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Ni-Catalyzed regio- and stereoselective addition of arylboronic acids to terminal alkynes with a directing group tether†

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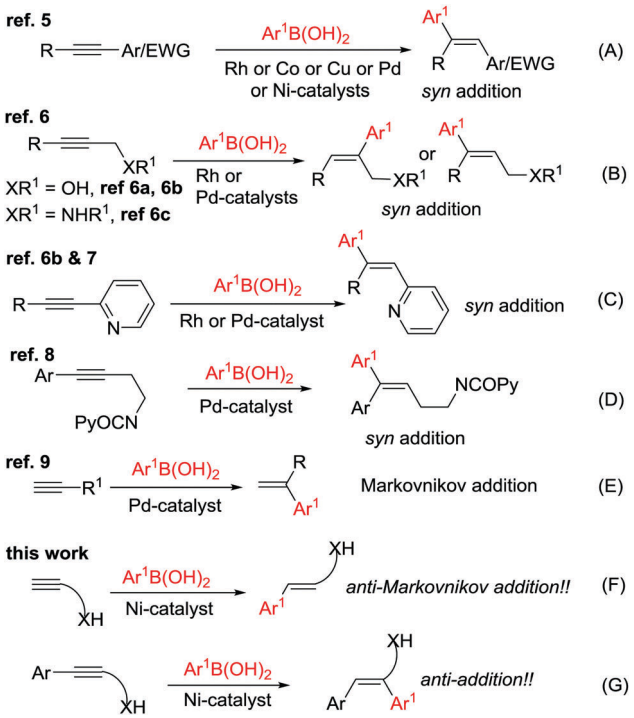
Addition of arylboronic acids to directing group tethered acetylenes in a regio and stereoselective manner using an inexpensive catalytic system is achieved for the first time to access highly sought after allyl/homoallyl alcohol/amine units. The apparent vinylnickel intermediate was successfully trapped by the Michael electrophiles to get defined tri- and tetra-substituted olefins. An interesting selectivity switch was observed with internal alkynes.

Substituted olefins are prominent structural motifs found in natural products, pharmaceuticals and organic materials. They are also very frequently encountered intermediates as they are subjects of a wide range of transformations. Consequently, enormous attention has been paid to their selective synthesis.[1–9] Carbonyl olefination reactions,[1,2] coupling between prefunctionalized partners[3] and eliminations[4] are the commonly used techniques to obtain them. Alkynes are also found to be versatile precursors for their synthesis, usually through reductions, conjugate additions and the metal mediated addition of R–M, especially generated from boronic acids.[5–9] The latter, namely hydroarylation, gained huge attention in recent times as it delivers the otherwise difficult structural patterns around olefin units. The selectivity is generally governed by kinetics (addition *via* 4-membered TS) and steric crowding in the substrate. Thus, the products are usually of *syn* addition and are with added aryl/alkyl groups on the less hindered terminus of the alkyne (Scheme 1A).[5] With an exception, the inherent electron bias in ynoates and ynones directs the nucleophile on deficient β-carbon.[5] Furthermore, Lautens *et al.*,[6a] Oh *et al.*[6b] and Marinelli *et al.*[6c] used propargylic functions to direct the regioselection (Scheme 1B). Pyridine was also used as a directing function through co-ordination with metal (Scheme 1C).[6b,7] Very recently, Engle *et al.* revealed amido pyridine at the homopropargylic end as the directing group in installing a nucleophile by overriding the intrinsic steric bias (Scheme 1D).[8]



Scheme 1 Addition of aryl boronic acids across alkynes.

Surprisingly, most of the study is restricted to only internal alkynes perhaps because the terminal alkynes readily undergo self-dimerization under metal mediated conditions. There are two reports by Hua *et al.* and Oh *et al.* on the addition of boronic acids to terminal alkynes to afford Markovnikov adducts (Scheme 1E).[9] The addition on terminal alkynes for anti-Markovnikov adducts and the *trans*-addition[10] across internal alkynes still remain formidable.

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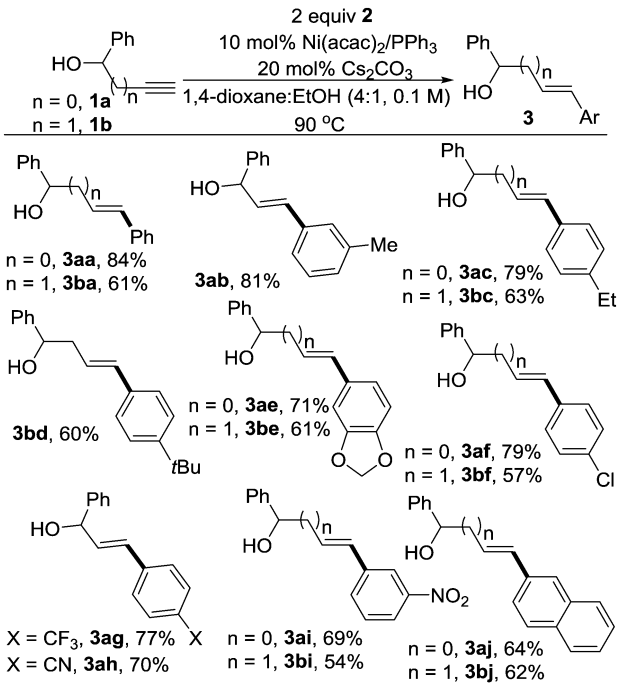
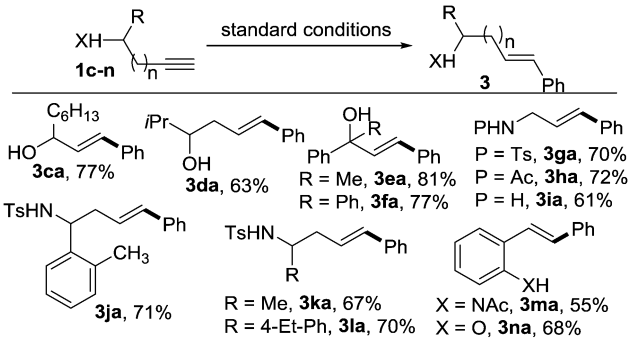
One example was given by each Zhu *et al.*[11] and Hua *et al.*[9a] for anti-Markovnikov addition of an aryl group when the acetylene was attached to a bulky tertiary center which however, proving its impracticality, could not be extended to similar other examples as described in the same respective papers. Kimber *et al.* reported the addition of aryl boronic acids on tertiary propargyl alcohols but the reaction actually occurred on *in situ* formed allenes which therefore led to the specific formation of dienes.[12] As part of our ongoing program of uncovering the new reactivities of alkynes,[13] we herein report the hitherto unattended anti-Markovnikov addition of arylboronic acids on terminal alkynes with a directing group tether. By the way, we showed an unusual anti-hydroarylation of internal alkynes with a hydroxyl tether (Scheme 1F and G). In both the cases, we could successfully trap the vinylnickel intermediates with Michael acceptors.

Optimization studies are detailed in the ESI.† With the standard conditions (slow addition of a mixture of substrate and 1 equiv. $ArB(OH)_2$ to the catalyst and 1 equiv. $ArB(OH)_2$ dissolved in 4 : 1 dioxane/EtOH system) in hand we investigated the generality of the reaction (Scheme 2). The scope of arylboronic acids against **1a** was initially studied. Alkyl substituted phenylboronic acids **2b–c** smoothly reacted, similar to **2a**, to give the corresponding products **3ab–ac** in 79–81% yields. Substrates **2e–g** with alkoxy and halo substitution showed no resistance in the reaction and delivered the products in decent yields. Electron withdrawing cyano and nitro functionalities survived very well in the reaction but with a slightly reduced yield when they are present at para substitution. 2-Naphthylboronic acid **2m** was also compatible with the reaction and afforded the product in a moderate yield of 68%. Delightedly, the reaction was identified to be equally extendable to the homopropargyl alcohol **1b**. For a thorough verification of the scope of the reaction we screened a series of arylboronic acids against **1b**. In general, the yields of the products from **1b** were lower than those from **1a**. Thus, phenyl and alkyl phenyl adducts **3ba–bd** were obtained in 61–64% yield. Electron rich arylboronic acids were slightly better in productivity (**3be** in 61%) than halo substituted (**3bf** in 57%) and electron poor (**3bi** in 54%) counterparts.



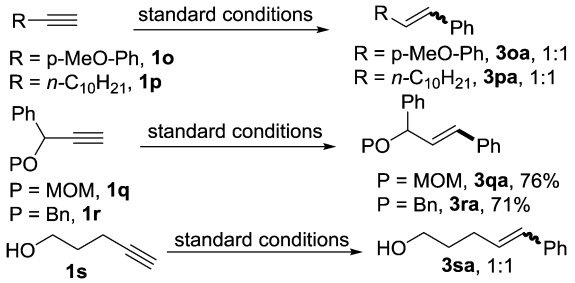
Scheme 2 Scope of boronic acids in hydroarylation.



Scheme 3 Scope of acetylenes in hydroarylation.

Next, we moved to scrutinize the acetylene substrate scope (Scheme 3). Non benzylic propargyl alcohol **1c** was first tested with **2a**. Pleasingly, it reacted smoothly to produce **3ca** as a single isomer in 77% yield. Similarly, non-benzylic homopropargyl alcohol **3d** successfully passed through hydrophenylation to deliver the corresponding homoallyl alcohol **3da** in 63% yield. Furthermore, tertiary propargyl alcohols **1e–f**, in spite of steric constraints, readily underwent the transformation with excellent yields. Delightedly, the reaction was found to be extended to propargyl amines with no resistance irrespective of the type of protecting group. Thus **1g–h** were converted to **3ga–ha** in 70–72% yields. Interestingly, unprotected propargyl amine was also transformed to the corresponding product **3ia** but in a moderate yield of 61%. Next, the scope of the reaction was further extended by subjecting the homopropargyl amines **1j–l** to the title transformation to obtain the homoallylic amines **3ja–la** in respectable yields. Very pleasingly, *ortho* acetylenic aniline **1m** and phenol **1n** were found as equally appropriate substrates for the regio and stereoselective hydroarylation to afford highly valuable[14] adducts **3ma–na**.

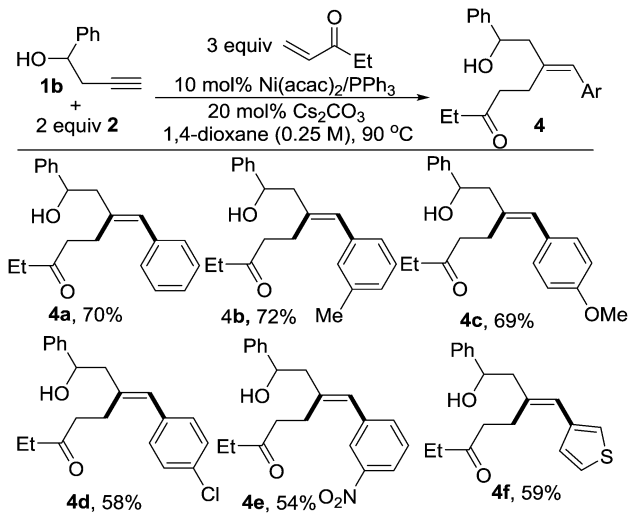
Subsequently, we investigated the necessity of the co-ordinating group for the above selective hydroarylation. When we subjected the phenylacetylene **1o** and dodecyne **1p** to the standard conditions (Scheme 4), almost a 1 : 1 mixture of stereoisomers was formed demonstrating the necessity of the co-ordinating group in a nearby domain of the substrate. Surprisingly, MOM protected propargyl alcohol **1q** delivered **3qa** as a single isomer with high regio and stereoselection indicating that even a weak co-ordination is enough for the execution of the title reaction. Further expanding the substrate scope, even the benzyl protected variant **1r** was transformed to the desired product **3ra** with the same selectivity. However, pentynol **1s** gave a mixture of isomers invoking that the directing group distanced to more than two carbons does not serve the purpose.



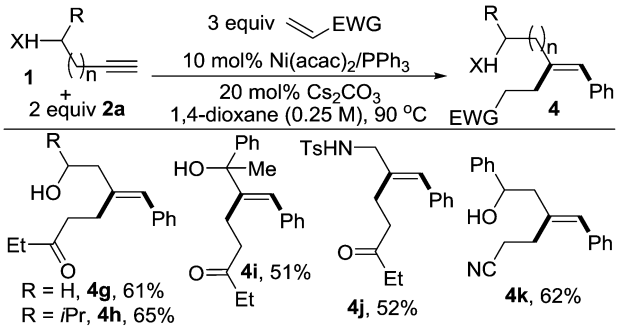
Scheme 4 Role of the chelating group in hydroarylation.

We then headed to probe that whether the apparent carbo-nickel intermediate is truly carbophilic which led to polymerization that we discussed in the optimization studies. A reaction without the protic co-solvent (EtOH) was conducted in the presence of a Michael acceptor EVK to trap the intermediate. This would also afford an advantage of constructing defined tri-substituted olefin. We avoided the protic co-solvent to increase the life time of the intermediate. As anticipated, the reaction between **1b** and **2a** in the presence of EVK cleanly produced the expected trisubstituted olefin **4a** in 76% yield (Scheme 5). We immediately set to study the scope of this highly useful transformation. Initially, various arylboronic acids were employed in the reaction. Substrates with alkyl, alkoxy, halo, nitro, and heteroaryl groups successfully passed this regio and stereoselective sequential carboarylation to afford the products (**4b–f**) in moderate to high yields. The reaction was further tested on various homopropargyl, sterically hindered propargyl alcohols and propargyl amine and the desired products (**4g–j**) were successfully obtained (Scheme 6). Gratifyingly, acrylonitrile was also found to fruitfully trap the carbonickel intermediate to give cyanoalkyl substituted olefin **4k** in decent yield.

To further probe the mechanism by elucidating whether the coordinating group of the substrate forms a complex with metal prior to the addition, we conducted a reaction on internal alkyne which in principle should give the product with an aryl

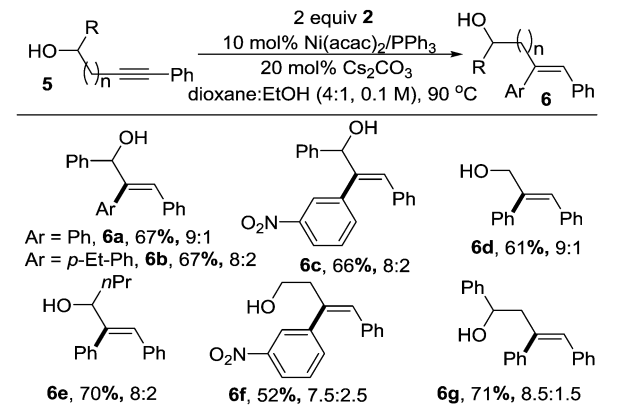


Scheme 5 Scope of arylboronic acids in carboarylation.

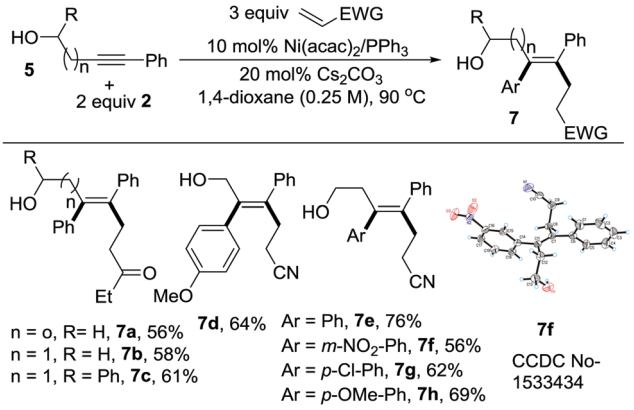


Scheme 6 Scope of acetylenes in carboarylation.

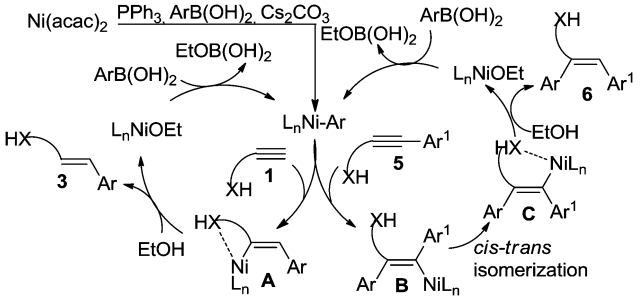
group on the carbon distal to the coordinating group. Very surprisingly, the reaction of **5a** with **2a** under the standard conditions resulted in **6a** with reversal of both regio and stereoselection demonstrating that there does not exist any coordination between DG and the nickel complex prior to the addition (Scheme 7). But the immediate post addition co-ordination is necessary which thereby stabilizes the resultant stereoisomer. In the present case, the opposite regioselection, which is determined purely by steric factors, led to *cis–trans* isomerization probably through back donation due to a lack of the possibility of intramolecular stabilization with the help of DG. The *trans* isomer is then stabilized by the co-ordination and hence it does not convert back to the *cis*-isomer and as a result the overall stereoselection also turns to nonconventional. We also thoroughly verified the scope of this hitherto hardly explored *trans* addition reaction. Both alkyl and aryl substituted propargyl and homopropargyl alcohols were successfully transformed to the respective products (**6b–g**) in moderate to good yields. Arylboronic acids with alkyl, and nitro substitution were tested to show the generality of the reaction. Note that small amounts of other regioisomers from 9 : 1 to 7.5 : 2.5 ratios were obtained obviously due to less steric differences between the two terminals of the alkyne. Agreeably, the vinyl nickel intermediate in this case could also be successfully trapped by the Michael acceptors EVK and acrylonitrile to obtain the tetrasubstituted olefins **7a–h** (Scheme 8). Surprisingly, tetrasubstituted olefins were obtained *via* the *syn* carboarylation pathway, in which the



Scheme 7 Ni-Catalyzed hydroarylation of internal alkynes.



Scheme 8 Tetrasubstituted olefins *via* carboarylation.



Scheme 9 Mechanism for Ni-catalyzed hydroarylation.

vinylnickel intermediate formed after carbonickelation was immediately trapped by the Michael acceptors without leaving room for *cis–trans* isomerization.

Based on all the above investigative experiments, we proposed a mechanism as shown in Scheme 9. Accordingly, the ArNiLn complex (formed *via* addition reductive elimination)[10b] was added in a *syn* fashion to acetylene with an aryl group dropped at the less hindered terminal carbon (**A**). A strong co-ordination was soon evolved with the nearby flanking DG which halted the *cis–trans* isomerization. Subsequent protodenickelation with EtOH released the olefin **3** and the resultant LnNiOEt upon reaction with second $ArB(OH)_2$ gave back LnNiAr for the next cycle. In the case of internal alkyne, the addition resulted in a reverse regioselection due to steric factors and the resultant vinyl nickel intermediate **B** underwent *cis–trans* isomerization. Since the *trans* isomer **C** was immobilized with intramolecular co-ordination the reverse isomerism to the *cis* isomer did not occur. **C** then underwent a protodenickelation to afford the *trans* addition adduct **6**.

In conclusion, we revealed for the first time the regio and stereoselective addition of arylboronic acids to terminal alkynes with a directing group tether. A wide variety of highly useful allylic/homoallylic alcohols, allyl/homoallyl amines and *ortho*-alkenyl aniline & phenols in both unprotected and protected forms were smoothly accessed. Adding all the possible value addition to the core discovery, a thorough investigative search of the mechanism led us to unveil the pathways for all di-, tri- and tetra-substituted olefins.

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