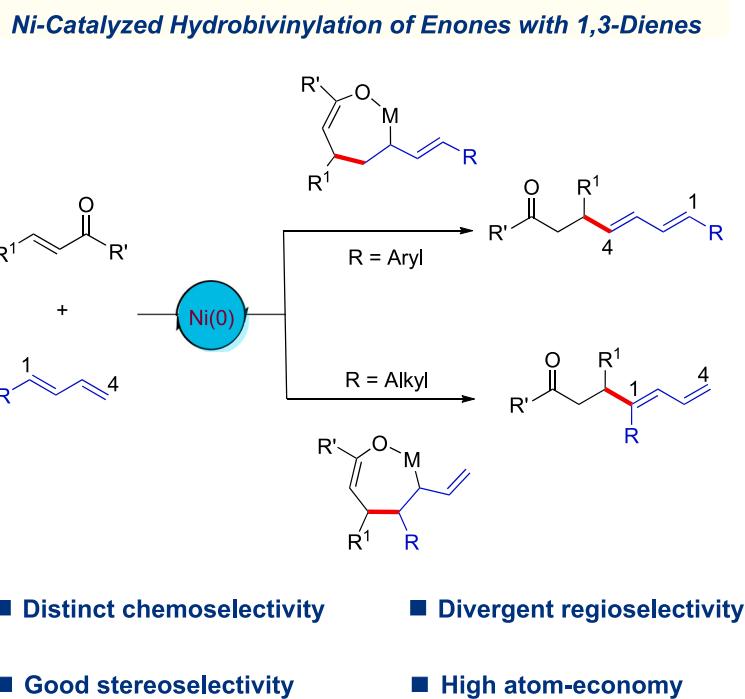


Article

Nickel-catalyzed hydrobivinylation of enones with 1,3-dienes



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Highlights

Regiodivergent hydrobivinylation of enones with dienes under nickel catalysis

Synthesis of disubstituted dienes in good regio- and stereoselectivity

Diverse synthetic transformations of diene products

The coupling of dienes with α,β -unsaturated ketones generally affords dehydroallylated products under low-valent metal catalysis, and developing systems with different selectivity is highly desirable. Li et al. demonstrate a nickel(0)-catalyzed regiodivergent hydrobivinylation of enones with dienes wherein regiodivergence relies on the selective formation of distinct oxa-nickelacycles controlled by the charge distribution of dienes.



Article

Nickel-catalyzed hydrobivinylation of enones with 1,3-dienes

Ying Li,^{1,2} Wei-Song Zhang,^{1,2} Shao-Han Sun,^{1,2} Yong-Kang Mei,^{1,2} Ding-Wei Ji,¹ Yan-Cheng Hu,^{3,*} and Qing-An Chen^{1,2,4,*}

SUMMARY

Leveraging the power of organometallic chemistry for inventing diverse functionalization of dienes is of great significance in synthetic chemistry. The coupling of dienes with α,β -unsaturated ketones generally affords dehydroallylated products under low-valent metal catalysis. Therefore, it is highly appealing to exploit an efficient catalytic system to achieve a distinct chemoselectivity, especially with switchable regioselectivity. Through tuning the oxidative cyclometallation step, we herein report a nickel(0)-catalyzed regiodivergent hydrobivinylation of enones with dienes. Aryldienes participate in the transformation efficiently, providing 1,4-disubstituted dienes in good regio- and stereoselectivity. By contrast, the addition site switches to the C1 position in the case of alkylidenes. The key to this strategy's success depends on the preferential formation of oxa-nickelacycle. Besides, the resulting diene products could undergo an array of elaborate transformations, which highlights the potential of this protocol.

INTRODUCTION

Over the past decade, inventing diverse catalytic functionalization of dienes has drawn tremendous attention, as it can provide a rapid entry to build up molecular complexity in a concise manner.^{1–10} A universal design principle relies on tuning the elementary organometallic steps. Oxidative cyclometallation, as a fundamental step, is generally involved in the coupling of two unsaturated partners.^{11–24} For instance, with the aid of low-valent Ru, Co, and Fe catalysts, α,β -unsaturated ketones and 1,3-dienes can easily undergo oxidative cyclometallation to generate a seven-membered metallacycle, followed by β -hydrogen elimination and reductive elimination to afford dehydroallylated products (Figure 1, top).^{25–32} Although this strategy is applicable, it is highly desirable to exploit an alternative system to achieve a distinct chemoselectivity, especially with switchable regioselectivity.

Nickel catalysis is another powerful tool for promoting the oxidative cyclometallation process.^{19,33–43} Of particular note is that, as shown by the groups of Zhou and Ye, 1,3-dienes often exhibit diverse reactivities under nickel catalysis.^{39,44–47} Inspired by these precedents and our long-standing interests in diene chemistry,^{48–52} we envisioned that nickel catalysis might alter the elementary steps in the coupling between α,β -unsaturated ketones and 1,3-dienes. If the carbonyl group, instead of a terminal carbon–carbon double bond, could participate in the oxidative cyclometallation, it will form a distinct metallacycle.^{29,53–56} The presence of oxygen atoms in the resulting metallacycle may facilitate a prepositive protonolysis.¹⁵ A subsequent β -hydrogen elimination will deliver hydrobivinylated products other than

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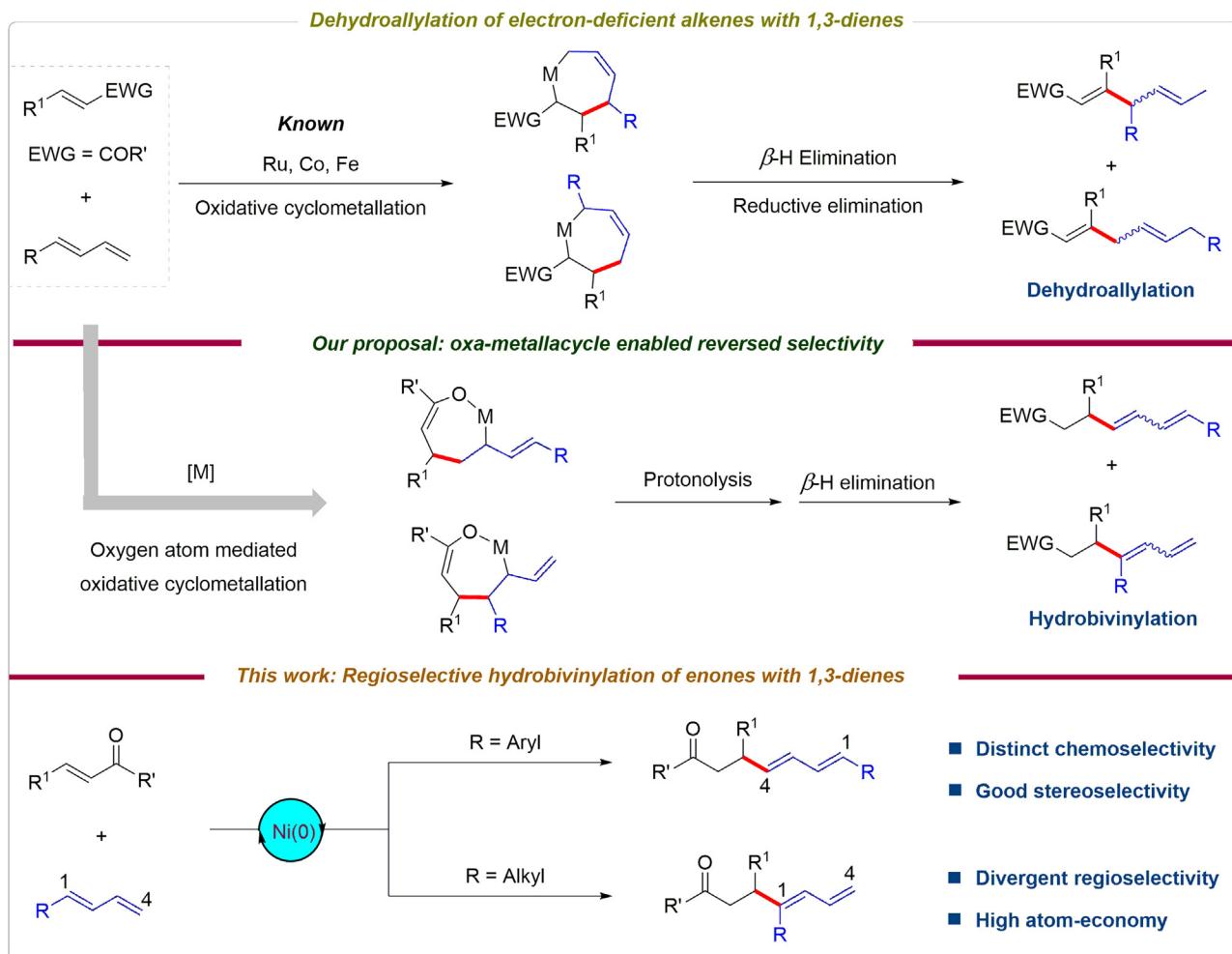


Figure 1. Hydrobivinylation of enones with 1,3-dienes

Nickel catalysis enables complementary regioselectivity to existing dehydroallylation methodologies.

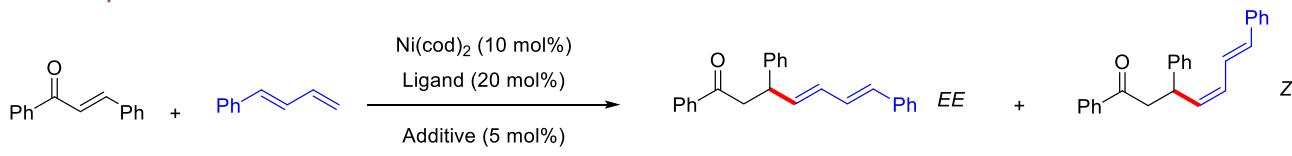
dehydroallylated products (Figure 1, middle). Herein, this goal is achieved by nickel catalysis, and more importantly, controllable regiodivergent hydrobivinylation of enones is established successfully (Figure 1, bottom). The substrate-modulated regiodivergence is likely due to the selective formation of distinct oxa-nickelacycles controlled by the charge distribution of 1,3-diene. This protocol enables a facile synthesis of 1,4-disubstituted dienes and 1,1-disubstituted dienes, which are difficult to prepare otherwise.

RESULTS AND DISCUSSION

Optimization

Initially, chalcone (**1a**) and phenylbutadiene (**2a**) were selected as the model substrates to verify our hypothesis (Table 1). When using Ni(cod)₂ and PCy₃ as a catalyst combo, the reaction did not take place in toluene or dioxane at 80°C (entries 1 and 2). Pleasingly, upon varying protic alcohol solvents that can promote the protonolysis step, the expected product **3aa** was readily formed (entries 3–6). MeOH and EtOH led to **3aa** in a good yields and a moderate *EE/EZ* ratio, while bulky ^tBuOH could enhance the selectivity but lower the reactivity. Other monophosphine ligands such as PPh₃ and PPhCy₂ were less effective for the reaction in ^tBuOH (entries 7 and

Table 1. Optimization of the reaction conditions



1a	2a	Solvent, 80 °C	3aa (EE + ZE)		
Entry ^a	Ligand	Additive	Solvent	3aa (%) ^b	EE/ZE ^b
1	PCy ₃	–	toluene	ND	–
2	PCy ₃	–	dioxane	ND	–
3	PCy ₃	–	MeOH	89	6:1
4	PCy ₃	–	EtOH	80	7:1
5	PCy ₃	–	^t BuOH	36	8:1
6	PCy ₃	–	^t BuOH	32	22:1
7	PPh ₃	–	^t BuOH	ND	–
8	PPhCy ₂	–	^t BuOH	41	10:1
9	PCy ₃	1,4-BQ	^t BuOH	98	21:1
10	PCy ₃	chloranil	^t BuOH	44	11:1
11	PCy ₃	2,6-DMBQ	^t BuOH	59	16:1
12	PCy ₃	1,4-NQ	^t BuOH	92 (82) ^c	28:1 (21:1) ^c
13	–	1,4-NQ	^t BuOH	ND	–
14 ^d	PCy ₃	1,4-NQ	^t BuOH	67	20:1
15 ^e	PCy ₃	1,4-NQ	^t BuOH	85	23:1

ND, not detected; 1,4-BQ, 1,4-benzoquinone; 1,4-NQ, 1,4-naphthoquinone; 2,6-DMBQ, 2,6-dimethylbenzoquinone.

^aConditions: 1a (0.20 mmol), 2a (0.20 mmol), Ni(cod)₂ (10 mol %), ligand (20 mol %), additive (5 mol %), solvent (1 mL), 80°C, 24 h.

^bYield and selectivity were determined by GC-FID analysis of crude mixture with 1,3,5-trimethoxybenzene as the internal standard.

^cThe yield and ratio in parentheses refer to that of isolated product 3a.

^d70°C.

^e90°C.

8). Recently, Engle et al. reported that quinone can serve as an effective ligand to stabilize the Ni(0) catalyst.⁵⁷ Based on this fact, a series of quinone additives were subsequently surveyed. To our delight, with the aid of 1,4-benzoquinone (1,4-BQ), the yield of **3aa** was improved to 98% while maintaining its high selectivity (entry 9). In comparison, chloranil and 2,6-dimethylbenzoquinone (2,6-DMBQ) gave inferior outcomes (entries 10 and 11). In the case of 1,4-naphthoquinone (1,4-NQ), **3aa** was afforded in 92% yield with an *EE/EZ* ratio up to 28:1 (entry 12). Besides, no desired product was detected in the absence of PCy₃ (entry 13). Thus, both 1,4-NQ and PCy₃ were crucial for the high efficiency of the reaction. Increasing or decreasing the temperature had adverse effects on the reaction (entries 14 and 15).

Substrate scope

With the optimized reaction conditions in hand, we then explored the substrate scope for hydrobivinylation of enone with 1,3-diene (Figure 2; see supplemental experimental procedures 4.2). Both the electron-donating substituents (**3ac** and **3ad**) and the electron-withdrawing substituents (**3ae** and **3af**) at the *para*-position of phenyl group R¹ proceeded through this transformation efficiently with selectivities maintained in high level. The substituents such as OMe, Me, and F, regardless of whether they were at *meta*- or *ortho*-positions, were all compatible with the reaction (**3ag–3al**). Besides, the 2-naphthyl-derived substrate was also amenable to the protocol, giving rise to product **3am** in a decent yield. 4-OMe and 4-F substituents at the phenyl ring of the R² group were well tolerated with the process (**3an** and **3ao**). 2-Me-substituted chalcone resulted in a diminished yield (**3ap**), probably due to the steric hindrance. Notably, natural product metochalcone underwent this hydrobivinylation smoothly to afford product **3aq** in 86% yield with 19:1 stereoselectivity.^{58,59} Moreover, alkyl-substituted enones proved to be applicable as well under the standard conditions (**3ar** and **3as**). The coupling between dimethyl-substituted enone and 1-phenyl-1,3-diene produced the expected adduct **3at** in 82% yield. In addition, trisubstituted enone **1u** could also participate in this transformation, leading to the formation of product **3au** in a slightly decreased yield and diastereoselectivity. When terminal unsubstituted substrate 1,2-diphenylprop-2-enone was employed, a complicated mixture was afforded.

The scope with respect to 1,3-dienes was further examined (Figure 2). A variety of arylbutadienes bearing different groups were all accommodated, and the corresponding products were furnished in good yields and selectivities (**3ca–3cf**). The congested mesityl diene could also participate in the process (**3cg**). To our delight, heterocyclic dienes were suitable substrates as well (**3ch** and **3ci**). Furthermore, the hydrobivinylations of chalcone with 2,3-dimethylbutadiene and butadiene also took place readily, giving rise to products **3cj–3cl** with 70%–80% yield. When using an alkyl diene such as phenylethyl butadiene as substrate, the coupling led to a mixture of the expected adduct **3cm** and isomerization product **3cm'**, as well as a small amount of 1,1-disubstituted diene **4b** (see supplemental experimental procedures; Figure S3). The oxidative cyclometallation between phenylethyl butadiene and chalcone produces seven- and nine-membered nickelacycles via π -allylnickel form, followed by β -hydrogen elimination to yield products **3cm** and **3cm'**, respectively. The observation of product **4b** is likely ascribed to the electronic properties. Compared with 1-aryl butadiene, the electron-rich alkyl group on 1,3-diene makes the corresponding C2 and C4 positions more electronegative.⁶⁰ Thus, in this case, migratory insertion of 1-alkylbutadiene can also take place at the C1 site.

Considering the importance of regiodivergence in synthetic chemistry, additional efforts were directed toward enhancing the efficiency of this unique C1 coupling

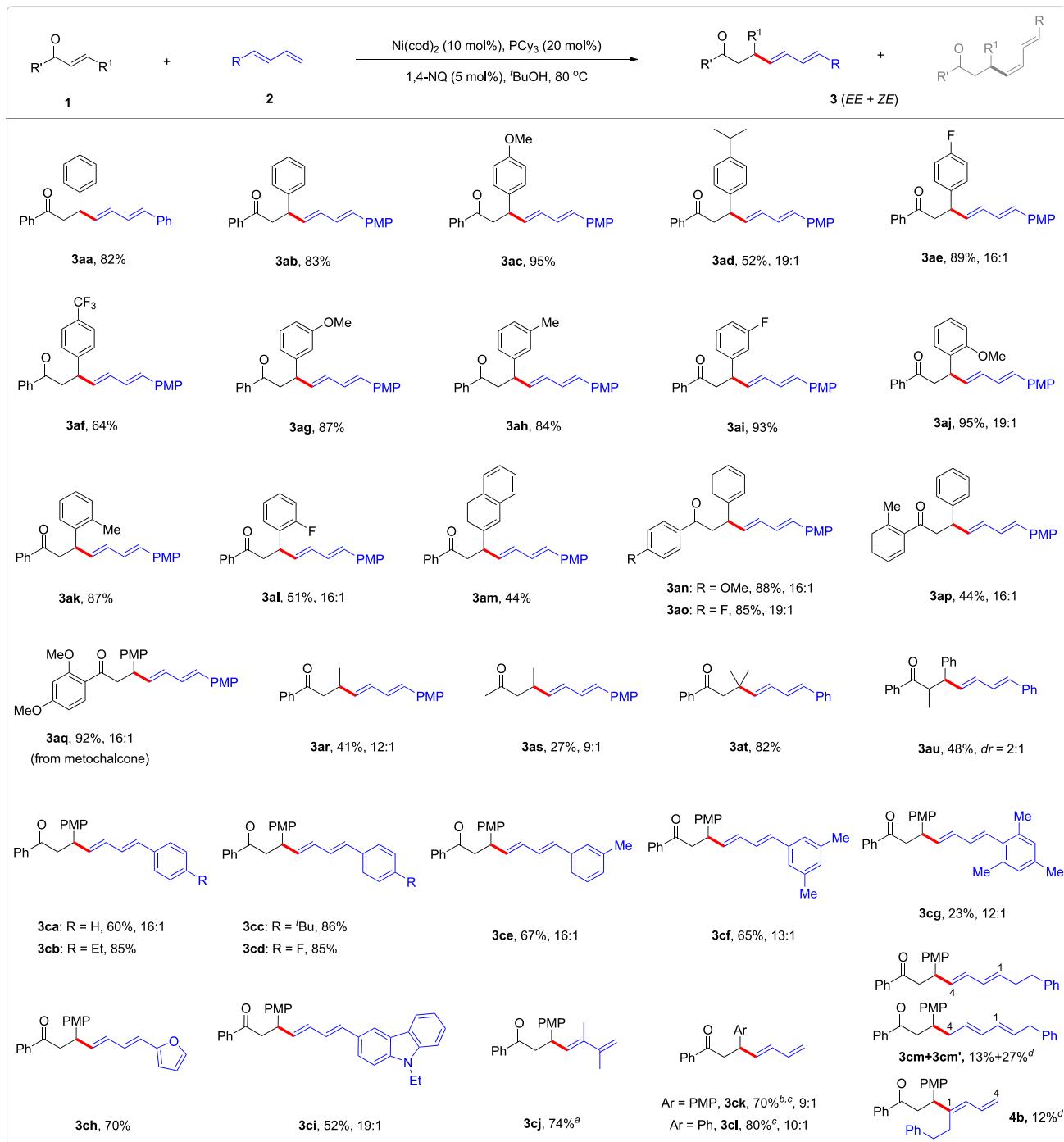


Figure 2. Substrate scope for Ni-catalyzed hydrobivinylation of enones with aryl-substituted dienes

Conditions: **1** (0.20 mmol), **2** (0.24 mmol), $\text{Ni}(\text{cod})_2$ (10 mol %), PCy_3 (20 mol %), 1,4-NQ (5 mol %), ${}^t\text{BuOH}$ (1.0 mL), 80°C , 24 h. Generally, E/Z of diene **2** was $>20:1$. But as for diene **2i**, E/Z was 2.5:1. Isolated yields of products are given. EE/EZ of products was determined by ^1H NMR, and unless otherwise stated, the ratio was $>20:1$.

^a ${}^t\text{PrOH}$, 70°C .

^bMeOH, 50°C .

^cButadiene (0.60 mmol).

^dSee Figure 4C for details. Abbreviations: 1,4-NQ, 1,4-naphthoquinone; PMP, para-methoxyphenyl.

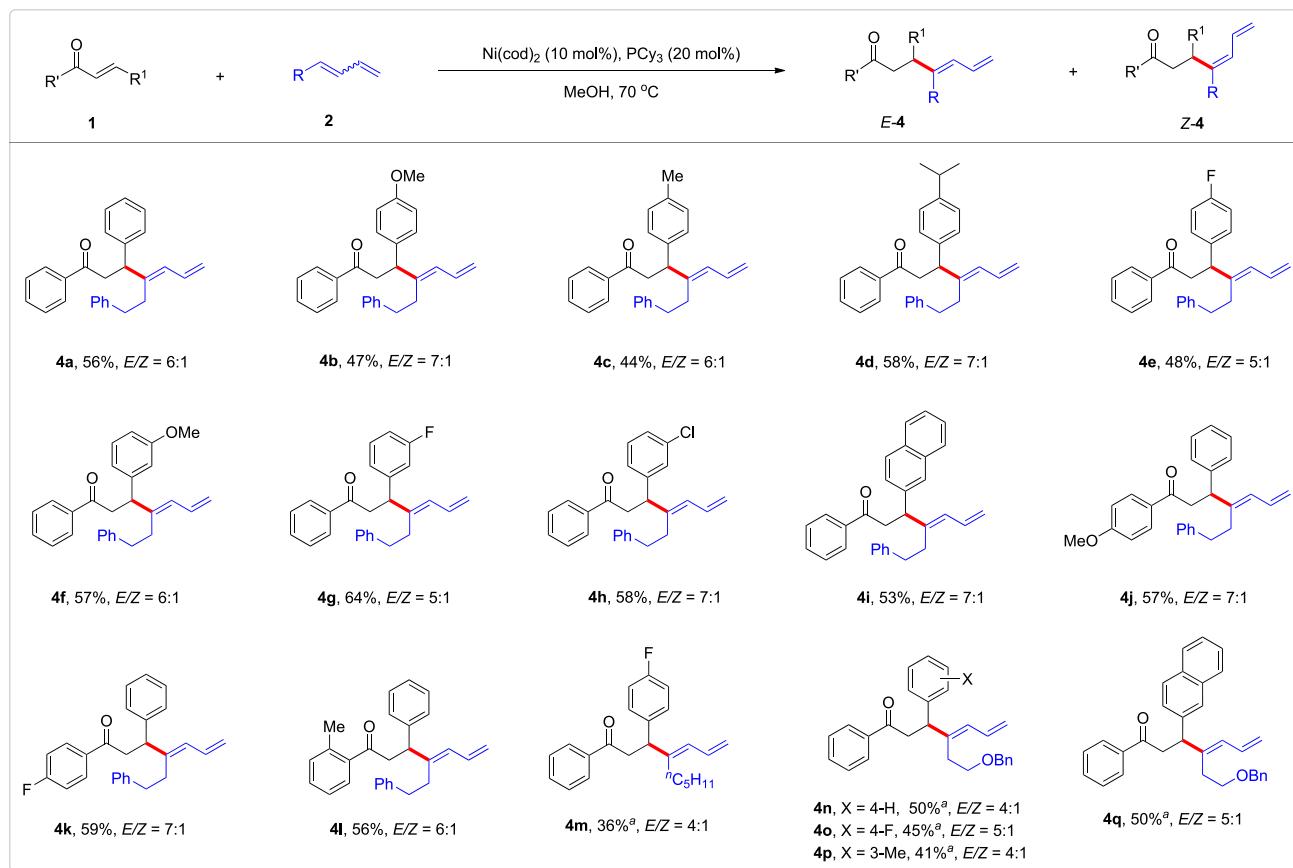


Figure 3. Substrate scope for Ni-catalyzed hydrobivinylation of enones with alkyl-substituted dienes

Conditions: 1 (0.20 mmol), 2 (0.24 mmol), Ni(*cod*)₂ (10 mol %), PCy₃ (20 mol %), MeOH (1.0 mL), 70 °C, 24 h. Generally, E/Z of substrate 2 was around 1:1. But as for pentyl-derived diene, E/Z was >20:1. Isolated yields of products are given, and E/Z was determined by ¹H NMR.

^aE- and Z-products were separable, and the yield of pure E isomer is given.

process. After careful evaluations on solvents, ligands, and temperature (for details, see [supplemental experimental procedures](#) and [Table S1](#)), the best result (4a, 56% yield, 6:1 E/Z) was achieved when the reaction was performed in MeOH at 70 °C with Ni(*cod*)₂/PCy₃ as the catalyst. Under these modified conditions, we also evaluated the generality of this protocol ([Figure 3](#); see [supplemental experimental procedures 4.3](#)). A broad range of aryl-derived chalcones were well tolerated, and the electronic/steric factors of the substituents exerted no significant effect on the outcome (4b–4l). 1-Pentylbutadiene was a viable partner as well, and notably, an E-type product could be separated completely from its Z isomer (4m). When (benzyloxy)ethyl was engaged in the R group, the hydrobivinylation also occurred steadily, offering the target E-products (4n–4q) in moderate yields.

Mechanistic study

To shed light on the reaction mechanism of this regiodivergent hydrobivinylation, a series of control experiments were carried out. [Figures 4A](#) and [4B](#) show the kinetic studies for both transformations. The yield of the stereoisomers (EE: 3aa, ZE: 3aa; E: 4a, Z: 4a) increased over time, but their corresponding ratio (EE/ZE; E/Z) remained constant during the reaction (see [supplemental experimental procedures](#); [Figures S1](#) and [S2](#)). These results demonstrate that no stereoisomerization of C=C bonds was engaged under the investigated conditions. As depicted in [Figure 4C](#),

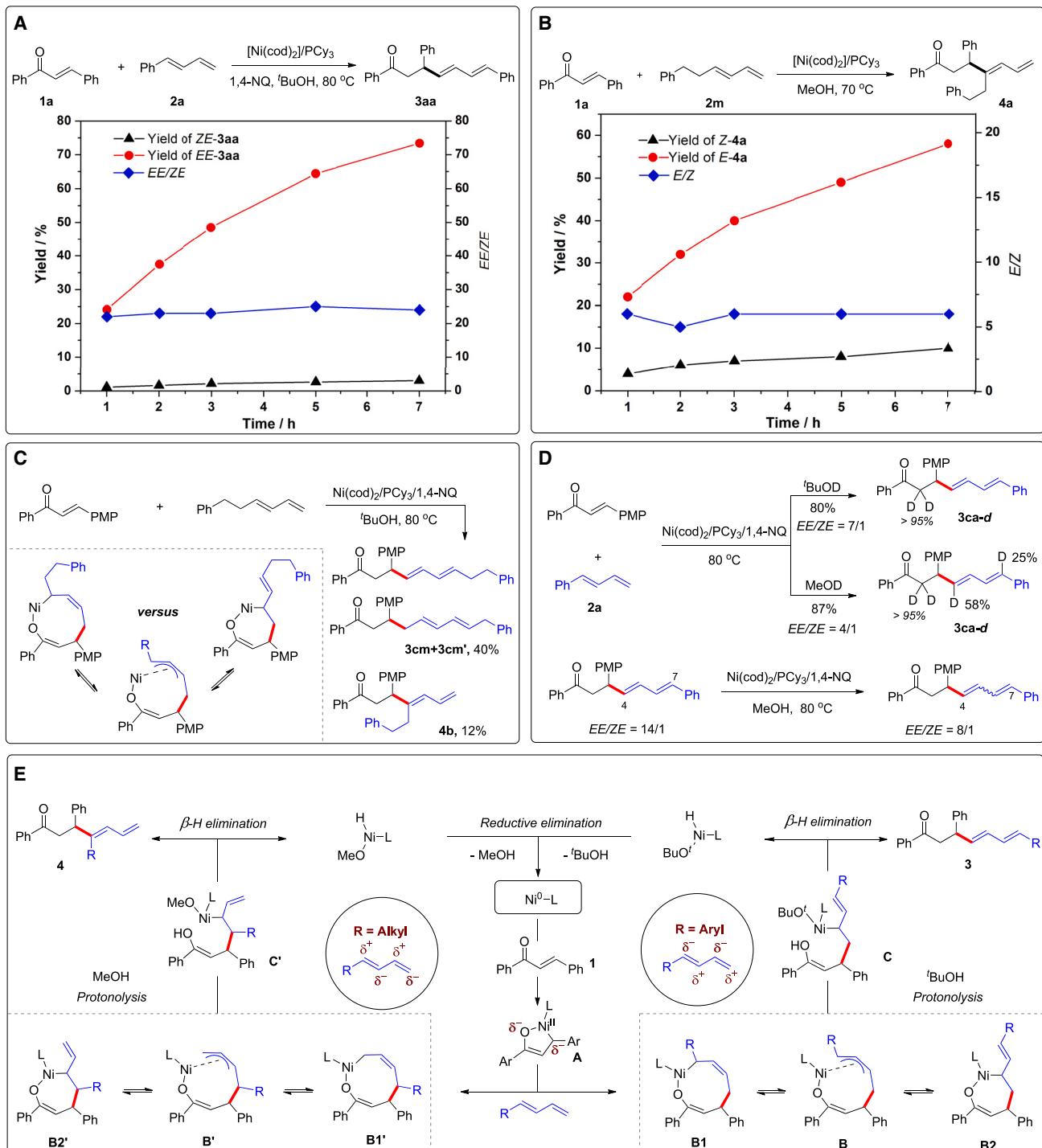


Figure 4. Mechanistic investigations and plausible mechanism

- (A) Kinetic studies on Ni-catalyzed hydrobivinylation of enones.
- (B) Kinetic studies on Ni-catalyzed hydrobivinylation of enones.
- (C) The presence of π -allyl nickelacycle.
- (D) Control experiments.
- (E) Proposed mechanism.

submitting phenylethyl butadiene to the Ni(0)/ PCy_3 /1,4-NQ system resulted in a mixture of products **3cm** and **3cm'** (see [supplemental experimental procedures](#) and [Figure S3](#)). This phenomenon implies that the oxidative cyclometallation likely produces seven- and nine-membered nickelacycles, which can undergo interconversion via π -allylnickel intermediate.

We next conducted deuterium-labeling experiments using $^t\text{BuOD}$ and MeOD as solvents ([Figure 4D](#); see [supplemental experimental procedures](#); [Figures S4](#) and [S5](#)). For nickel catalysis in $^t\text{BuOD}$, H/D exchange was only observed at the methylene position (>95% D) of product **3ca** ($EE/\text{ZE} = 7/1$). In comparison, when varying to MeOD , the deuterium atoms were incorporated into the methylene position (>95% D) and the diene motif (C4, 58% D, and C7, 25% D) of **3ca** ($EE/\text{ZE} = 4/1$). Besides, a treatment of **3ca** ($EE/\text{ZE} > 14/1$) with the standard conditions in MeOH resulted in a decrease of stereoselectivity ([Figure 4D](#)). These results reveal that low-valent nickel can react MeOH to form an undesired Ni-H species, which promotes *E/Z* isomerization of diene products via a domino sequence consisting of migratory insertion of diene into Ni-H and β -hydrogen elimination. In sharp contrast, the formation of Ni-H is hampered in $^t\text{BuOH}$ because of its steric hindrance, which can account for the high stereoselectivity of diene products in $^t\text{BuOH}$. Moreover, the deuterium content in the methylene position of product **3ca** is up to 95% D. This result suggests that the alcohol solvent is also responsible for protonolysis step, followed by enol-keto tautomerization to yield the final product. Therefore, the reactions in toluene and dioxane all failed because the protonolysis step is prohibited.

Based on these mechanistic investigations and previous works,^{61–65} a plausible mechanism of this regiodivergent hydrobivinylation is proposed in [Figure 4E](#). Both processes start with the oxidative cyclometallation of enone **1** with Ni(0) to give oxa-nickelacycle **A**.⁶⁶ Owing to the presence of an aryl group on the C1 position of 1-arylbutadiene, the C2 and C4 positions are more electropositive than the C1 and C3 positions. Therefore, a subsequent migratory insertion between Ni(II) species **A** and 1-arylbutadiene leads to the formation of π -allyl nickelacycle **B**. Replacing the aryl group with an electron-rich alkyl group on 1,3-diene makes the corresponding C2 and C4 positions electronegative. Thus, the migratory insertion can take place at the C1 position to generate species **B'** in the presence of 1-alkylbutadiene **2**. It should be mentioned that both complexes **B** and **B'** might have an equilibrium between seven- and nine-membered rings. Subsequently, the oxa-nickelacycles preferentially undergo protonolysis with alcohols to yield intermediates **C** and **C'**, followed by β -hydrogen elimination to give corresponding products **3** and **4**. An eventual reductive elimination regenerates Ni(0) catalyst and alcohols.

Synthetic transformation

Finally, further transformations of the resulting products were conducted to demonstrate the utility of this protocol ([Figure 5](#); see [supplemental experimental procedures](#) and [supplemental information S24–S26](#)). Under $\text{Ni}(\text{cod})_2/\text{PCy}_3$ catalysis, the diene motif of **3cl** could undergo 1,4-hydroborylation/oxidation to provide allylic alcohol **5a** in 40% yield with exclusive *Z*-stereoselectivity.⁶⁷ Cobalt-catalyzed reductive [2 + 1] cyclization between the terminal C=C bond of **3cl** with CH_2Br_2 proceeded smoothly, leading to cyclopropane **6a** in 81% yield with acceptable diastereoselectivity.⁶⁸ The condensation of the ketone motif and hydroxylamine furnished oxime **7a** in 83% yield.⁶⁹ In the presence of NaBH_4 and CeCl_3 , the chemoselective hydrogenation of ketone took place to produce alcohol **8a** in 82% yield.⁷⁰

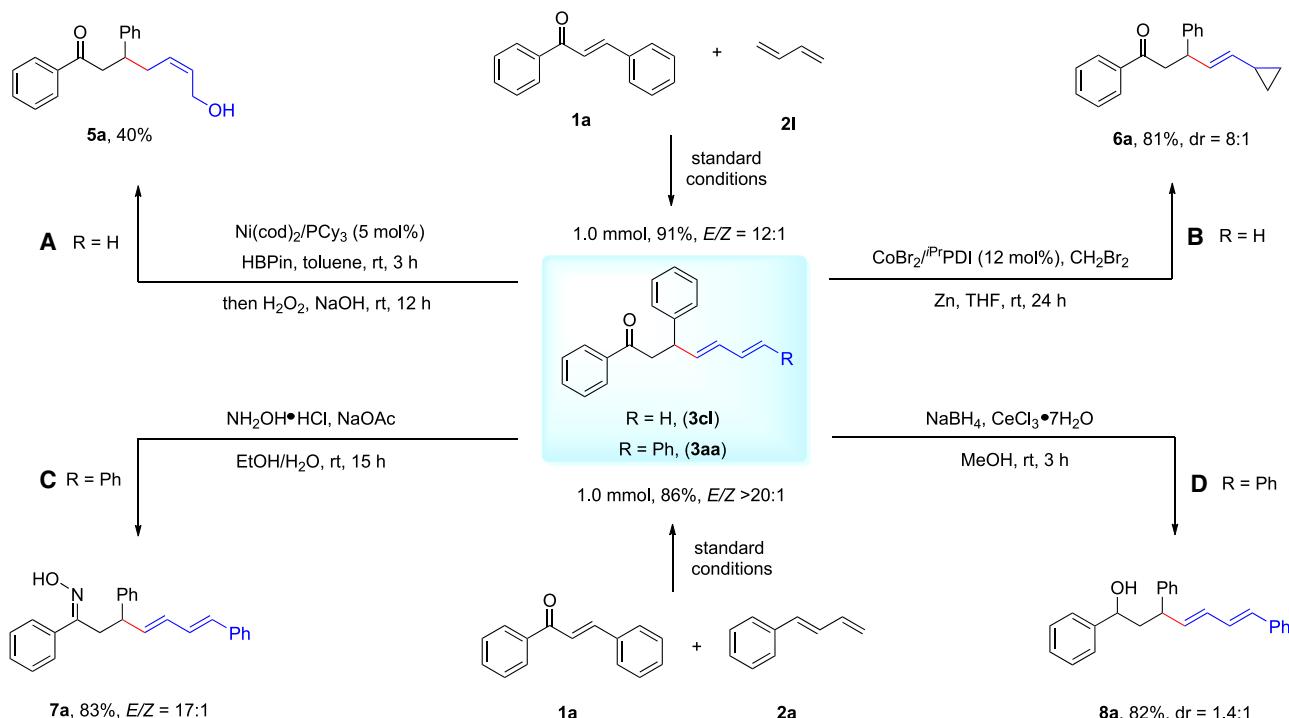


Figure 5. Synthetic transformations

- (A) Ni-catalyzed 1,4-hydroboration of diene product.
- (B) Co-catalyzed cyclopropanation of diene product.
- (C) Condensation of hydroxylamine and ketone motif in diene product.
- (D) Selective hydrogenation of ketone motif in diene product.

In conclusion, we have accomplished an efficient and atom-economical hydroboration of enones with 1,3-dienes under nickel catalysis. With the assistance of PCy_3 and 1,4-NQ, $\text{Ni}(\text{cod})_2$ catalyzed couplings of arylidienes and enones to deliver 1,4-disubstituted dienes in high yields and stereoselectivities. Interestingly, when alkylidienes were used as starting materials, the reaction favorably took place at the C1 position of dienes. This unique regiodivergence was probably attributed to the selective formation of distinct oxa-nickelacycles controlled by the charge distribution of 1,3-diene. The synthetic utility of this protocol was also highlighted by a series of useful elaborations of the products.

EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources and reagents should be directed to and will be fulfilled by the lead contact, Qing-An Chen (qachen@dicp.ac.cn).

Materials availability

Unique and stable reagents generated in this study will be made available on request, but we might require a payment and/or a completed materials transfer agreement if there is potential for commercial application.

Data and code availability

The authors declare that the data supporting the findings of this study are available within the article and the [supplemental information](#). All other data are available from the lead contact upon reasonable request.

Characterization and purification

Commercially available reagents were used without further purification. Other solvents were treated prior to use according to the standard methods. Unless otherwise stated, all reactions were conducted under inert atmosphere using standard Schlenk techniques or in a nitrogen-filled glovebox. ^1H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded at room temperature in CDCl_3 on 400 or 700 MHz instruments with tetramethylsilane (TMS) as the internal standard. Flash column chromatography was performed on silica gel (200–300 mesh). All reactions were monitored by thin-layer chromatography (TLC), NMR, or gas chromatography with flame-ionization detection (GC-FID) analysis. High-resolution mass spectrometry (HRMS) data were obtained with a Micromass HPLC-Q-TOF mass spectrometer (electrospray ionization [ESI]) or an Agilent 6540 Accurate-MS spectrometer (quadrupole time of flight [Q-TOF]).

Description of methods and characterization

Further experimental descriptions, general information, details of the reagents, and all syntheses and characterizations are provided in the [supplemental experimental procedures](#).

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.xcrp.2023.101602>.

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AUTHOR CONTRIBUTIONS

Q.-A.C. conceived and supervised the project. Q.-A.C., Y.L., and Y.-C.H. designed the experiments. Y.L., Y.-C.H., W.-S.Z., S.-H.S., Y.-K.M., and D.-W.J. performed the experiments and analyzed the data. All authors discussed the results and commented on the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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