

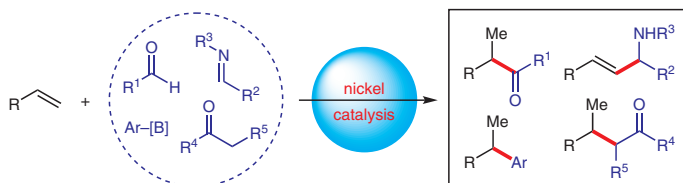
Nickel-Catalyzed Highly Atom-Economical C–C Coupling Reactions with π Components

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Abstract This account describes our latest advances in the field of nickel(0)-catalyzed hydrofunctionalization of π components. All reactions proceed either through internal hydride transfer or by using an external proton as the hydride source, thereby eliminating the use of stoichiometric amounts of reductants or oxidants. These nickel-catalyzed atom-economical coupling reactions demonstrate that nickel not only is an inexpensive metal catalyst, but also possesses unique and versatile catalytic abilities. Current limitations and the outlook of these reactions are also discussed.

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Key words alkenes, ketones, nickel, aldehydes, imines, coupling

1 Introduction

Nickel, as one of the first-row transition metals, has been explored in organometallic chemistry for over than 100 years. Because nickel is in the same group with palladium and platinum in the periodic table, it is often just regarded as a low-cost alternative for palladium or platinum in cross-coupling reactions. However, recent developments of nickel-catalyzed reactions clearly illustrate how the intrinsic properties of nickel make it valuable far beyond the low-cost replacement of palladium.¹ In 1922, the Nobel Laureate Paul Sabatier highlighted the specific behavior of

nickel catalysts by writing that “it can be compared to a spirited horse, delicate, difficult to control, and incapable of sustainable work.”² But then, Wilke made significant contributions to control this “spirited horse” by investigating the structure and reactivity of nickel(0) complexes, including synthesis of Ni(COD)₂ (COD, 1,5-cyclooctadiene).³ Since that time, the advance of organo-nickel chemistry has led to the development of several outstanding catalytic systems and practical applications in olefin oligomerization and reductive coupling reactions.⁴ In these transformations, nickel species showed distinct ability to coordinate and activate π components (alkenes, dienes, alkynes, etc.). Finding an eligible ligand has been the key to develop efficient homogeneous nickel catalysts. Montgomery⁵ and Jamison⁶ made prominent achievements in nickel catalysis by combination with various NHC (N-heterocyclic carbenes) and phosphine ligands in the reductive cyclization and coupling reactions of π components. RajanBabu,⁷ and Ho⁸ also made significant contributions to nickel catalysis by using chiral ligands in enantioselective dimerization of alkenes. On the basis of the chiral spiro ligands developed by our group,⁹ we reported nickel-catalyzed highly enantioselective transformations of π components, such as hydrovinylation reactions,¹⁰ reductive coupling reactions,¹¹ and alkylative coupling reactions.¹²

Nowadays, because of the growing demands for green chemistry, it becomes more and more important to transform raw materials into valuable products by an efficient and atom-economical method in recent organic synthesis.¹³ Hydrofunctionalization of a π -unsaturated compound to form C–C bonds seems to be an excellent fit because it allows assembling inexpensive, abundant π -unsaturated feedstocks to target molecules with inherently high atom economy, avoidance of byproducts, and manipulation of multiple bonds in one step. In this account, we summarized

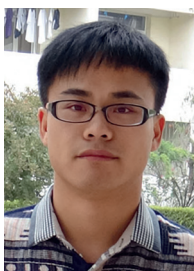
the latest advances from our groups in the field of nickel-catalyzed highly atom-economical coupling reactions with π components.

2 Nickel(0)-Catalyzed Hydroacylation of Styrenes with Simple Aldehydes

Transition-metal-catalyzed hydroacylation provides a direct and atom-economical approach to ketones from alkenes and aldehydes.¹⁴ Since the first example of this transformation reported by Sakai in 1972, the reaction has been extensively studied by using rhodium catalysts.¹⁵ However, owing to the fact that acyl-rhodium intermediates tend to undergo undesired decarbonylation during the course of intermolecular reactions, aldehydes used in the reactions usually need additional coordinating groups. To address this limitation of substrates, we envisioned developing efficient intermolecular hydroacylations of alkenes with simple aldehydes that do not have coordinating groups.

In 1990, Tsuda and Saegusa reported nickel-catalyzed hydroacylation of alkynes to give α,β -enones.¹⁶ Later on, Ogoshi developed a nickel-catalyzed intramolecular hydroacylation of alkenes.¹⁷ Inspired by these results, we hypothesized that intermolecular hydroacylation of simple aldehydes and alkenes could take place in a similar vein. Following this hypothesis, our group successfully developed the first nickel-catalyzed intermolecular hydroacylation reaction of simple aldehydes and alkenes in 2016.¹⁸ This reaction offers a straightforward access to various branched ketones in high yield and high selectivity (Scheme 1). Only catalyst $\text{Ni}(\text{COD})_2$ (COD = 1,5-cyclooctadiene) and phosphine ligand PCy_3 in 1,4-dioxane are used in the reaction, without the need of additional amine co-catalysts or coordinating groups on substrates that are widely used in Rh-catalyzed reactions. Various aliphatic aldehydes were well compatible with the hydroacylation reaction of styrene and its derivatives, providing the corresponding products in good to high yield, whereas aromatic aldehydes displayed a little lower reactivity. For example, for achieving good yields, benzaldehyde needs to react with either styrene derivatives bearing electron-withdrawing substituents or acrylamides (**3g-i**).

Biographical Sketches



Li-Jun Xiao was born in Hunan Province, China, in 1989. He received his B.Sc. degree from China Pharmaceutical University in 2012. In the same year, he joined Prof. Qi-Lin Zhou's group

at Nankai University and obtained his Ph.D. degree in 2017 with research on nickel-catalyzed C–C coupling reactions with π components. He then moved to the Scripps Research

Institute and now works as a postdoctoral researcher with Prof. Jin-Quan Yu on developing asymmetric transformation via sp^3 C–H activation.



Meng-Chun Ye received his B.S. degree from Lanzhou University in 2001 and his Ph.D. degree from the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences under the supervision of Prof.

Yong Tang in 2006. After three-year drug design experience in Prof. Hengming Ke's laboratory at University of North Carolina, Chapel Hill, he moved to the Scripps Research Institute in 2009, where he worked on C–H

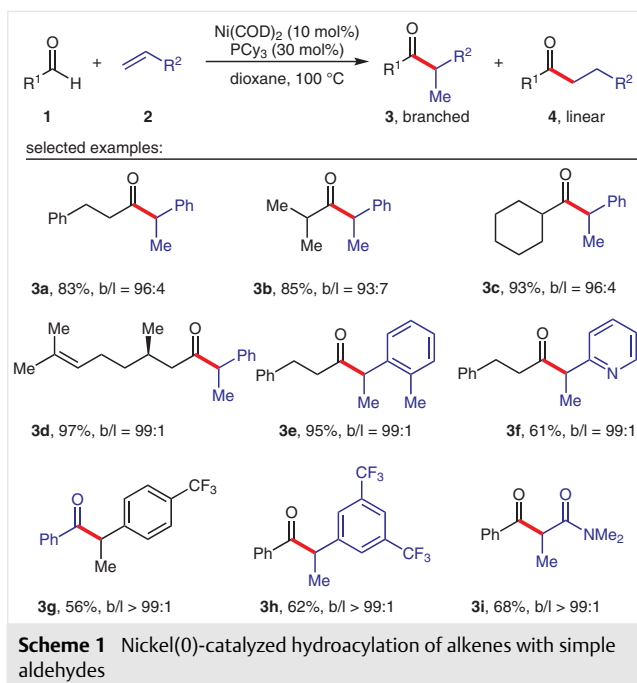
activation with Prof. Jin-Quan Yu. In 2014, he joined the faculty of the College of Chemistry at Nankai University in Tianjin, China. His current research interests focus on synergistic catalysis.



Qi-Lin Zhou received his B.S. degree from Lanzhou University in 1982, and his Ph.D. degree from the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences under the supervision of Prof. Yao-Zeng Huang in 1987. After several years

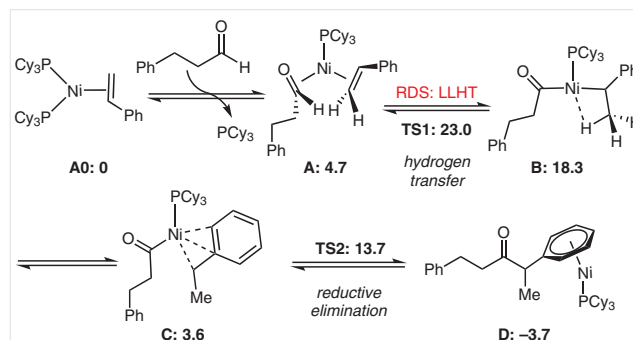
of postdoctoral research (with Prof. Klaus Müllen, Prof. Andreas Pfaltz, and Prof. Michael Doyle), he started his independent research at the East China University of Science and Technology, China in 1996. In 1999, he moved to the Institute of Ele-

mento-Organic Chemistry, Nankai University as Cheung Kong Scholar. His research interests include organometallics, asymmetric catalysis, and the synthesis of biologically active compounds.



The previous nickel-catalyzed coupling examples proposed an oxidative cyclization mechanism for the coupling of the alkene and the aldehyde, in which an external activating reagent such as silyltriflate¹⁹ or trimethylaluminum²⁰ is usually needed. To understand why there is no need of activators in our reaction, we investigated the mechanism by experiments and DFT calculations. The experimental data provide evidence for reversible formation of acyl-nickel-alkyl intermediate. DFT calculations show that carbonylic C–H bond of the aldehyde could transfer to a coordinated alkene through a LLHT (ligand-to-ligand hydrogen transfer) pathway without oxidative addition. On the basis of these results, a plausible mechanism was proposed for our reaction. As shown in Scheme 2, the catalytic cycle initiates with the nickel(0) complex **A0** that was formed by coordination of Ni(PCy₃)₂ with styrene. Then, the aldehyde replaces one of two PCy₃ ligands to generate the complex **A**, which is followed by a hydrogen transfer, termed as LLHT, from the bound aldehyde to the bound styrene via **TS1**. The resulting acyl-nickel-alkyl intermediate **B** isomerizes to a more stable species **C** in a η³-binding mode by rotating styrene along the Ni–C_{ben} bond. The following reductive elimination of **C** via a transition state **TS2** produces the complex **D**. Finally, **D** releases the branched product by binding with styrene and the PCy₃ ligand to regenerate the **A0** complex. The hydrogen transfer processes have the highest energy barriers in the catalytic cycle. Thus, the hydrogen transfer is the rate-determining step of the overall process, which is consistent with experimental observations and previous works.²¹ In addition, we considered another possible reac-

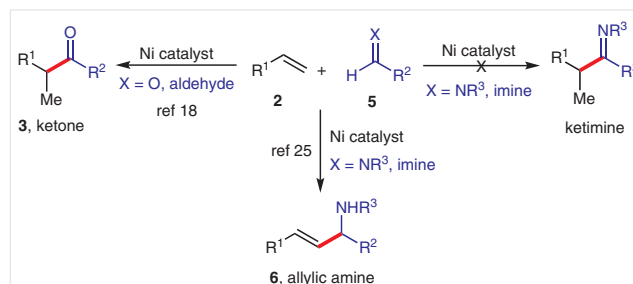
tion mechanism, which involves oxidative cyclization. The computational study shows that the pathway requires a very high activation energy (56.2 kcal mol⁻¹).



Scheme 2 Proposed catalytic cycle for nickel(0)-catalyzed hydroacylation of alkenes with DFT-calculated free energies (kcal mol⁻¹) in dioxane

3 Nickel(0)-Catalyzed Hydroalkenylation of Imines and Aldehydes with Alkenes

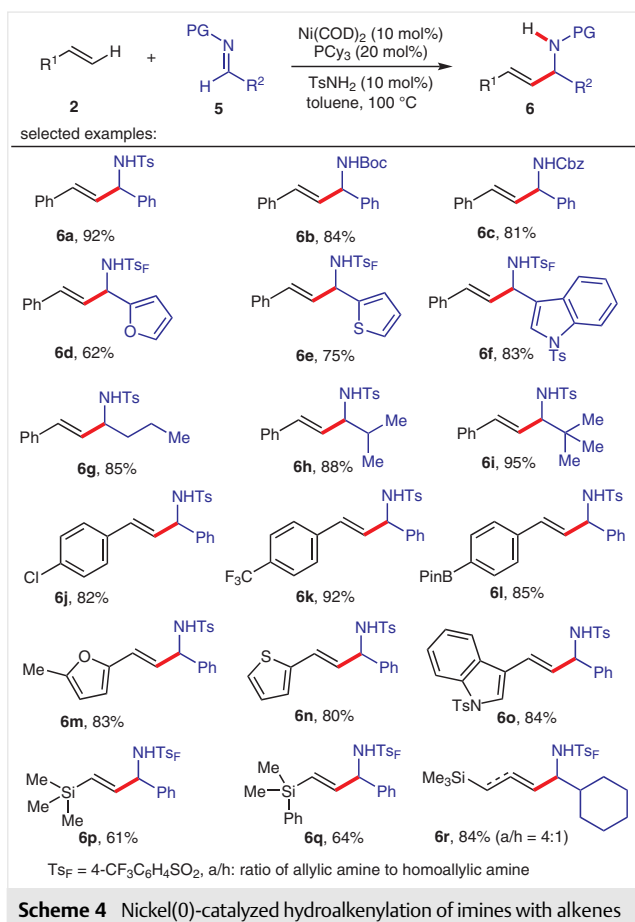
The nickel catalysts have been applied for the couplings of π components and carbonyl compounds.²² In 2005, Jamison and co-workers pioneered in achieving a nickel(0)-catalyzed coupling of aromatic and *tert*-butyl aldehydes with alkenes in the presence of Et₃SiOTf and Et₃N, providing allylic silyl ethers.²³ Subsequently, the same group reported a nickel(0)-catalyzed coupling of α,β-unsaturated aldehydes and ketones with alkenes in the presence of same activator reagents.²⁴ We recently developed a nickel(0)-catalyzed hydroacylation of alkenes with aldehydes.¹⁸ Owing to its excellent atom-economy, we became interested in expanding the methodology to imines. When the aldehyde was replaced by an imine, surprisingly, we obtained a small amount of allylic amine, instead of ketimine as expected (Scheme 3). We speculated that the mechanism of this transformation would be different from that of the hydroacylation reaction.



Scheme 3 Discovery of the nickel(0)-catalyzed hydroalkenylation of imines with alkenes

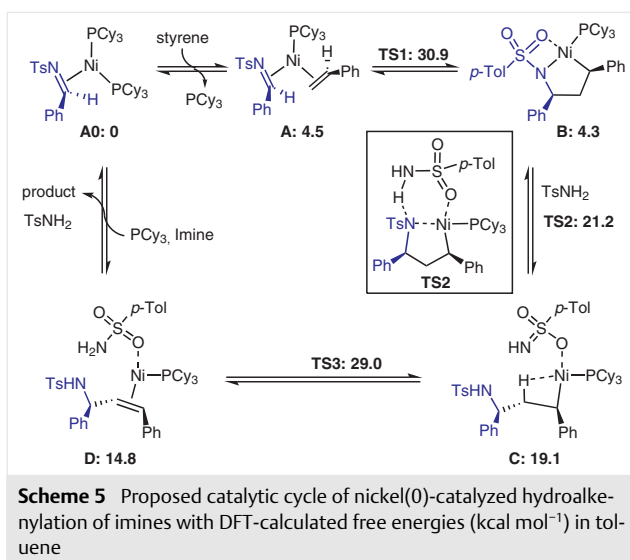
After extensive examinations of reaction parameters and detailed mechanism, we successfully developed a direct hydroalkenylation of imines with alkenes catalyzed by a

nickel(0)/PCy₃ complex in the presence of a catalytic amount of TsNH₂.²⁵ This protocol offers a straightforward method for the synthesis of allylic amines. The alkenes function like alkenyl–metal reagents that are used in conventional methods for the synthesis of allylic amines. A wide range of aromatic and aliphatic imines were compatible with the coupling reaction (Scheme 4). Various frequently-used protecting groups on the imine N atom were suitable beyond *p*-tosyl group. Aromatic aldimines derived from either aromatic or heteroaromatic aldehydes are good substrates. In addition, aliphatic aldimines bearing alkyl groups of varying steric bulk also gave the desired products in high yield. On the other hand, aryl and heteroaryl alkenes reacted with imine smoothly to give the desired products in good yield. It is worth noting that vinylsilanes were also suitable substrates, affording the useful silane-terminated allylic amines. Furthermore, the reactions of aliphatic alkenes with aldimines also worked well, delivering the coupling products in good yield but with a mixture of allylic and homoallylic amines.

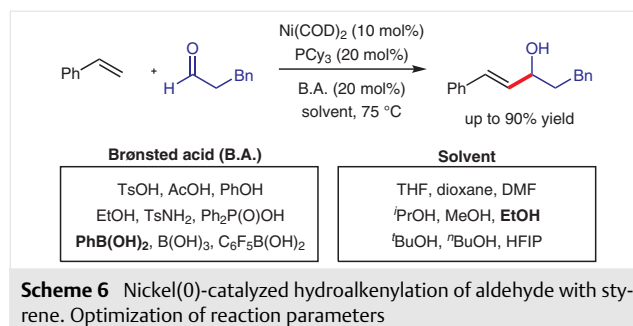


Control experiments and a KIE study were conducted to elucidate the mechanism of this nickel-catalyzed hydroalkenylation reaction. A plausible reaction path is pro-

posed on the basis of the experimental results and DFT study (Scheme 5). Oxidative cyclization of imine and alkene resulted in the formation of a five-membered azanickellacycle intermediate **B**. The Brønsted acid, TsNH₂, promoted the ring-opening of azanickellacycle to form the intermediate **C** through protonation of the N atom. Subsequent β-hydride elimination of the intermediate **C** would release an allylic amine product and regenerate the nickel catalyst and TsNH₂. During the whole process, TsNH₂ acts like a proton shuttle to transfer the olefinic hydrogen to the imine.

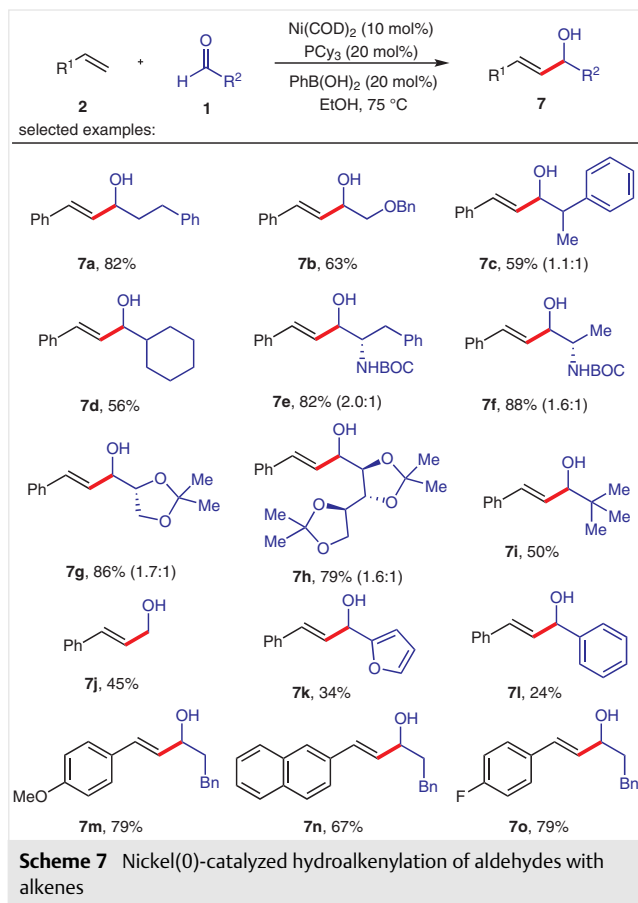


Compared with imines, aldehydes show relatively lower reactivity in the hydroalkenylation reaction with alkenes. Extensive investigation of reaction parameters revealed that PhB(OH)₂ is the optimal Brønsted acid. Alcoholic solvent also plays a critical role in improving the reactivity. By using EtOH as the solvent and PCy₃ as the ligand, up to 90% yield could be obtained for the model reaction of styrene and 3-phenylpropanal (Scheme 6).²⁶



Under the optimal conditions, the scope of alkenes and aldehydes were examined. The results in Scheme 7 showed that styrene and its derivatives were well compatible with the reaction, whereas aliphatic alkenes, especially α-ole-

ins, were not efficient. Impressively, the reaction can be applied to a broad range of aliphatic aldehydes with selectivity solely for linear products and up to 88% yield. By contrast, these enolizable aldehydes cannot be tolerated in the reaction when using stoichiometric amounts of strong activator TESOTf. Owing to lower reactivity, aromatic and heteroaromatic aldehydes did not react well, giving only 24–45% yield.

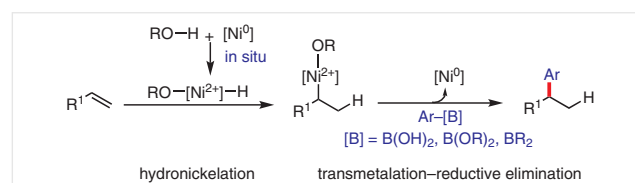


4 Nickel(0)-Catalyzed Hydroarylation of Styrenes and 1,3-Dienes with Organoboronic Derivatives

With the aim of exploring versatile types of hydrofunctionalization reactions of alkenes, we became interested in hydroarylation—the addition of hydrogen and an aryl group across an alkene—which offers a straightforward method for the synthesis of alkylarenes. To date, hydroarylation reactions can be classified into two categories based upon differences in generating active M–H species. One forms M–H through C–H bond activation of arenes,²⁷ and the other uses hydride reagents to form M–H.²⁸ The former usually requires arenes bearing a directing group or heteroarenes, whereas the latter works only under reductive conditions.

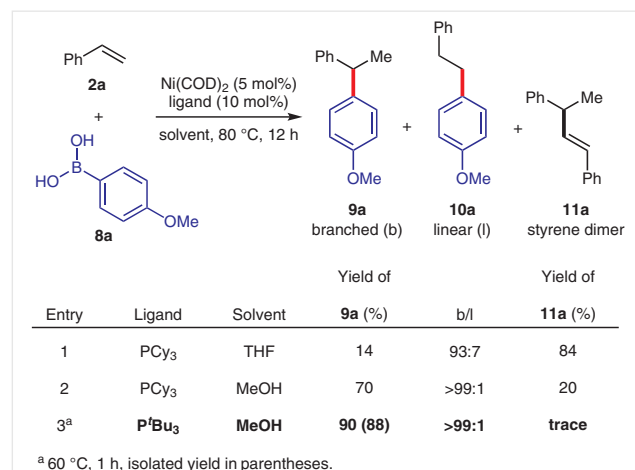
Therefore, a new strategy to achieve hydroarylation by the use of more general substrates and more easy-to-handle conditions, for example, redox-neutral conditions, is fascinating and important.

Recent advances in the nickel-catalyzed hydrocarboxylation reaction showed that the proton of water could react with nickel(0) to generate an active Ni–H species *in situ*.²⁹ We hypothesized that a RO–Ni–H intermediate could be obtained by the reaction of ROH with the nickel(0) (Scheme 8). The resulting active Ni–H species might be inserted by an alkene to form an alkylnickel intermediate, which could be followed by a transmetalation with organoboron and a reductive elimination to produce hydroarylation products. The whole process would avoid the use of any reductants or oxidants (Scheme 8).



Scheme 8 Proposal for nickel(0)-catalyzed hydroarylation

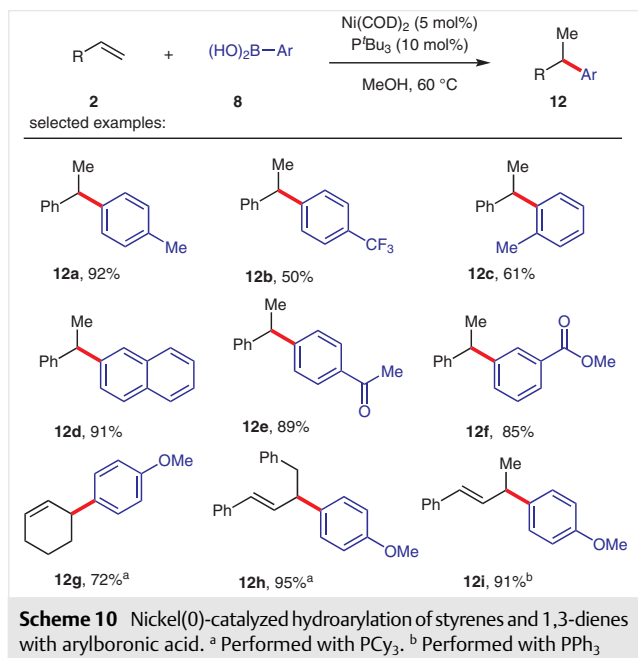
On the basis of this hypothesis, various alcohols were screened. When the reaction was performed in methanol by using nickel(0)/PCy₃ as the catalyst, the branched hydroarylation product was obtained in good yield.³⁰ We were delighted to find that the bulky and electron-rich phosphine ligand, P^tBu₃, not only prevented styrene dimerization but also allowed the reaction to occur at lower temperature (Scheme 9).



Scheme 9 Selected conditions for nickel(0)-catalyzed hydroarylation

The scope of the hydroarylation reaction was then investigated (Scheme 10). A variety of styrenes and arylboronic acids could be used as substrates under the optimal reaction conditions, offering the hydroarylation products in

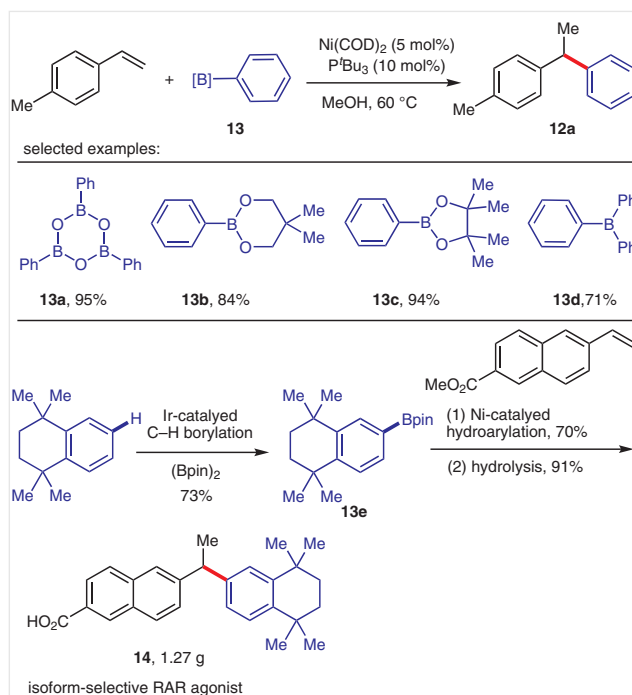
high yields with excellent regioselectivity. For diene substrates, both Ni/PCy₃ and Ni/PPh₃ catalyst provided better results than the Ni/P^tBu₃ catalyst. The aromatic 1,3-dienes and cyclic 1,3-dienes reacted with (4-methoxyphenyl)boronic acid (**8a**), giving exclusively the allylic arylation product in good to high yields.



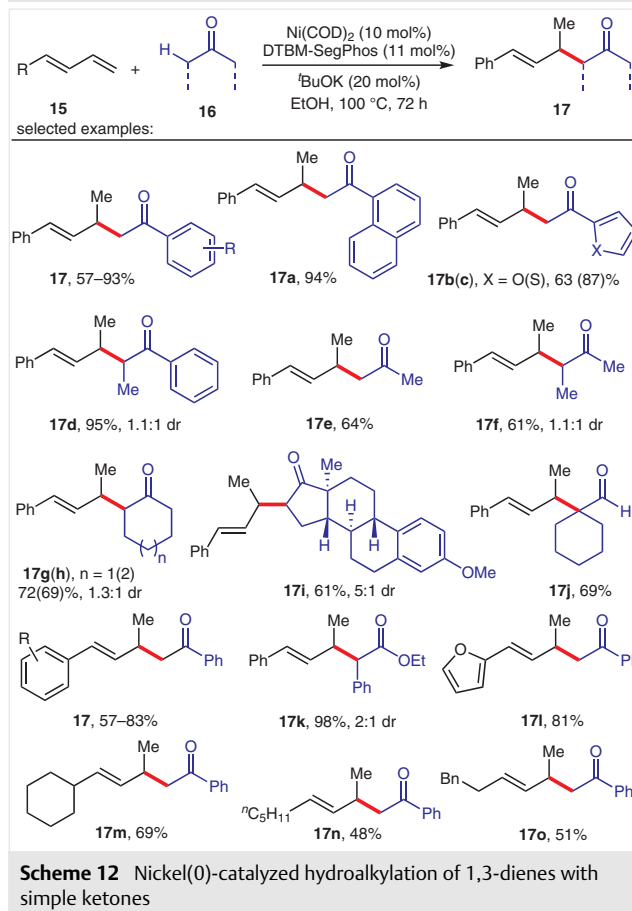
Notably, in addition to arylboronic acids, arylboroxines, arylboronic esters, and boranes could also be used as hydroarylation reagents in this Ni-catalyzed hydroarylation reaction (Scheme 11). The synthetic utility of this protocol was further demonstrated by combination of this Ni-catalyzed hydroarylation with an Ir-catalyzed C–H borylation reaction,³¹ affording an efficient and straightforward access to a retinoic acid receptor agonist (**14**)³² in good yield on a gram scale (Scheme 11).

5 Nickel(0)-Catalyzed Hydroalkylation of 1,3-Dienes with Simple Ketones

Since Hata's report of a palladium-catalyzed addition of 1,3-dicarbonyl compounds to dienes in the early 1970s,³³ significant progress has been made on palladium- and rhodium-catalyzed coupling of activated nucleophiles with unsaturated hydrocarbons such as 1,3-dienes, allenes, and alkynes.³⁴ These coupling reactions usually involve an addition of M–H to the unsaturated hydrocarbon to generate an electrophilic metal–π-allyl intermediate, which reacts with the activated nucleophiles. However, the coupling of relatively inert nucleophiles such as enols/enolates of simple ketones with these unsaturated hydrocarbons has not been well explored.³⁵



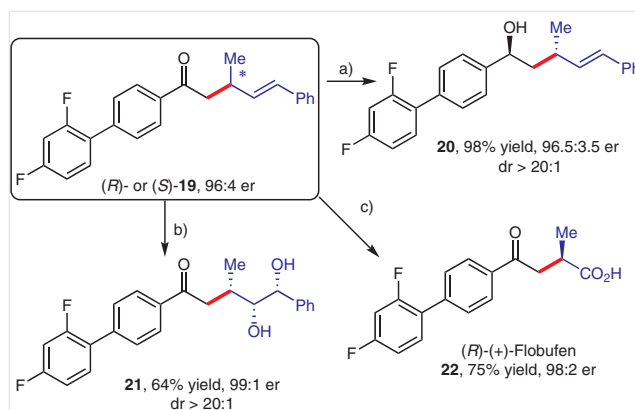
Scheme 11 Nickel(0)-catalyzed hydroarylation of styrenes and 1,3-dienes with various organoboronic derivatives



On the basis of the hydroarylation reaction in which the alcohol reacted with nickel(0) to generate the active catalyst species Ni-H, we envisioned that 1,3-dienes could react with Ni-H to produce Ni- π -allyl intermediates, which would be nucleophilically attacked by simple ketones to yield γ,δ -unsaturated ketones. Following this hypothesis, recently, we successfully developed a protocol for highly regioselective addition reactions between 1,3-dienes and simple ketones mediated by a nickel catalyst with DTBM-SegPhos as a ligand.³⁶ A wide range of aromatic and aliphatic ketones could be directly coupled with 1,3-dienes, providing synthetically useful γ,δ -unsaturated ketones in high yield and regioselectivity (Scheme 12). Notably, less reactive nucleophiles such as cyclohexanecarboxaldehyde (**17j**) and ethyl phenylacetate (**17k**) also showed good reactivity in the reaction.

Next, we devoted our efforts to achieving an asymmetric version. Among numerous screened chiral ligands, DTBM-HO-BIPHEP proved to be the optimal one, allowing additions of unstabilized carbon nucleophiles to unsaturated hydrocarbons in high regio- and enantioselectivity (Scheme 13).

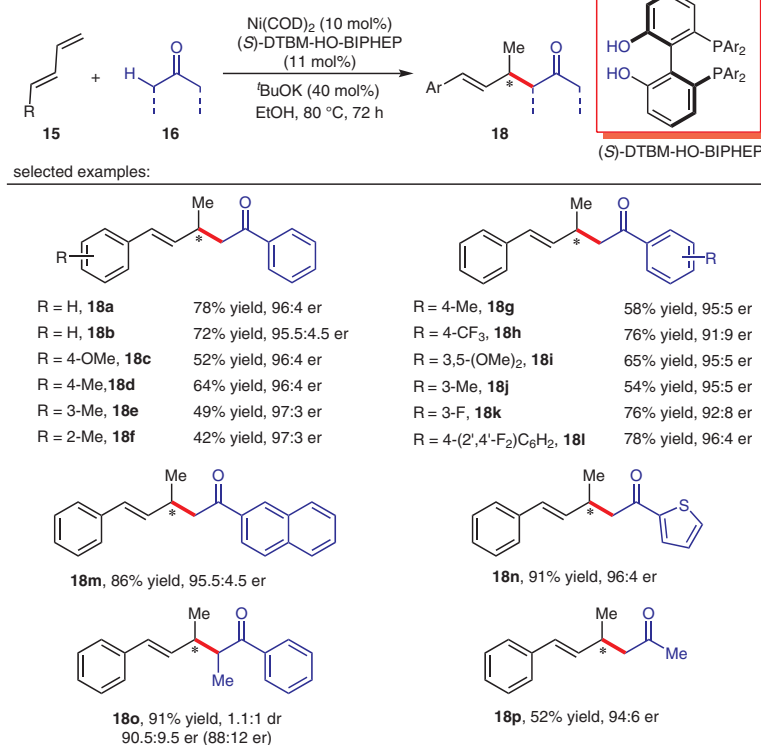
In addition, chiral products of the reaction are versatile building blocks in synthetic chemistry, as demonstrated by the synthesis of bioactive compounds including (*R*)-Flobufen (**22**) (Scheme 14).³⁷



Scheme 14 Product transformations

6 Summary and Outlook

This account summarized our recent advances in the field of nickel(0)-catalyzed atom-economical C-C coupling of π components, including hydroacylation, hydroalkenylation, hydroarylation, and hydroalkylation reactions. Both the hydroacylation and hydroalkenylation occur through an internal hydride transfer, representing highly atom-economic and byproduct-free coupling pathways. The hydroarylation and hydroalkylation use the proton of the alcohol



Scheme 13 Nickel(0)-catalyzed asymmetric hydroalkylation of 1,3-dienes with simple ketones

as the hydride source. All reactions show that nickel not only is an inexpensive transition metal but also owns unique catalytic abilities that are significantly different from those of precious metal catalysts. We envision that the studies covered herein offer conceptual and practical insights into the future design of nickel-catalyzed coupling reactions. However, our current reactions are mainly restricted to styrene and derivatives. In the future, an extension of the scope of alkenes to general aliphatic alkenes, especially bulkily-available α -olefins, would be more attractive. In addition, the asymmetric version has only been achieved in the hydroalkylation of 1,3-dienes with simple ketones. Therefore, developing asymmetric variants of other transformations would be extremely valuable in this field.

Funding Information

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