$\ln k' = \ln k + a \ln [Ni] \qquad (2)$$

the reaction order with respect to the metal can be derived from equation 2 by measuring the apparent rate constant at different Ni concentrations (Figure 2). A *value of a= 0.5 is obtained for the reaction order with respect to Ni*. This suggests that a dimeric complex could be involved in the rate-limiting step. The reaction orders contrast with those previously reported for Ni-catalyzed alkyl-aryl couplings of aryl Grignard reagents and alkyl halides, which show for which second order in both the nucleophile and the catalyst, and zero order in the nucleophile.[18]

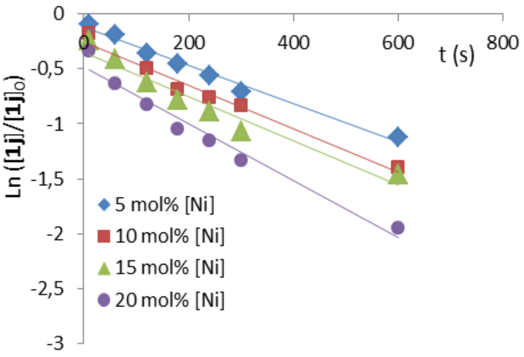


Figure 2. Reaction kinetics for different Ni concentrations.

In order to get additional information we calculated the reaction and activation steps for putative reaction steps at DFT level.

Computational studies

The results of the reduction experiments of the Ni precatalysts with alkylzinc halide strongly supported the formation of Ni(I) active complexes. On the other hand, Ni(I)-alkyl complexes have been appointed as the competent species for Negishi, Kumada, and Suzuki cross-couplings involving alkyl electrophiles.[9,17] We chose (phen)Ni-Me (**I**) as a model for the active catalyst. Interestingly, we found that **I** may dimerize to a diamagnetic complex **Idim** exothermically (-1.4 kcal mol^{-1}, Figure 3).[19]

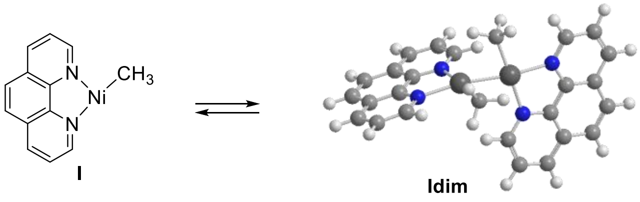


Figure 3. Calculated structure for Ni(I) dimer **Idim**.

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This complex shows a Ni-Ni bond distance of 2.29 Å, indicating a metal-metal interaction (Van der Waals radium of Ni is 1.63 Å). Formation of **Idim** explains the absence of signal when conducting the EPR experiments on the solution of the reduced precatalyst. Facile dissociation affords the active complex **I**, which has the unpaired electron localized on Ni (spin density calculations), in contrast to the related complexes containing tpy or pybox previously described,[9b,17c] for which this electron resides on the π^*-orbitals of the ligand (see Supporting Information). Complex **I** is able to readily react with the propargyl bromide to afford a square-planar Ni(II) derivative and a propargyl radical in an exothermic process (-22.5 kcal mol^{-1}, Figure 4).

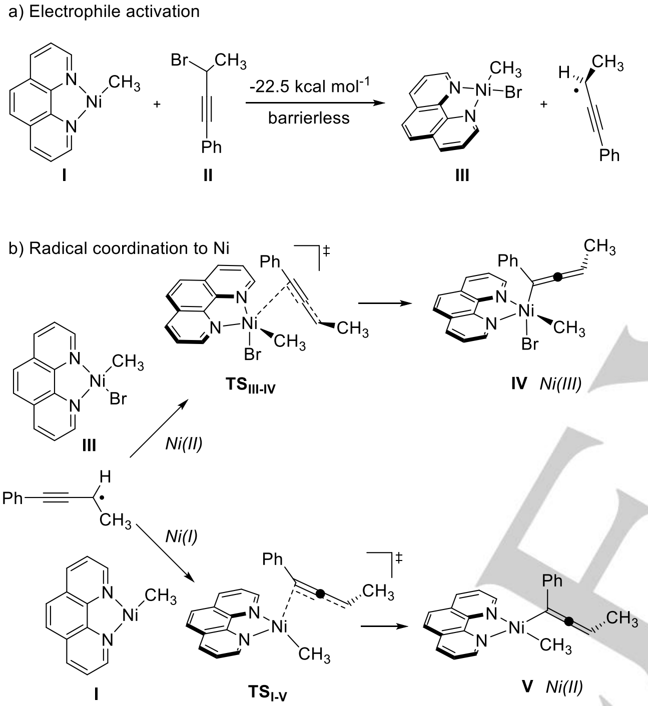
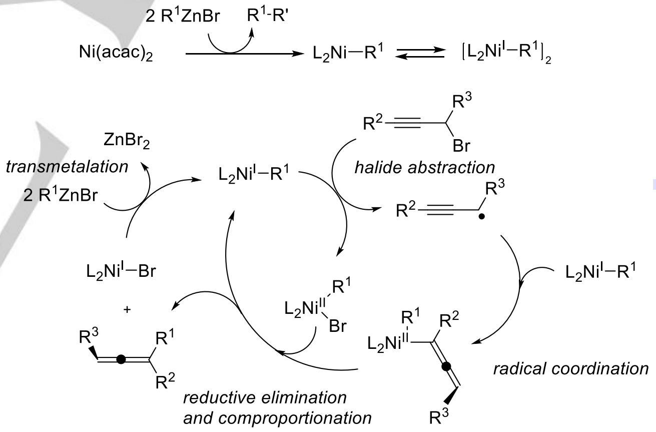


Figure 4. Calculated oxidative addition process. ZPE-corrected relative energies (kcal mol^{-1}) are calculated in THF (PCM) at B3LYP/6-311G(2df,2p) (C,H,N) cc-pVTZ (Ni,Br)//B3LYP/6-31G(d) (C,H,N) LANL2DZ (Ni, Br) level. Calculated ΔG in gas–phase are shown in brackets.

Scanning of the potential energy surface demonstrates that this halogen abstraction takes place with no activation barrier. Alternative activation of propargyl bromide **II** by halide complex (phen)NiBr has been calculated to be endothermic (0.6 kcal mol^{-1}) and cannot compete with activation by **I**, in contrast to that proposed for the Ni-catalyzed coupling of propargyl bromides and bis(aryl)Zn reagents in the presence of pybox ligands.[12] Once the electrophile has been activated, the resulting radical may react with either the alkyl-Ni(II) complex formed in the same reaction (**III**) or, alternatively, it may react with alkyl-Ni(I) species. The latter process has been proposed for Ni-catalyzed alkyl-alkyl cross-couplings on the basis of experimental evidence and computational support.[18b] We initially searched for transition states for the coordination of the radical to Ni(II) in **III** to give diorgano-Ni(III) complexes. Interestingly, structures leading to allenyl-Ni derivatives, and not their propargyl analogues, were located.[20] Activation energy for coordination to Ni(II) complex **III** through **$TS_{III\text{-}IV}$** is 17.9 kcal mol^{-1} (ΔG_a = 17.0 kcal mol^{-1}) and leads to allene complex **IV** in an exothermic process (-3.6 kcal mol^{-1}) entropically disfavoured (ΔG = +5.4 kcal mol^{-1}). Alternative coordination to Ni(I) derivative **I** through triplet **$TS_{I\text{-}V}$** is far more favorable both kinetic and thermodynamically. Thus, calculated activation energy is 2.9 kcal mol^{-1} (ΔG_a = 13.7 kcal mol^{-1}) and the process is highly exothermic (-58.0 kcal mol^{-1}, (ΔG = -11.6 kcal mol^{-1}). In conclusion, *alkyl-Ni(I) derivative is more reactive towards propargyl radical*, and therefore formation of Ni(II) complex **V** constitutes the preferred pathway. In addition, according to kinetic data, we propose reaction of alkyl-Ni complex **I** with propargyl radical as the rate limiting step. Equilibrium between **I** and **Idim** explains the 0.5 order with respect to Ni. No transition state could be located for the formation of a propargyl-Ni(II) derivative instead of the allenyl-Ni isomer. It is important to note that coordination of the radical is slower compared to previous C-Br activation, and fixes the regioselectivity of the reaction. Formation of relatively long-lived propargyl radicals explains products **5** observed when running the reaction in the presence of TEMPO (Scheme 6). Finally, relatively fast reductive elimination would lead to the final product.



Scheme 9. Proposed reaction pathway.

Seminal studies by Kochi revealed that reductive elimination from (alkyl)(aryl)Ni(II) complexes is difficult and may require prior oxidation to Ni(III).[21] Alternatively, coordination of electron deficient olefins has been also proposed to induce this process.[22] At this stage we cannot propose a detailed mechanism, but fast reductive elimination is compatible with the experimental evidence. Complex **III** may be involved in the formation of Ni(I) promoting, participating or even after reductive elimination. Regeneration of the active species **I** takes place by fast transmetalation with the alkylzinc halide, in accord with the zero-order found for the organozinc. In addition, our previous work on a related system afforded a calculated low activation energy.[10]

To sum up, stereochemical, titration and kinetic experiments, along with computational data lead us to propose the reaction pathway shown in Scheme 9. Precatalyst is reduced to the active alkyl-Ni(I) species by the nucleophile, which dimerizes to a diamagnetic complex. The subsequent extremely fast bromide abstraction is followed by rate-determining radical coordination to dimeric Ni(I) species, which constitutes the catalyst resting state. This process also fixes the observed regioselectivity. Fast reductive elimination affords the coupling product, with the tentative participation of previously formed (alkyl)Ni(II)Br intermediate. Two different Ni(I) complexes are formed: the active alkyl-Ni(I) and Ni(I)Br, which is converted into the active species by transmetalation, and restarts the cycle.

Conclusions

In conclusion, we have developed an unprecedented Ni-catalyzed cross-coupling reaction of propargyl halides leading to allenes using alkylzinc reagents as nucleophiles. The reaction shows broad scope and functional group compatibility, and it is complementary with previously reported work. The reaction mechanism has been studied by means of experimental and computational tools. The reaction shows first order in the electrophile, zero order in the nucleophile, and half order with respect to the catalyst. It seems to be catalyzed by Ni(I) complexes and to involve propargyl radicals whose coordination to Ni(I) determines the regiochemical outcome of the reaction. In contrast to other related reactions, nucleophile concentration is kinetically irrelevant, pointing to a fast irreversible transmetalation step. Data support the formation of a Ni(I) dimer as the catalyst resting state. The involvement of radicals opens the possibility to develop new cascade processes, and the key coordination the former to Ni suggests that enantioselective processes may be discovered for this kind of systems.

Acknowledgements

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Keywords: Nickel • Cross-coupling • Allenes • Reaction mechanisms • Density functional calculations

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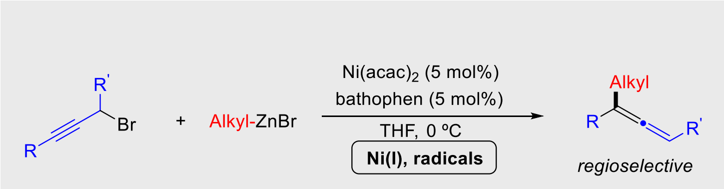

Text for Table of Contents: Coupling of alkyl bromides and alkylzinc reagents to allenes shows excellent complementary regioselectivity, is catalyzed by Ni(I) complexes, and involves radical intermediates

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