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Nickel-Catalyzed Chemodivergent Coupling of Acyl Diphenylimines and Butadiene

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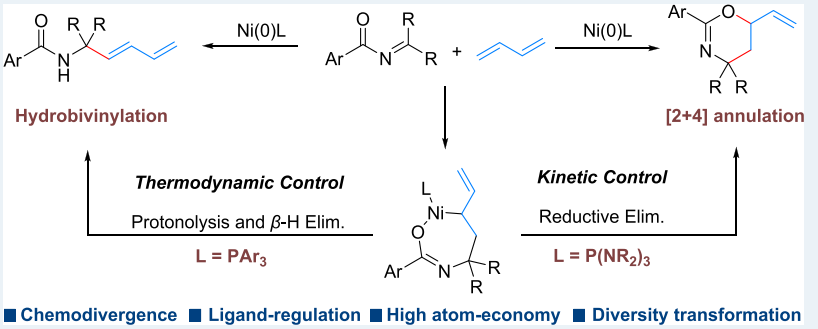

ABSTRACT: Chemodivergent reactions enable the selective synthesis of structurally distinct products from identical starting materials, representing a practical strategy to maximize synthetic efficiency and molecular diversity in organic synthesis. 1,3-Butadiene, one of the most abundant bulk chemicals, inherently tends to undergo Diels–Alder [4 + 2] cycloaddition with electron-deficient dienophiles. However, developing ligand-controlled chemodivergent transformations of butadiene with a less reactive substrate remains a significant challenge. Herein, we report a nickel(0)-catalyzed chemodivergent coupling of acyl imines and butadiene, where the chemoselectivity is precisely regulated by ligand manipulation. Mechanistic studies reveal that the reaction outcome is determined by the relative rates of β-H elimination and reductive elimination from a key seven-membered oxa-nickelacycle intermediate. A triaminophosphine ligand facilitates direct reductive elimination, affording kinetically controlled [2 + 4] annulated oxazine products. In contrast, a triarylphosphine ligand promotes β-H elimination, delivering thermodynamically favored hydrobivinylated dienyl amide products. This protocol features broad substrate scope and high step and atom economy and is amenable to gram-scale synthesis. Its practical utility is demonstrated by diverse postsynthetic derivatizations, as well as the applications in complex molecule synthesis. This work not only expands the synthetic toolbox for butadiene transformations but also provides a paradigm for ligand-controlled chemodivergence by exploiting the reactivity of oxa-nickelacycle species.

KEYWORDS: *acyl imine, butadiene, nickel catalysis, chemoselectivity, ligand control*

INTRODUCTION

Constructing high-value-added chemicals from abundant, low-cost feedstocks via efficient transformations is a core goal in modern synthetic chemistry. As a key C4 synthon with annual production exceeding 10 million tons, butadiene is the simplest conjugated diene with diverse reactivity, making it an ideal platform for the assembly of molecular complexity.[1−6] Among its various transformations, the Diels–Alder cycloaddition is particularly noteworthy, where butadiene usually acts as the diene to undergo efficient [4 + 2] cyclization with typical dienophiles (e.g., enones), enabling one-step construction of complex six-membered cyclic skeletons (Figure 1A).[7−13] Under transition-metal catalysis, however, this inherent tendency can be thoroughly switched. Facilitated by low-valent transition metal catalysts (e.g., Fe,[14−16] Co,[17−22] and Rh[23−27]), an emerging protocol usually allows an oxidative cyclometalation step to occur first and form a seven-membered metallacycle, followed by β-H elimination and subsequent reductive elimination to afford the hydroalkenylated products (Figure 1B). While existing methods prove applicable, it is still highly desirable to develop an alternative catalytic system that exhibits different chemoselectivity.

Nickel complexes serve as important players in oxidative cyclometalation,[28−41] facilitating the formation of nickelacycle

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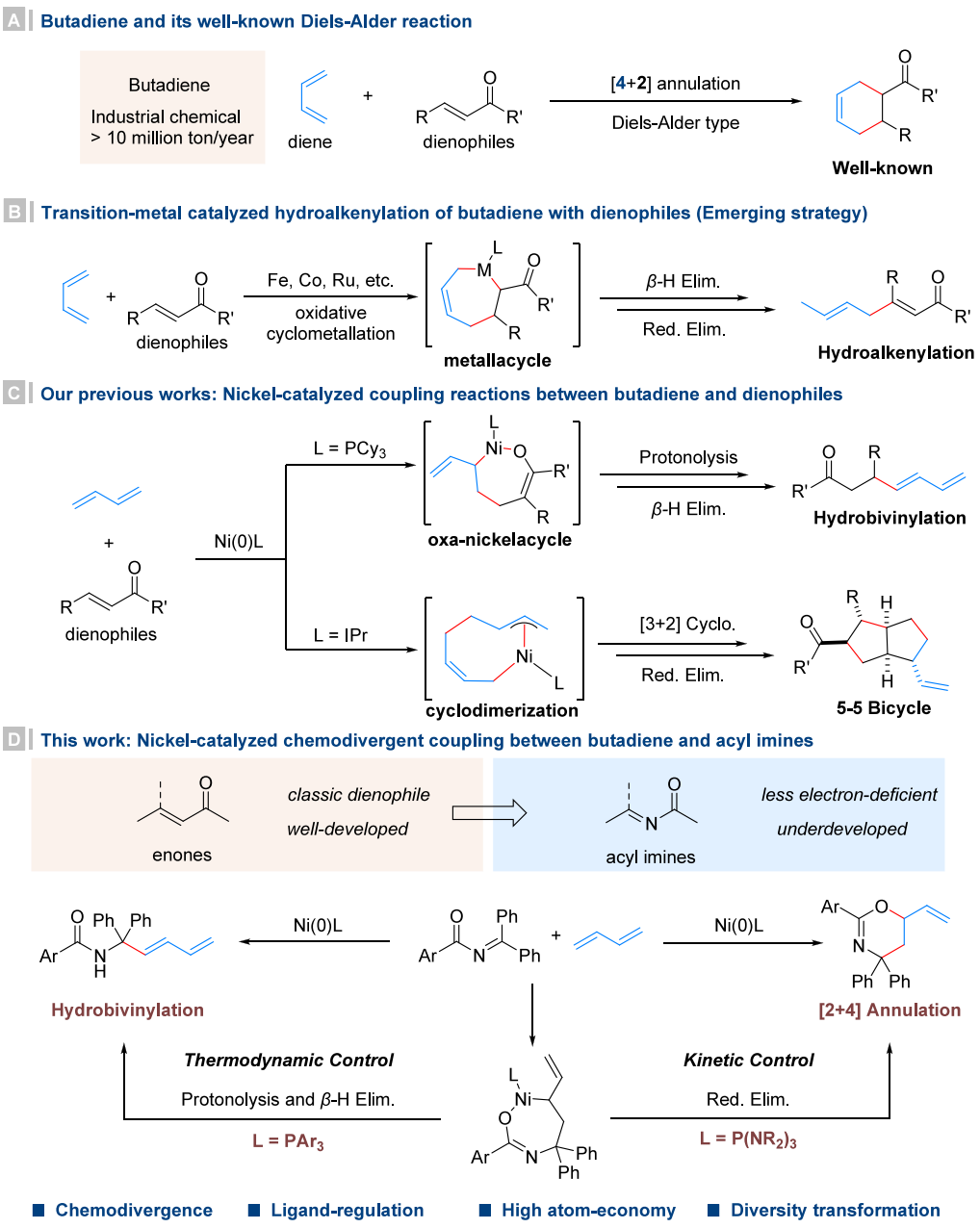

Figure 1. Nickel-catalyzed hydrobivinylation and [2 + 4] annulation between butadiene and acyl imines. (A) Butadiene and its well-known Diels−Alder reaction. (B) Transition-metal-catalyzed hydroalkenylation of butadiene with dienophiles. (C) Our previous works: nickel-catalyzed coupling reactions between butadiene and dienophiles. (D) This work: nickel-catalyzed chemodivergent coupling between butadiene and acyl imines.

intermediates from two distinct alkenes or alkynes.[42−46] Previously, our group has demonstrated that the chemoselectivity of such reactions can be efficiently modulated by modifying nickel catalysis (Figure 1C). For instance, with PCy_3 as a ligand, hydrobivinylation, rather than the aforementioned hydroalkenylation, can be achieved *via* an oxa-nickelacycle intermediate derived from the oxidative cyclometalation of 1,3-butadiene and enones.[47] In contrast, when a bulky *N*-heterocyclic carbene ligand (IPr) is employed, oxidative cyclometalation first occurs between two molecules of 1,3-diene and a Ni(0) species, leading to novel 5-5-bicyclic products.[48] Compared to enones, acyl imines are less electron-deficient and are typically sluggish dienophiles in the traditional Diels−Alder reaction.[49−53] Consequently, the chemistry between acyl imines and dienes remains underdeveloped. Building on this foundation and leveraging our long-standing interest in diene chemistry,[54−58] we report herein a chemodivergent coupling between acyl imines and butadiene enabled by tailored nickel catalysis. The key to success lies in the precise regulation of the relative rates of β-H elimination and reductive elimination from the oxa-nickelacycle intermediate through ligand control. As a result, the reaction selectively delivers either kinetically controlled [2 + 4] annulated oxazine products or thermodynamically controlled dienyl amide products (Figure 1D). Notably, oxazines are a class of valuable six-membered heterocycles widely distributed in biologically active molecules and pharmaceutical

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agents.[59−63] Meanwhile, dienyl amides are versatile building blocks in organic synthesis and can be readily converted into diverse complex products.[64−67] Thus, this atom-economic protocol may offer a robust platform for the rapid construction of functional molecules.

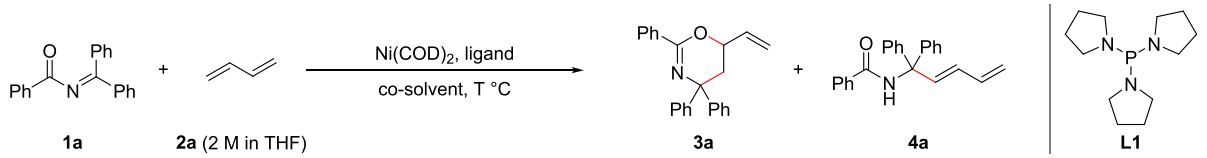
Initially, *N*-(diphenylmethylene)benzamide (**1a**) and 1,3-butadiene (**2a**) were selected as the model substrates to verify our hypothesis (Table 1). In the presence of $Ni(COD)_2$ and PPh_3 and using THF as a solvent, the oxazine **3a** and dienyl amide **4a** were obtained in 11% and 5% yield, respectively (entry 1). Examination of the solvent effects revealed that DMSO could efficiently promote the yield of product **4a** to 71% (entries 2−5). Further ligand screening indicated that triarylphosphine ligands favored the formation of **4a**, where the employment of $P(p\text{-Tol})_3$ could afford **4a** in 89% yield with excellent chemoselectivity (entries 5−7). In contrast, the more electron-rich and sterically hindered trialkyl- or triaminophosphine ligands facilitated the [2 + 4] annulation (entries 9−11). Among these, **L1** proved optimal, producing product **3a** in 54% yield alongside 7% of **4a** (entry 11). Increasing the amount of butadiene, only employing a THF solution of butadiene as the solvent, and lowering the temperature to 50 °C improved the yield of **3a** to 78% (entry 12). When 10 mol % $Ni(COD)_2$ and 20 mol % **L1** were employed, **3a** could be successfully obtained in 96% yield with >20:1 chemoselectivity (entry 13). Control experiments confirmed that both the catalyst $Ni(COD)_2$ and ligand were essential (entries 14−16).

With the optimized reaction conditions in hand, the substrate scope of acyl imines and dienes was investigated (Figure 2). Using **L1** as the ligand, a diverse range of oxazines was delivered through [2 + 4] annulation (condition A). The model product **3a** was isolated in 89% yield, and its structure was confirmed by single-crystal X-ray diffraction (CCDC 2523323). Acyl imines containing methyl and *t*-butyl at the *para*-position of the aromatic ring conjugated with the carbonyl group reacted smoothly, affording the oxazines **3b** and **3c** in 65% and 72% yields, respectively. In comparison, electron-withdrawing groups such as ester, halides, and CF_3 showed relatively less reactivity (**3d**−**3h**). *Meta*- and *ortho*-substituted acyl imines gave the corresponding products **3i**−**3m** in moderate yields (46−82%). This protocol was also compatible with different aromatic groups, such as naphthyl (**3n**), thienyl (**3o**), and furyl (**3p**). Next, different diene substrates were evaluated. Apart from simple 1,3-butadiene, the aromatic dienes were amenable to [2 + 4] annulation with 65 and 61% yields (**3q** and **3r**). The structure of product **3q** was confirmed by single-crystal X-ray diffraction (CCDC 2523330). The alkyl diene was also a suitable substrate, delivering the product **3s** with 56% yield and 8/1 *E*/*Z* selectivity. In addition, 2,3-dimethyl butadiene with high steric hindrance was assembled, affording the product **3t** in 27% yield. Isoprene and myrcene could undergo this reaction to give desired products with regioisomers (**3u**−**3v**).

RESULTS AND DISCUSSION

Subsequently, the substrate scope was explored by altering $P(p\text{-Tol})_3$ as a ligand (condition B). Under the optimized conditions, *N*-(diphenylmethylene)benzamide **1a** was converted to **4a** in 84% isolated yield. A variety of electron-donating groups (methyl, *t*-butyl, and methoxyl) were compatible with this protocol, giving the corresponding products **4b**−**4d** and **4i**−**4j** in 66−93% yields. Additionally, electron-withdrawing substituents, such as ester, F,

Table 1. Optimization for a Chemodivergent Coupling of Acyl Imine and Butadiene[a]



1a **2a** (2 M in THF) **3a** **4a** **L1**

entry	ligand	cosolvent	3a (%)	4a (%)
1	PPh_3	THF	11	5
2	PPh_3	MeOH	0	30
3	PPh_3	EtOH	0	47
4	PPh_3	CH_3CN	38	35
5	PPh_3	DMSO	8	71
6	$P(p\text{-Tol})_3$	DMSO	0	89
7	$P(4\text{-}FC_6H_4)_3$	DMSO	2	74
8	PCy_3	DMSO	29	0
9	$P(NMe_2)_3$	DMSO	46	22
10	$P(NEt_2)_3$	DMSO	47	7
11	**L1**	DMSO	54	7
12[b,c]	**L1**		78	0
13[b,c,d]	**L1**		96	4
14		DMSO	N.D.	N.D.
15[e]	**L1**	DMSO	N.D.	N.D.
16[e]	$P(p\text{-Tol})_3$	DMSO	N.D.	N.D.

[a]Standard conditions: **1a** (0.20 mmol), **2a** (0.40 mmol, 2 M in THF), $Ni(COD)_2$ (5 mol %), ligand (10 mol %), cosolvent (0.5 mL), 60 °C, under N_2. Yields were determined by GC-FID analysis of the crude reaction mixture using mesitylene as an internal standard. [b]**2a** (0.60 mmol, 2 M in THF). [c]50 °C. [d]$Ni(COD)_2$ (10 mol %), **L1** (20 mol %). [e]No $Ni(COD)_2$.

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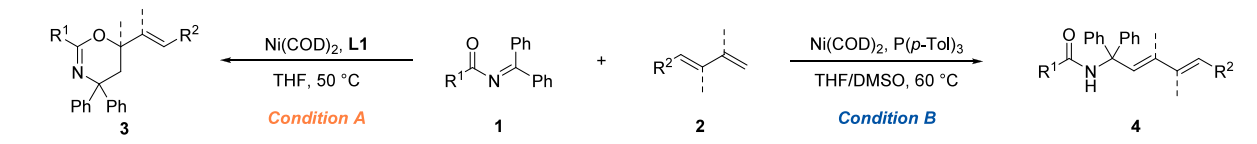
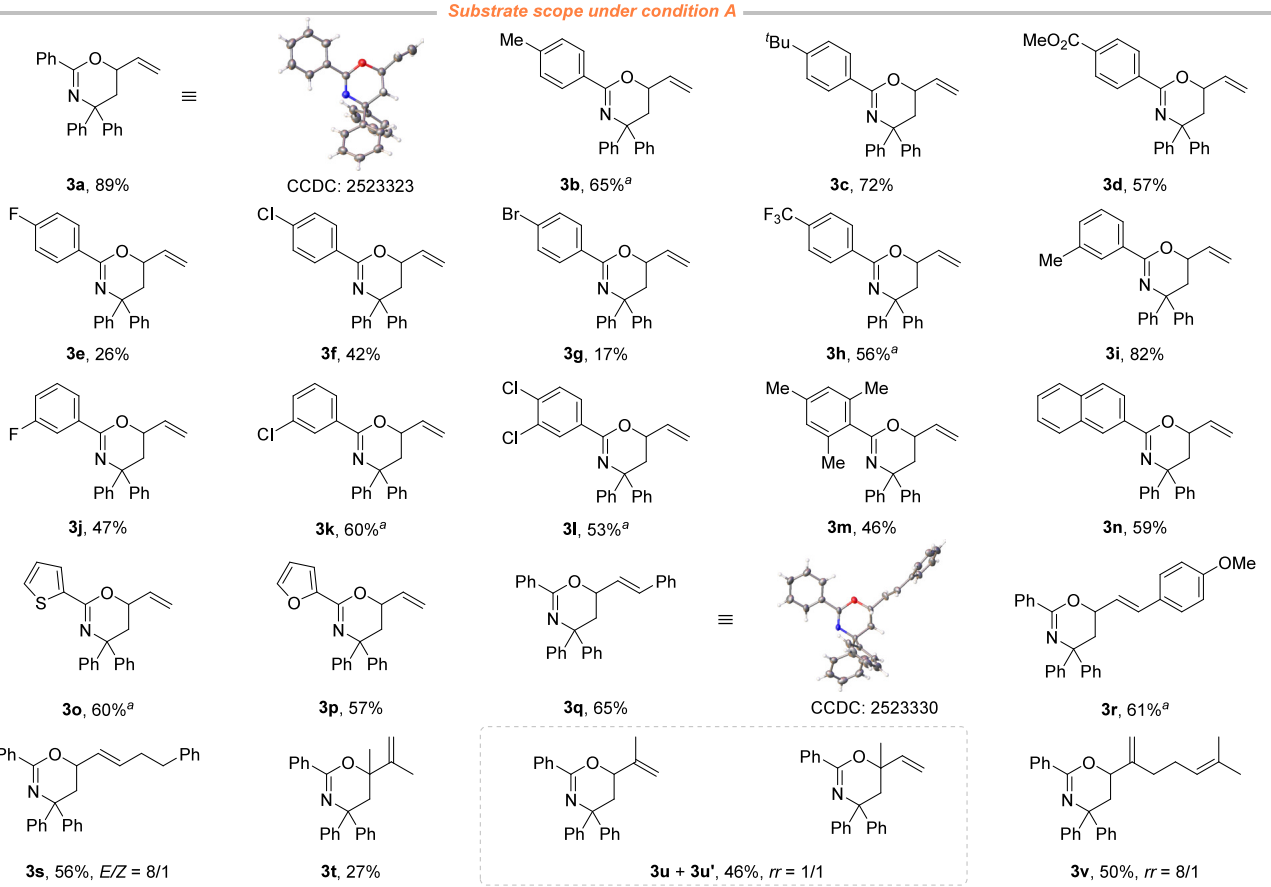


Substrate scope under condition A



Substrate scope under condition B

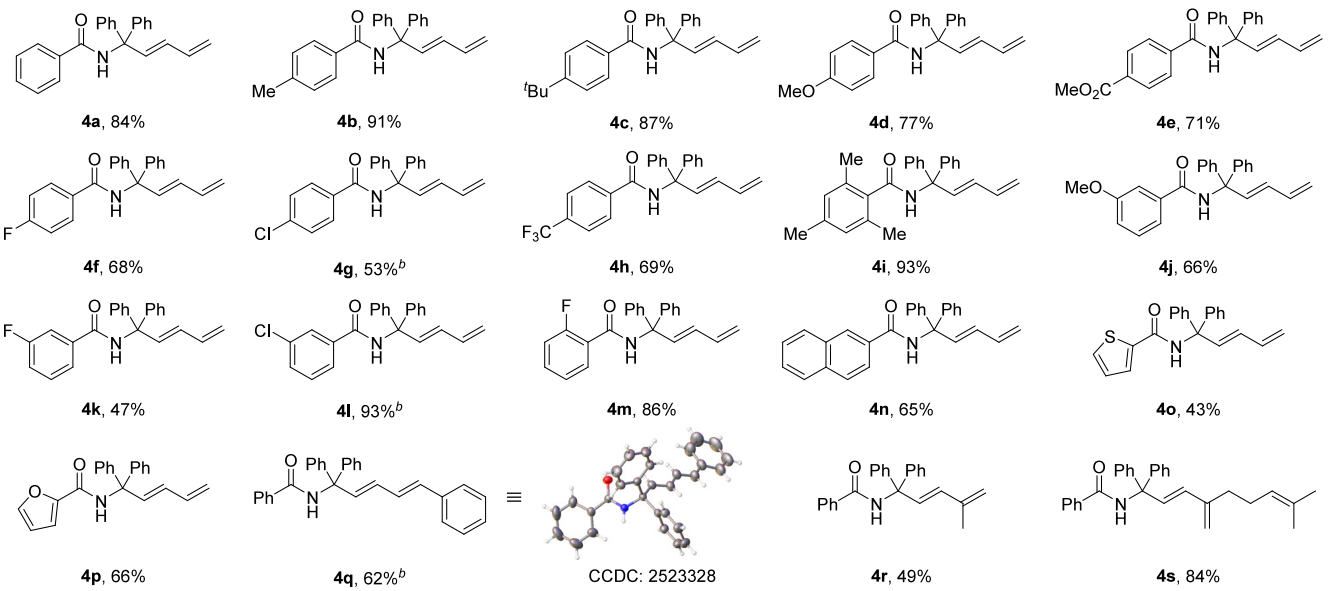


Figure 2. Substrate scope of acyl imines and dienes. Condition A: **1** (0.20 mmol), **2** (0.60 mmol, 2 M in THF), $Ni(COD)_2$ (10 mol %), **L1** (20 mol %), 50 °C, 18 h, under N_2. Condition B: **1** (0.20 mmol), **2** (0.40 mmol, 2 M in THF), $Ni(COD)_2$ (5 mol %), $P(p\text{-Tol})_3$ (10 mol %), DMSO (0.5 mL), 60 °C, 18 h, under N_2. Isolated yields were given. [a]48 h. [b]MeOH (10 μL).

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Cl, and CF_3, were all amenable to the current reaction conditions, generating **4e**−**4h** and **4k**−**4m** in 47−93% yields. This protocol also accommodated different aromatic groups, such as naphthyl, thienyl, and furyl, affording **4n**−**4p** in 43−66% yields. The phenyl diene was incorporated in the hydrobivinylation reaction as well, delivering **4q** in 62% yield. The structure of product **4q** was confirmed by single-crystal X-ray diffraction (CCDC 2523328). Isoprene and myrcene could also undergo this reaction in 49% and 84% yields, respectively (**4r** and **4s**). For less reactive substrates (**4g**, **4l**, and **4q**), the addition of methanol can significantly improve the yields of dienyl amide products (53−93%), presumably by facilitating the ring-opening process of the oxa-nickelacycle intermediate via protonolysis (see the mechanism section for details). In addition, no telomerization product between MeOH and 1,3-butadiene was observed in these cases (see page S24 in the Supporting Information).[68−69] Notably, the present protocol features good stereoselective control, affording all dienyl amide products with an *E*/*Z* ratio >20:1.[70]

To shed light on the reaction mechanism of this chemodivergent coupling, a series of experiments were carried out (Figure 3). Kinetic experiments were conducted by using model substrates under two conditions. Under the condition A, the yield of **3a** increased over time, while the yield of **4a** remained low throughout the reaction (Figure 3A). Under the condition B, product **3a** formed more rapidly in the initial stage but was gradually consumed over 4 h. Meanwhile, a steady increase was observed in the formation of product **4a** (Figure 3B). The influence of temperature on reaction selectivity was subsequently investigated using **L1** or $P(p\text{-Tol})_3$ (Figure 3C,D). When **L1** was employed as the ligand, 50 °C proved optimal for the formation of **3a** and the yield of **4a** increased gradually as the temperature rose. With $P(p\text{-Tol})_3$ as the ligand, low temperatures also favored the generation of **3a**, whereas higher temperatures predominantly afforded **4a**. These findings all indicate that oxazine product **3a** is the kinetic product, favored by the electron-rich, bulky ligand **L1** at lower temperatures, while the dienyl amide **4a** is the thermodynamic product, promoted by the $P(p\text{-Tol})_3$ ligand at elevated temperatures.

To further explore the mechanism, transformation experiments between **3a** and **4a** were performed (Figure 3E). Initial control experiments established that **3a** and **4a** do not interconvert under condition A or condition B (eqs 1) and (2). However, when **3a** was introduced into a reaction mixture containing **1d** and **2a** in the presence of $Ni(COD)_2$ and $P(p\text{-Tol})_3$, two distinct hydrobivinylated products **4a** and **4d** were isolated (eq 3). To gain deeper mechanistic insight into this transformation, the effects of various additives were examined (eq 4). Under $Ni(COD)_2/P(p\text{-Tol})_3$ catalysis, the addition of 10 mol % **1a** afforded **4a** in 66% yield, whereas only 2% yield was obtained in the presence of **L1** (entry 1). In comparison, no conversion was observed when 1,3-butadiene **2a** was used as an additive (entry 2). The dienyl amide product itself could also promote this transformation (entry 3). Furthermore, a catalytic amount of methanol efficiently promoted the formation of **4a** in 90% yield with $P(p\text{-Tol})_3$ as the ligand, but only 29% yield was observed with **L1** (entry 4). These results suggest that a protic additive may facilitate protonolysis of **3a**. We therefore speculated that decomposition of *N*-(diphenylmethylene)-benzamide may release free benzamide, which could act as an initial promoter under the actual reaction conditions. Indeed, adding 10 mol % benzamide increased the yield of **4a** to 79% (entry 5). We also conducted a decomposition experiment under the standard conditions, which afforded free benzamide in 11% yield (eq 5).

Based on these mechanistic investigations, a plausible mechanism for the nickel-catalyzed chemodivergent coupling of acyl imines with butadiene is proposed in Figure 3F. Both pathways begin with oxidative cyclometalation of acyl imine **1a** and $Ni(COD)_2$ to form oxa-nickelacycle **A**. A subsequent migratory insertion between Ni(II) species **A** and butadiene leads to the formation of allyl nickelacycle **B**. When the bulky ligand **L1** is employed, allyl nickelacycle **B** undergoes direct reductive elimination, delivering the kinetic product **3a**. In contrast, switching to $P(p\text{-Tol})_3$ directs the pathway toward protonolysis of intermediate **B** prior to reductive elimination, generating the more stable thermodynamic product **4a**. Notably, under $Ni(COD)_2/P(p\text{-Tol})_3$ catalysis, the kinetic product **3a** can reinsert into the nickel catalyst to regenerate allyl nickelacycle **B**, ultimately leading to the thermodynamic product **4a**. Conversely, product **4a** does not undergo the reverse reinsertion to revert to **3a.**

To illustrate the application of this nickel-catalyzed chemodivergent coupling reaction, scale-up reactions at a 5 mmol scale were performed, delivering 1.12 g of **3a** in 66% yield and 1.29 g of **4a** in 76% yield (Figure 4A). Then, various transformations of two types of products were performed (Figure 4B). Epoxidation of **3r** by *m*-CPBA delivered epoxide **5** in 77% yield (*dr* 2/1). Using the Hoveyda−Grubbs catalyst (HG2), the olefin metathesis of **3a** with phenyl acrylate yielded compound **6**. In the absence of an external alkene, an olefin metathesis of two molecules of **3a** at 70 °C provided dimeric compound **7** in 44% yield. Bromomethoxylation product **8** could be accessed from alkene **3a** in the presence of NBS and MeOH with 68% yield. Interestingly, the oxazine product **9** could be formed via two sequential Alder−ene reactions between oxazine **3a** and benzyne precursor 2-(trimethylsilyl)-phenyl trifluoromethanesulfonate (see page S28 in the Supporting Information for the mechanism).[71] Furthermore, the hydroselenation product **10** was obtained in 46% yield from diene **4a** and PhSeSePh under nickel catalysis. Compound **4a** could undergo [4 + 2] cycloaddition with the benzyne precursor to afford ring-fused product **11** in 54% yield. Through a bromonium ion-mediated intramolecular nucleophilic cyclization, oxazoline product **12** was obtained in 74% yield with NBS. Similarly, epoxidation of dienyl amide **4a** with m-CPBA followed by subsequent intramolecular nucleophilic attack generated product **13** in 67% yield (for the proposed mechanism, see pages S29−S30 in the Supporting Information). Moreover, when an excess of *m*-CPBA was employed, the oxazoline product underwent epoxidation, affording highly oxygenated products **15** and **15'** in 62% yield. Additionally, the oxazoline products **13** and **15** could be further functionalized *via* esterification to afford highly functionalized compounds **14** and **16**. The structures of these complicated compounds **6**, **8**, **9**, **11**, **12**, and **16** were further confirmed through single-crystal X-ray crystallography (CCDC 2523332, 2523329, 2523331, 2523337, 2523334, and 2523336).

■ CONCLUSIONS

In summary, we have developed a practical and efficient nickel-catalyzed chemodivergent coupling strategy for acyl imines and butadiene, achieving selective synthesis of two distinct classes of high-value products through precise ligand control. The key

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Figure 3. Mechanism studies. (A) Kinetic studies under the condition A. (B) Kinetic studies under the condition B. (C) Investigation of reaction temperature with **L1**. (D) Investigation of reaction temperature with P(p-Tol)$_3$. (E) Transformation studies. (F) Possible mechanism.

innovation lies in regulating the reactivity of the seven-membered oxa-nickelacycle intermediate: triaminophosphine ligand **L1** promotes reductive elimination to afford [2 + 4] annulated oxazines (kinetic products), while the triarylphosphine ligand facilitates protonolysis and β-H elimination to generate hydrobivinylated dienyl amides (thermodynamic products). Mechanistic investigations confirm the kinetic-thermodynamic control of the reaction, with the oxazine products capable of reverting to the thermodynamic dienyl amides under Ni catalysis. This protocol overcomes the inherent Diels−Alder reactivity of butadiene to enable chemodivergent transformation with less electron-deficient acyl

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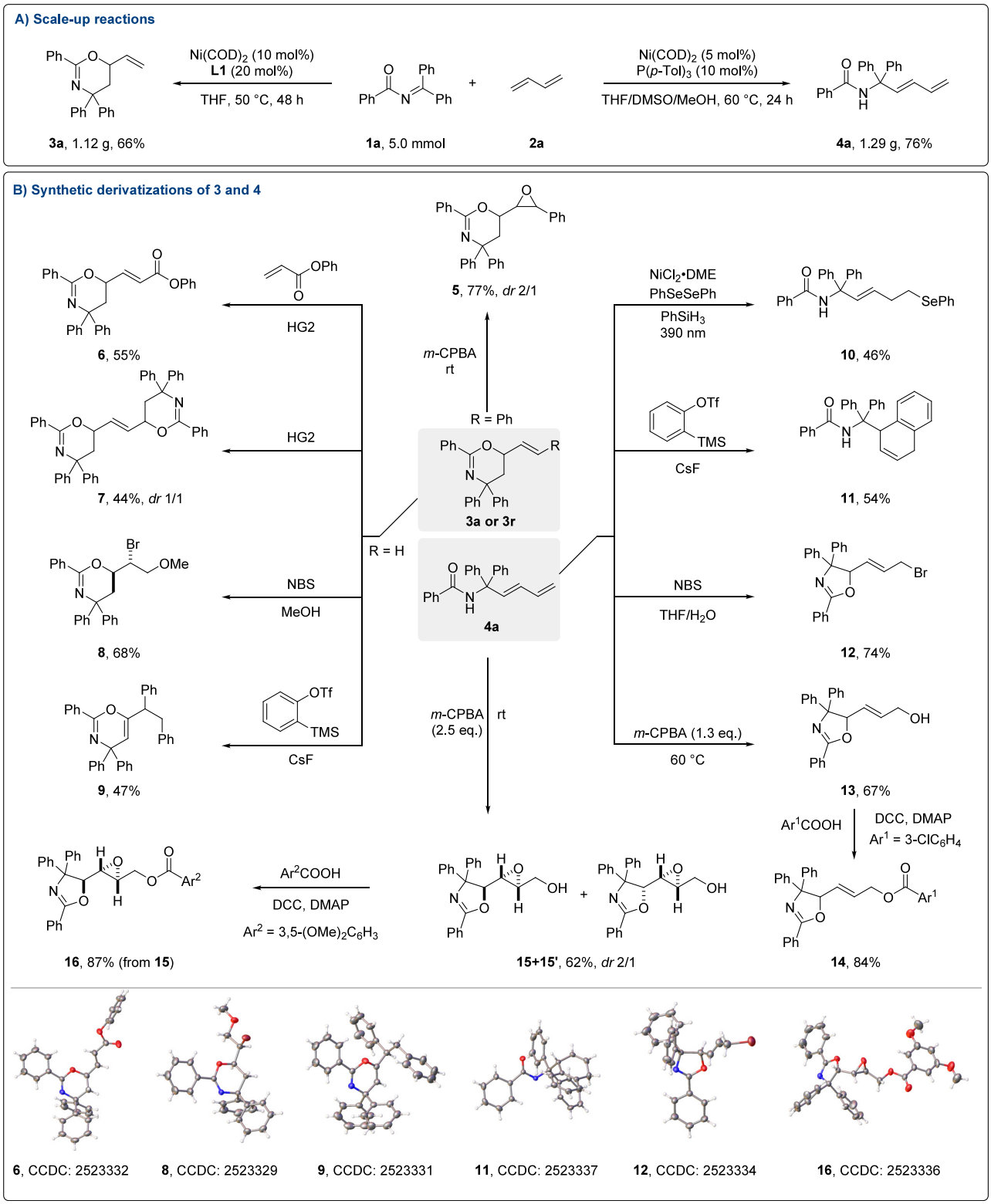

Figure 4. Scale-up reactions and synthetic derivatizations. (A) Scale-up reactions. (B) Synthetic derivatizations of **3** and **4**.

imines. It achieves high step and atom economy without preactivation of substrates. Gram-scale synthesis and diverse postsynthetic derivatizations further highlight its potential in organic synthesis. We anticipate that this chemodivergent strategy will inspire the development of more ligand-regulated transformations of bulk dienes, contributing to the efficient synthesis of complex molecules in pharmaceutical and material chemistry.

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EXPERIMENTAL SECTION

All information regarding the materials and methods used in this work is listed in the Supporting Information.

General Procedures for the Synthesis of [2 + 4] Annulated Oxazines

To an oven-dried 4 mL vial with a PTFE-coated stirring bar were added **1** (0.20 mmol), **2a** (0.60 mmol, 2 M in THF), $Ni(COD)_2$ (10 mol %), and **L1** (20 mol %) in the nitrogen glovebox. The reaction mixture was stirred at 50 °C for 18−48 h. After the reaction was completed, the reaction mixture was purified by column chromatography on silica gel using petroleum ether and ethyl acetate to afford the corresponding product **3.**

General Procedures for the Synthesis of Hydrobivinylated Dienyl Amides

To an oven-dried 4 mL vial with a PTFE-coated stirring bar were added **1** (0.20 mmol), **2** (0.40 mmol), $Ni(COD)_2$ (5 mol %), P(*p*-Tol)$_3$ (10 mol %), and DMSO (0.5 mL) in the nitrogen glovebox. The reaction mixture was stirred at 60 °C for 18 h. After the reaction was completed, the reaction mixture was purified by column chromatography on silica gel using petroleum ether and ethyl acetate to afford the corresponding product **4**.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.6c01844.

Experimental procedures, characterization data, and NMR spectra (PDF)

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Author contributions

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

Notes

The authors declare no competing financial interest.

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