

Directed Nickel-Catalyzed Regio- and Diastereoselective Arylamination of Unactivated Alkenes

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Professor Chao Wang's group, from Tianjin Normal University (P. R. of China), has been interested in transition-metal-catalyzed difunctionalization of unactivated alkenes via a directing group strategy for some time. Previously, the group reported a regioselective Ni-catalyzed 2,1-diarylation and aryl-alkylation of homoallylic amine derivatives, bearing a picolinamide (PA) auxiliary, with commercially available arylboronic acids and organohalides.¹ "Transition-metal-catalyzed three-component, dicarbo-functionalization of alkenes, which enables the expeditious construction of molecular complexity, has drawn tremendous attention in recent years," said Professor Wang.²⁻⁴ "Although intermolecular three-component dicarbo-functionalization of alkenes has achieved some success in recent years, carbohetero-functionalization of olefins remained underexploited and rare. C–C and C–N bonds are two of the most ubiquitous bonds in nature, and arylation of olefins represents a powerful and attractive synthetic tool for the simultaneous introduction of aryl and amino groups across alkenes, to enable the rapid increase in molecular complexity from abundant and readily available materials," explained Professor Wang. He continued: "Intramolecular arylation with an alkene acceptor tethered to either the aryl halide or active nitrogen functionality using transition-metal catalysts has been developed for the synthesis of nitrogen-containing cycles. In comparison, intermolecular arylation providing access to arylolefin-based acyclic molecules is particularly difficult and remains rare, owing to its high entropic cost and the problem of controlling the chemoselectivity of multicomponent reactions."

This project emerged when Professor Wang discussed with his students the possibility of achieving the challenging arylation by replacing organohalides with aminating electrophiles (Scheme 1A). "To the best of our knowledge, intermolecular olefin arylation of unactivated alkenes with arylboronic acids and N–O electrophiles was rather elusive," said Professor Wang. He continued: "Indeed, the development of this protocol for arylation of unactivated alkenes was limited by three fundamental issues: (1) undesired competitive cross-coupling between arylboron reagents and O-benzoylhydroxylamines, (2) the low binding affinity of unactivated alkenes to metal centers, especially for internal alkenes, and (3) the difficulty to control regioselectivity, such as arylation

vs aminoarylation, and 1,2-arylation vs 1,n-arylation via chain-walking isomerization."

Professor Wang recalls that the group started this investigation with an extensive optimization campaign to enable Ni-catalyzed arylation of homoallylic amine substrates containing a directing group with phenylboronic acid and piperidino benzoate and the results indicated the coordination of the PA directing group and NiBr₂·DME was an excellent catalytic system to afford the product of 1,2-arylation of unactivated alkenes. "This new protocol was compatible with terminal and internal alkenyl amines of different chain lengths, a broad range of primary and secondary amine sources, and exhibited excellent functional group tolerance (Scheme 1B)," said Professor Wang. Interestingly, the reaction of α -substituted terminal alkenes led to the formation of *trans*-isomeric products with high levels of diastereoselectivity, in which two skipped stereocenters were established. "To the group's delight, PA protected allylic amines and a variety of terminal and internal bis-homoallyl amines underwent arylation to regioselectively provide the desired products, indicating four- and six-membered nickelacycles were formed and these can be stabilized in the catalytic system. In addition, our protocol was suitable for large-scale synthesis and the synthetic utility of this method was further demonstrated by the modification of pharmaceutical agents," recalled Professor Wang.

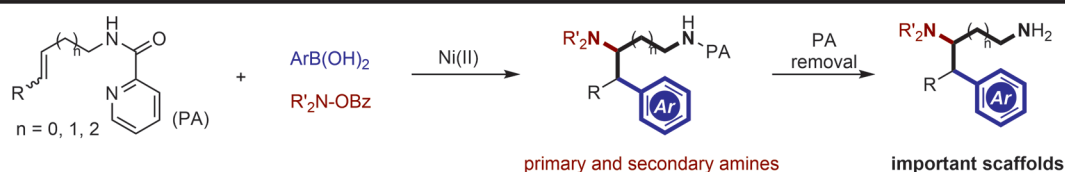
To elucidate the mechanism, a series of control experiments were conducted. For example, stoichiometric reaction of the alkene substrate with NiBr₂·DME followed by treatment with phenylboronic acid was conducted to generate Ni(I)–Ar complex (Scheme 1C). Addition of methanol to the solution of complex furnished the hydroarylation product in 86% yield upon alcoholic protonation, and the complex reacted with piperidino benzoate to afford the expected product in 57% yield. Professor Wang commented: "These results demonstrated that the reaction could be initiated by transmetalation of arylboronic acid with Ni(II) precatalyst and subsequent alkene insertion occurred prior to engagement with an electrophile to give the observed regiochemical outcome. While attempts to isolate and identify the intermediate failed, the proposed nickel intermediate ligated with DMF was detected by HR-MS (ESI) analysis." As such, Professor Wang proposed

that the reaction proceeds via a $\text{Ni}^{\text{I}}/\text{Ni}^{\text{III}}$ catalytic cycle rather than a $\text{Ni}^0/\text{Ni}^{\text{II}}$ cycle.

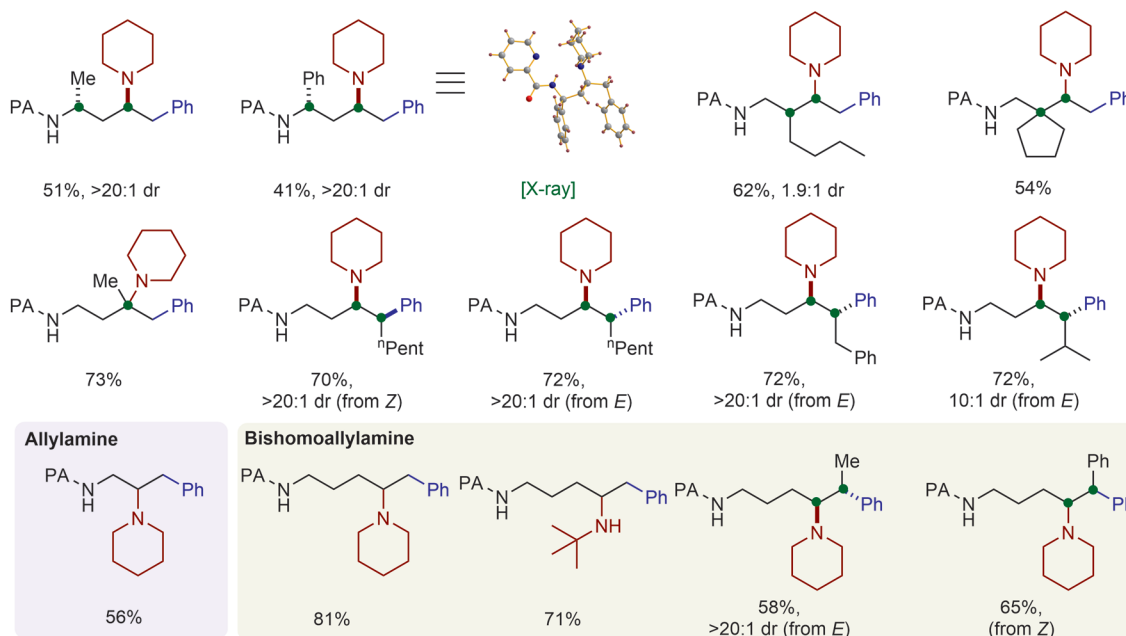
Professor Wang concluded: “We have disclosed a methodology for the regio- and diastereoselective intermolecular arylation of unactivated alkenes with a base-metal catalyst and readily available reagents, under simple conditions.

The removable bidentate PA auxiliary facilitated the formation of stabilized 4-, 5-, or 6-membered nickelacycles and enabled the difunctionalization of both terminal and internal alkenyl amines, leading to the concomitant introduction of important aryl groups and structurally diverse amino groups across the C=C bonds, with good functional group compatibility. We be-

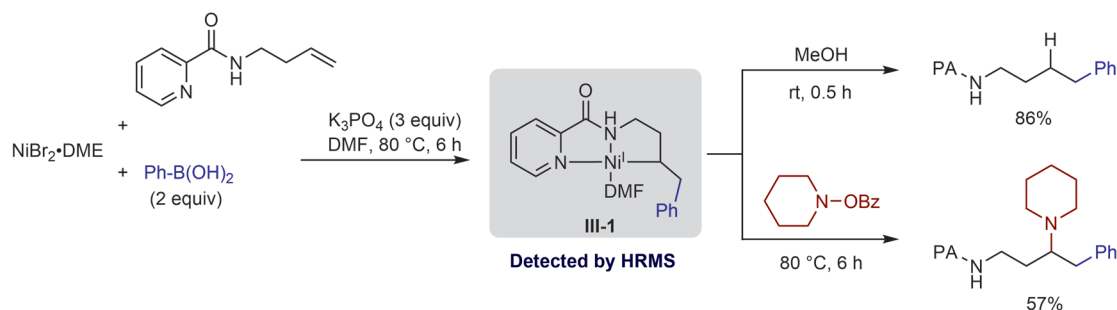
A This work: new approach for *syn*-arylation of unactivated alkenes



B Selected examples



C Control experiment using Ni(II) catalyst



Scheme 1 Directed nickel-catalyzed regio- and diastereoselective arylation of unactivated alkenes

lieve our work will open a new avenue for the regioselective difunctionalization of unactivated alkenes, and facilitate progress in drug discovery. The expansion of this strategy to other electrophiles for alkene carbohetero-functionalization is currently underway in our lab.”



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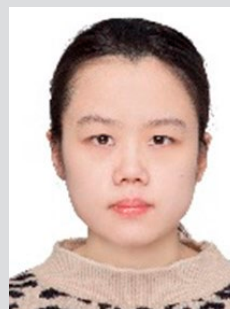
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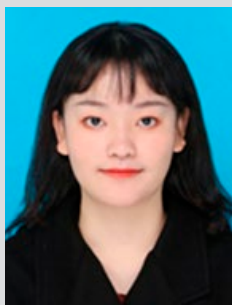
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