Ni-Catalyzed Enantioselective Three-Component Reductive Alkylacylation of Enamides

Jichao Xiao,[1] Tingting Jia,[1] Shuang Chen,[1] Mengxiao Pan,[1] Xingwei Li[1,2]*

[1] School of Chemistry and Chemical Engineering, Shaanxi Normal University, Xi'an, Shanxi 710062

[2] Institute of Molecular Science and Engineering, Institute of Frontier and Interdisciplinary Sciences, Shandong University, Qingdao, Shandong 266237

*Corresponding Author(s): Xingwei Li: Email Address: lixw@snnu.edu.cn

Abstract

Chiral alpha-amino ketones have found extensive applications as functional molecules. A nickel-catalyzed, enantioselective, and fully intermolecular three-component 1,2-alkylacylation of *N*-acyl enamides has been realized with tertiary alkyl bromides and carboxylic acid-derived electrophiles as the coupling reagents. This reductive coupling strategy is operationally simple, exhibiting broad substrate scope and excellent functional group tolerance using readily available starting materials and allowing rapid access to structurally complex α-amino ketone derivatives in high enantioselectivity. A suitable chiral biimidazoline ligand together with additional chelation of the amide carbonyl group in a Ni alkyl intermediate facilitates the enantioselective control by suppressing the background reaction, accounting for the excellent enantioselectivity. Mechanistic studies indicated intermediacy of radical species.

Keywords

chiral alpha-amino ketone • symmetric radical chemistry • cross-electrophile coupling • nickel • three-component alkylacylation

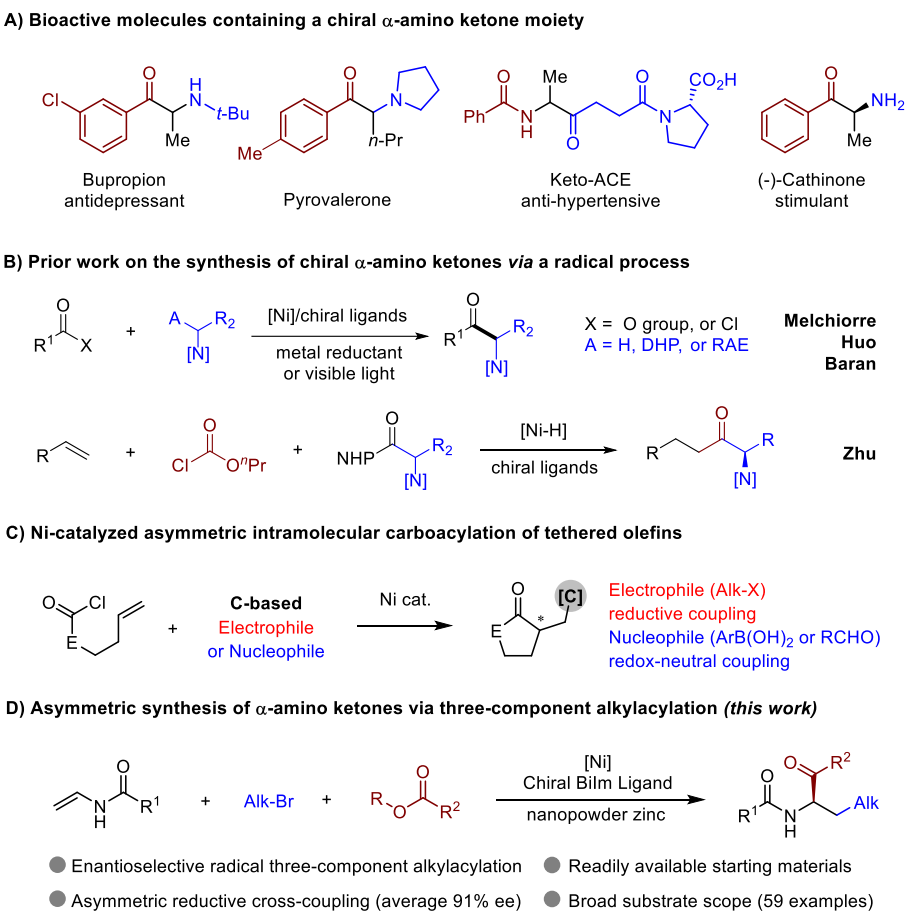
Introduction

Chiral α-amino ketones are a key structural motif in various bioactive molecules and pharmaceuticals, and they are also valuable building blocks in synthetic chemistry (Scheme **1A**).[1-4] Accordingly, the development of efficient asymmetric approaches for synthesis of chiral α-amino ketones has been a long-lasting pursuit in organic chemistry.[5-8] Reported classic synthetic routes typically involve nucleophilic amination of α-halogenated ketones, electrophilic amination of suitable enolates, and homologation of chiral α-amino acids.[9-19] Nevertheless, these two-electron-based strategies often suffer from limitations, such as poor availability of the nitrogen source, racemic synthesis or racemization of product, requirement of multiple steps, and/or harsh reaction conditions. Owing to the unique properties of nickel catalysts, recently, the groups of Melchiorre,[20] Huo,[21]

and Baran[22] elegantly developed nickel-catalyzed asymmetric synthesis of enantio-enriched α-amino ketones via the coupling of an amine-containing reagent and an electrophilic acyl source (Scheme **1B**). Meanwhile, the Zhu group reported synthesis of α-amino ketones via reductive coupling of olefins with a carbonyl source and a redox-active ester.[23] Despite the advances, there remains an increasing demand for the development of efficient and concise protocols that permit a rapid assembly of α-amino ketones with high levels of complexity, modularity, and diversity from readily available commodities.

On the other hand, nickel-catalyzed asymmetric functionalization of olefins stands out as a prominent strategy toward facile construction of chiral complex molecules owing to the unique roles of Ni catalysts that readily participate in single electron transfer (SET) and reductive elimination.[24-26] Consequently, catalytic three-component radical difunctionalizations of alkenes represent a powerful strategy for rapid enhancement of molecular complexity by simultaneously forging two functionalities in one single operation, thus enriching the synthetic toolbox to access synthetic building blocks, medicines, and bioactive molecules.[27-36] However, enantioselective control of the target stereogenic center remains a formidable challenge. Impressive progress has been made in nickel-catalyzed asymmetric radical three-component difunctionalizations of alkenes. These coupling systems include diarylation,[37] alkyl-arylation,[38-44] alkyl-alkenylation,[45,46] aryl-alkylation,[47] and sulfonyl-carbolation[48,49] under redox-neutral or reductive conditions, where organohalides serve as the terminal (the 3rd) component.[50,51] However, as an important class of dicarbofunctionalizaiton, asymmetric carboacylation reactions have received less attention and are restricted to two categories of intramolecular couplings. A carbamoyl halide-tethered olefin may react with a carbon terminating reagent via cyclization and C-C coupling under redox-neutral or reductive conditions (Scheme **1C**).[52-61] Alternatively, an aryl iodide-tethered olefin may react with an acylating reagent to fulfil the similar type of reaction.[62] More recently, the groups of Chu,[63] Stanley,[64] Wang,[65] Yuan[66] and other[67-71] have developed various methods for fully three-component *racemic* carboacylation of olefins. In most cases, a nickel acyl species captured a secondary radical species to deliver the final product through reductive elimination. However, the exceptionally high instability and reactivity of open-shell radical intermediates poses significant challenges in enantioselective control in these three-component reactions in general.[72-74] In addition, the carbon radical intermediate may also undergo uncatalyzed C-C coupling with a reactive acylating regent, leading to a background reaction. To the best of our knowledge, enantioselective fully three-component 1,2-alkylacylation of alkenes remains unknown. Therefore, the development of 1,2-alkylacylation reactions toward asymmetric synthesis of α-amino ketones will be an intriguing but challenging task.

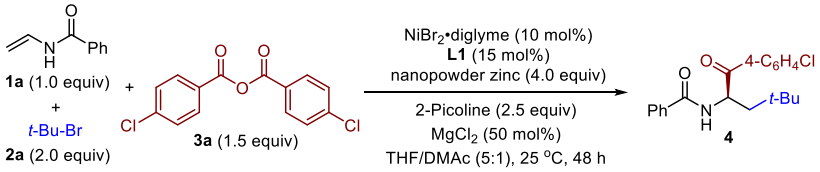
Herein, we now describe modular synthesis of enantio-enriched α-amino ketones via an efficient nickel-catalyzed enantioselective 1,2-alkylacylation of enamides with an alkyl bromide and an acylating regent, which demonstrates an example of the integration of fully three-component carboacylation of alkenes with a high level of enantioselectivity for the first time (Scheme **1D**).



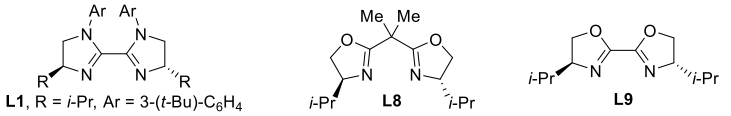
Results and Discussion

By taking advantage of the chelating effect during the formation of an organonickel intermediate, our initial investigation of asymmetric carboacylation was conducted using *N*-vinylbenzamide (**1a**) as the olefin and 2-bromo-2-methylpropane (**2a**) and 4-chlorobenzoic anhydride (**3a**) as the coupling components (Table **1**). Through systematic investigation of the reaction parameters, the final optimal conditions were found to comprise a chiral biimidazoline (BiIm) ligand **L1**, $NiBr_2$•diglyme as a precatalyst, nanopowder zinc (40−60 nm) as a reductant, and $MgCl_2$ and 2-picoline as additives in THF/DMAc (5:1, 0.1 M) at room temperature for 48 h, from which conditions the α-amino ketone **4** was isolated in 81% yield and 92% ee (entry 1). A ligand screen revealed that chiral BiIm ligands (**L1**-**L7**, entries 1-7) were consistently superior to other oxazoline-based ligands (**L8**-**L11**, entries 8-11). BiIm skeletons with other alkyl chains or other aryl protecting groups (**L2**−**L7**) worked with comparable efficiency but with slightly decreased enantioselectivity, while Box ligand (**L8**), BiOx (**L9**), Pyrox (**L10**), and Pybox (**L11**) all gave sluggish reactions. Control experiments indicated that the nickel catalyst, ligand, nanopowder zinc, magnesium chloride, 2-picoline and the solvent (entries 13−19) each played a pivotal role in this transformation. The racemic α-amino ketone product can still be obtained in low yield in the absence of the ligand **L1** or nickel catalyst (entries 13 and 14), indicating a

Table 1. Optimization of Reaction Conditions



Entry	Deviation from standard conditions	Yield (%)[a]	ee (%)[b]
1	none	82	92
2	**L2** instead of **L1**	81	91
3	**L3** instead of **L1**	75	87
4	**L4** instead of **L1**	77	87
5	**L5** instead of **L1**	65	77
6	**L6** instead of **L1**	70	79
7	**L7** instead of **L1**	23	21
8	**L8** instead of **L1**	43	12
9	**L9** instead of **L1**	67	31
10	**L10** instead of **L1**	32	15
11	**L11** instead of **L1**	13	45
12	zinc instead of nanopowder zinc	53	91
13	no **L1**	26	0
14	no $NiBr_2$•diglyme	21	0
15	no nanopowder zinc	0	---
16	no $MgCl_2$	18	93
17	no 2-Picoline	44	92
18	THF only	38	72
19	DMAC only	85	89

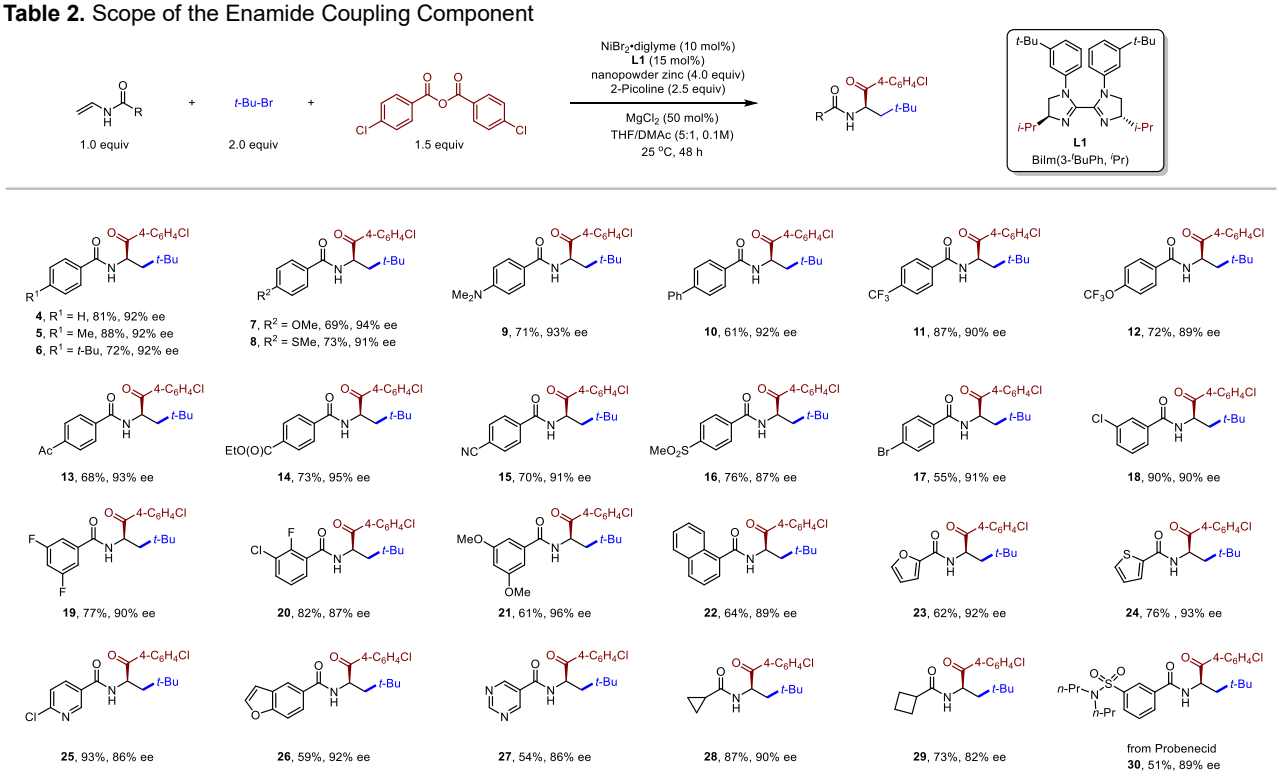


Optimal reaction conditions: enamide (**1a**, 0.1 mmol), alkyl bromide (0.2 mmol), acid anhydride (**3a**, 0.15 mmol), $NiBr_2$•diglyme (10 mol%), **L1** (15 mol%), picoline, $MgCl_2$, nanopowder Zn (4 equiv), and DMAc/THF was stirred at 25 °C for 48 h. Isolated yield. The ee was determined using HPLC with a chiral stationary phase.

background reaction. Of note, the particle size of the Zn reductant is vital; nanopowder zinc can dramatically improve the efficiency when compared with other reductants (entry 12, see the Supporting Information for more information). Furthermore, omitting the $MgCl_2$ and 2-picoline additives led to a substantial decrease of the reaction efficiency, albeit with no erosion of the enantioselectivity (entries 16 and 17). Screening of the solvent indicated that comparable results can be obtained in a single

DMAc solvent, but introduction of THF further improved the enantioselectivity (entries 18 and 19, see the Supporting Information for more information).

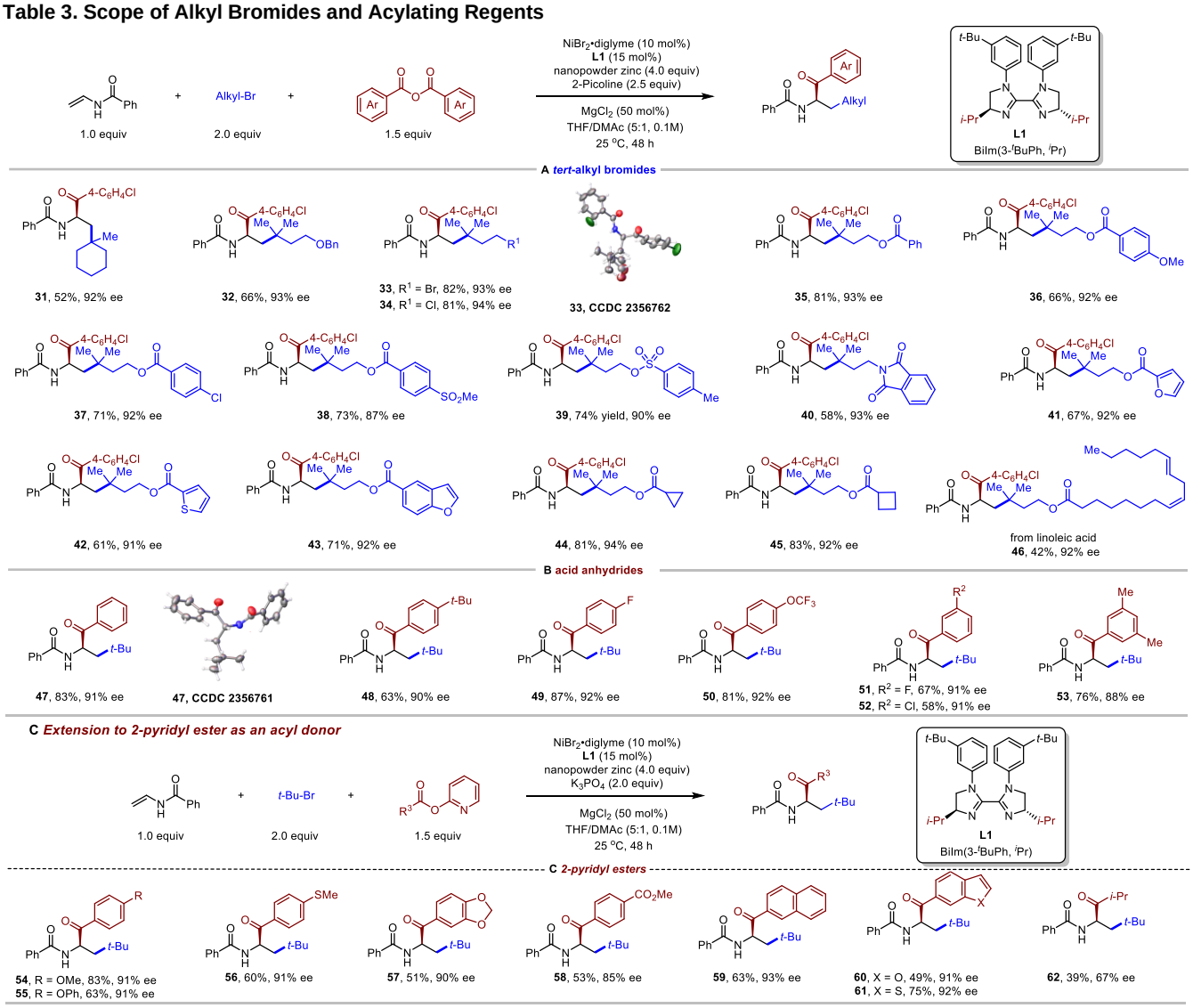
Table 2. Scope of the Enamide Coupling Component



Reaction Conditions: enamide (0.1 mmol), alkyl bromide (0.2 mmol), acid anhydride (0.15 mmol), $NiBr_2$•diglyme (10 mol%), Ligand **L1** (15 mol%), picoline, $MgCl_2$, and nanopowder Zn (4 equiv) in DMAc/THF was stirred at 25 °C for 48 h. Isolated yield. The ee was determined using HPLC with a chiral stationary phase.

With the optimized conditions in hand, we next investigated the generality of this three-component carboacylation. As illustrated in Table **2**, vinyl amides bearing a wide variety of substituents delivered the desired products in good to excellent yields with good to excellent enantioselectivities. Enamides with an electron-donating (**5**–**9** and **21**) or -withdrawing (**10**–**20** and **30**) substituent at different positions of the benzene ring coupled efficiently, affording the α-amino ketones in 55−90% yields and 87−94% ee. Such mild reaction conditions allowed the use of a diverse spectrum of functional groups, including ether (**7** and **12**), thiolether (**8**), amine (**9**), ketone (**13**), ester (**14**), nitrile (**15**), sulfone (**16**), and aminosulfonyl (**30**). Notably, some potentially reactive functionality such as aryl bromide (**17**) and chlorides (**18**, **20** and **25**) were left intact, offering opportunities for further useful transformations. A series of heterocycles including furan (**23**), thiophene (**24**), pyridine (**25**), benzofuran (**26**), and pyrimidine (**27**), which are frequently found in pharmaceutically active molecules, were also compatible. To our delight, cycloalkyl-substituted amides were also viable (**28** and **29**), albeit with attenuated enantioselectivity (82-90% ee). In contrast, 1,1-and 1,2-disubstituted internal olefins turned out to inapplicable under the standard conditions (see the Supporting Information for unsuccessful olefins).

Table 3. Scope of Alkyl Bromides and Acylating Regents

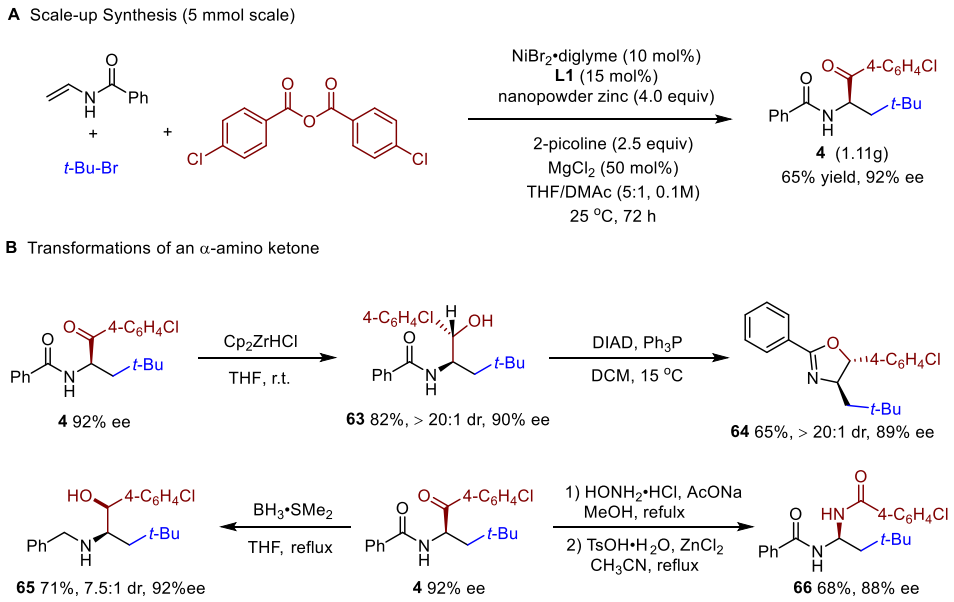


Reaction Conditions: enamide (0.1 mmol), alkyl bromide (0.2 mmol), acid anhydride or 2-pyridyl ester (0.15 mmol), $NiBr_2$•diglyme (10 mol%), ligand **L1** (15 mol%), picoline (or K_3PO_4), $MgCl_2$, and nanopowder Zn (4 equiv) in DMAc/THF was stirred at 25 °C for 48 h. Isolated yield. The ee was determined using HPLC with a chiral stationary phase.

After defining the scope of vinyl amides, attention was then turned to the scope of the alkyl bromide component. Both cyclic tertiary bromides (**31**) and open-chained tertiary bromides (**32-46**) proved to be amenable to the coupling conditions (Table **3A**). We were pleased to find excellent functional group compatibility for the tertiary alkyl bromides component. Functional groups such as ether (**32**), primary alkyl bromide/chloride (**33** and **34**), aryl chloride (**37**), sulfone (**38**), tosylate (**39**), phthalimide (**40**), strained ring (**44** and **45**), and an internal alkene (**46**) were compatible, affording the corresponding products in moderate to good yields (58–82%) and excellent enantioselectivities (up to 94% ee). The absolute configuration for products **33** and **47** has been confirmed by X-ray crystallographic analyses. Interestingly, when the substrate contains both tertiary and primary alkyl bromide, the reaction is completely selective for the more sterically congested C−Br bond to give product **33** in 82% yield

and 93% ee, leaving primary alkyl bromide unchanged, indicative of a stable radical species. Notably, heterocyclic substrates such as furan (**41**), thiophene (**42**), and benzofuran (**43**) were equally suitable for this chemistry. Unfortunately, primary and secondary alkyl bromides were found to be unreactive in our protocol, giving rise to only two-component coupling reaction with the benzoic acid anhydride.

We next demonstrated the substrate spectrum with respect to the acyl donors. Both electron-rich and -deficient groups on the different positions of the aromatic ring of the benzoic anhydrides were tolerated, furnishing the desired α-amino ketones **47-53** in moderate to good efficiency (Table **3B**). Additionally, we wondered whether other acyl precursors are suitable for this asymmetric three-component reductive alkylacylation. Gratifyingly, 2-pyridyl esters were identified to be compatible with our protocol after subtle changes of the reaction conditions (K_3PO_4 instead of 2-picoline as a base, Table **3C**). Accordingly, a variety of 2-pyridyl esters were examined. A series of functional groups, including ether (**54** and **55**), thioether (**56**), ester (**58**), 2-naphthyl (**59**), benzofuran (**60**), and benzothiophene (**61**), were nicely accommodated. Besides aryl 2-pyridyl esters, an aliphatic acid-derived 2-pyridyl ester (**62**) also exhibited moderate reactivity.

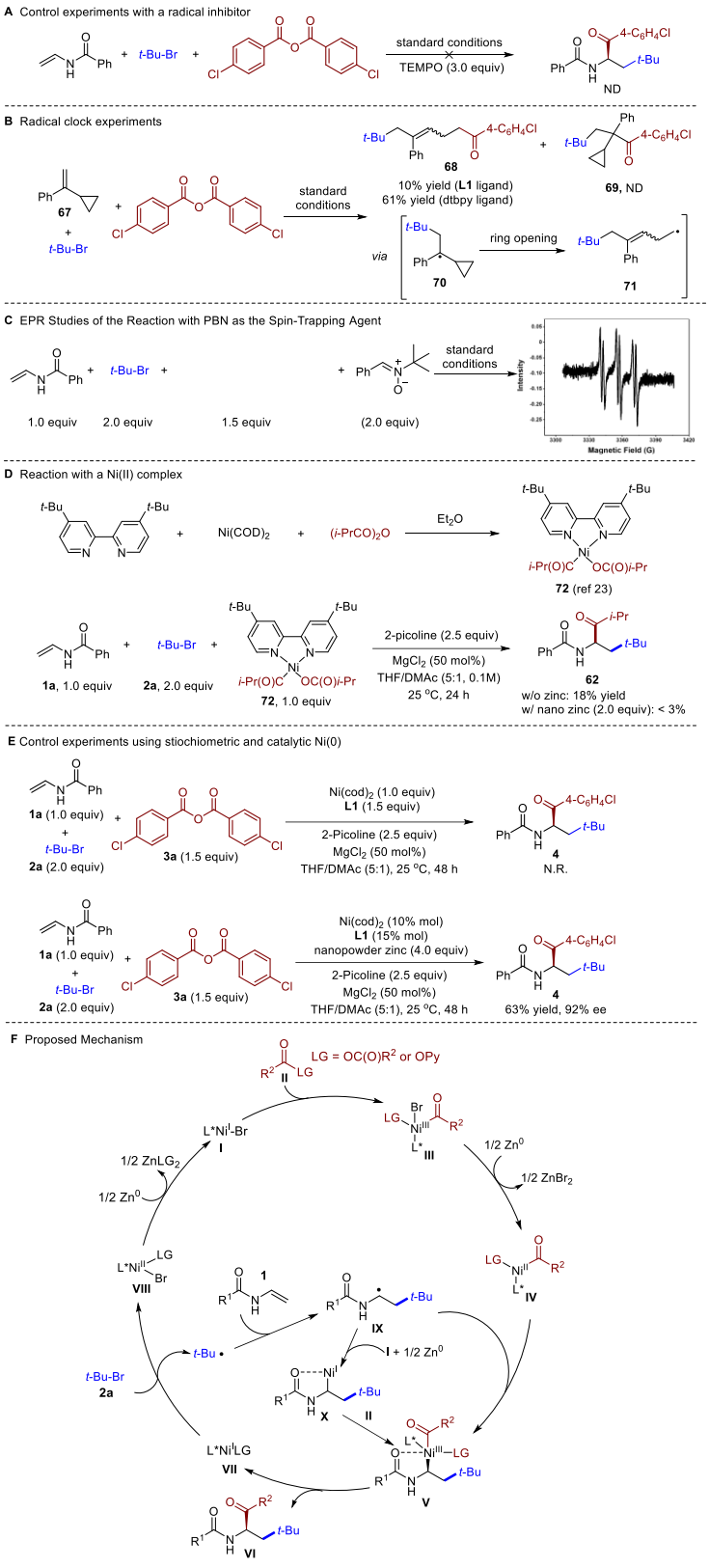


Scheme 2. Gram-Scale Experiment and Synthetic Transformations

To further demonstrate the synthetic utility of our protocol, a gram-scale (5 mmol scale) reaction was carried out. Product **4** was isolated in a synthetically useful yield (1.11 g) with excellent enantioselectivity (92% ee, Scheme **2A**). Chemoselective reduction of the ketone carbonyl group afforded product **63** in good yield and high diastereoselectivity (Scheme 2**B**). The reduction-Mitsunobu reaction of **4** afforded a chiral oxazoline **64** bearing two chiral centers in high dr, which could be a potential chiral ligand. Reduction of the carbonyls in both the ketone and the amide moieties afforded the amino alcohol **65** in 7.5:1 dr.

Condensation between **4** and hydroxyamine followed by a Beckmann rearrangement afforded amide **66** in good yield. In all cases, only slight, if any, erosion of the enantiopurity was observed.

To shed light on the mechanism of this novel nickel-catalyzed asymmetric alkylacylation system, a series of experiments were conducted. The desired alkylacylation reaction was completely inhibited when a radical scavenger was added (Scheme **3A**). Next, a radical-clock experiment using a α-cyclopropyl styrene **67** was conducted (Scheme **3B**), and only the ring-opened product **68** was obtained through a sequential radical addition, ring opening, and acylation process, whereas the formation of the direct cross-coupled product **69** was not observed. This result indicated the formation of a *tert*-butyl radical which, upon addition to the alkene, delivers a new carbon radical that can be intercepted by the acyl-Ni species. The formation of radical species was further confirmed by an electron paramagnetic resonance (EPR) study using a spin-trapping agent phenyl tert-butyl nitrone (PBN, Scheme **3C**). Additionally, a nickel(II) acyl complex **72**[75] was prepared to elucidate the nature of the active nickel species in the catalytic cycle. The stoichiometric reaction of Ni(II)-complex **72**, *N*-vinylbenzamide **1a,** and 2-bromo-2-methylpropane **2a** in the absence of any zinc reductant gave the desired cross-coupled product **62** in 18% yield, whereas only traces of **62** were detected when a stoichiometric amount of nanopowder zinc was introduced (Scheme **3D**). Taken together, these results suggest that the putative acyl-Ni(II) complex could be a productive intermediate in this catalytic cycle. The fact that zinc reductant was not needed for the stoichiometric reaction indicates a Ni(I) acyl species is likely not relevant. No corresponding product **4** could be observed when employing stoichiometric $Ni(cod)_2$ but lacking the zinc reductant, whereas catalytic amount $Ni(cod)_2$ with stoichiometric zinc resulted in the formation of product **4** in 63% yield. These outcome suggests that the reduction of Ni(III) acyl species **III** to Ni(II) acyl intermediate **IV** is likely required in the current protocol.



Scheme 3. Mechanistic Studies

On the basis of our mechanistic investigations and insight from prior studies,[65,66,75,76] a plausible mechanism of this asymmetric three-component alkylacylation reaction is proposed (Scheme **3E**). Initially, Ni(I) species **I** may be formed via reduction of the Ni(II) precatalyst. Oxidative addition of the Ni(I) species **I** to the anhydrides or 2-pyridyl esters **II** generates a Ni(III) intermediate **III**, which reduced by zinc to give Ni(II) intermediate **IV**. Concurrently, the tertiary alkyl bromide **2a** is reduced by a Ni(I) complex **VII** to give a *tert*-butyl radical together with a Ni(II) species (reduction of **2a** by nanopowder zinc to give the tertiary alkyl radical cannot be rule out now). Subsequent addition of the tert-butyl radical to the vinyl amides **1** affords a secondary alkyl radical **IX**. At this juncture, oxidative addition of the radical **IX** to Ni(II) **IV** delivers Ni(III) species **V**, which then undergoes reductive elimination to release the chiral α-amino ketone product and a Ni(I) species **VII**. The Ni(II) intermediate **VIII** is then reduced by nanopowder zinc as facilitated by $MgCl_2$[75,76] to regenerate the Ni(I) **I** to complete the catalytic cycle. We anticipate that the chelation of the carbonyl group to the BiIM-ligated nickel center would be beneficial to control the stereoselectivity in the radical capture step (**IV** + **IX** → **V**).[38-40,45,77] Alternatively, the alkyl radical **IX** may be captured by Ni(I), then through reduction by zinc to form Ni(I) complex **X**, followed by oxidative addition of **II** to deliver the same Ni(III) species **V**. Nevertheless, further efforts are required to fully elucidate the reaction details.

Conclusion

In conclusion, we present herein the first enantioselective, fully intermolecular three-component 1,2-alkylacylation of alkenes using tertiary alkyl bromides and an anhydride or a 2-pyridyl esters under reductive conditions. This mild and efficient protocol allows for the straightforward construction of structurally diverse enantioenriched α-amino ketones with good efficiency and excellent enantioselectivity from readily available electrophiles, avoiding the using of preformed air- or moisture-sensitive organometallic reagents. The amide group in the olefin substrate displays a vital role in enhancing regio- and enantioselectivity as well as the reactivity. Studies to further uncover the detailed mechanism of this transformation and expansion to other olefins and electrophiles are ongoing in our laboratory.

Supporting Information

The Supporting Information is available and includes [Experimental details and procedures; spectra for all unknown compounds (PDF)].

Conflict of Interest (required)

The authors declare no competing interests.

Acknowledgements

Financial support from the NSFC (Nos. 22301171 and 22371175) and research fund from the SNNU are gratefully acknowledged.

Author contributions

J.X. and X.L. designed the project, co-wrote the manuscript, analyzed the data, discussed the results, and commented on the manuscript. J.X., T.J., S.C., and M.P. conducted the experiments. All authors contributed to discussions.

References

1 Almquist, R. G., Chao, W.-R., Ellis, M. E. & Johnson, H. L. Synthesis and Biological Activity of a Ketomethylene Analogue of a Tripeptide Inhibitor of Angiotensin Converting Enzyme. *J. Med. Chem.* **23**, 1392-1398 (1980).

2 Perrine, D. M., Ross, J. T., Nervi, S. J. & Zimmerman, R. H. a Short, One-Pot-Synthesis-of-Bupropion-(Zyban-Wellbutrin). *J. Chem. Educ.* **77**, 1479-1480 (2000).

3 Nchinda, A. T., Chibale, K., Redelinghuys, P. & Sturrock, E. D. Synthesis of novel keto-ACE analogues as domain-selective angiotensin I-converting enzyme inhibitors. *Bioorg. Med. Chem. Lett.* **16**, 4612-4615 (2006).

4 Carroll, F. I. *et al.* Synthesis and Biological Evaluation of Bupropion Analogues as Potential Pharmacotherapies for Cocaine Addiction. *J. Med. Chem.* **52**, 6768-6781 (2009).

5 Smith, A. M. R. & Hii, K. K. Transition Metal Catalyzed Enantioselective α-Heterofunctionalization of Carbonyl Compounds. *Chem. Rev.* **111**, 1637-1656 (2010).

6 Zhou, F., Liao, F.-M., Yu, J.-S. & Zhou, J. Catalytic Asymmetric Electrophilic Amination Reactions To Form Nitrogen-Bearing Tetrasubstituted Carbon Stereocenters. *Synthesis* **46**, 2983-3003 (2014).

7 Torre, A. d. l., Tona, V. & Maulide, N. Reversing Polarity: Carbonyl α‐Aminations with Nitrogen Nucleophiles. *Angew. Chem. Int. Ed.* **56**, 12416-12423 (2017).

8 Allen, L. A. T., Raclea, R.-C., Natho, P. & Parsons, P. J. Recent advances in the synthesis of α-amino ketones. *Org. Biomol. Chem.* **19**, 498-513 (2021).

9 Urban, F. J. & Jasys, V. J. Process Research on [(2S)-(3-Fluorophenyl)-(1S)-(5-oxotetrahydrofuran2-yl)ethyl]carbamic Acid tert-Butyl Ester, a Lactone Intermediate for an Aspartyl Protease Inhibitor. *Org. Process Res. Dev.* **8**, 169−175 (2004).

10 Suyama, T. L. & Gerwick, W. H. Practical Total Syntheses of Epiquinamide Enantiomers. *Org. Lett.* **8**, 4541-4543 (2006).

11 Li, W. *et al.* New Electrophilic Addition of α-Diazoesters with Ketones for Enantioselective C–N Bond Formation. *J. Am. Chem. Soc.* **133**, 15268-15271 (2011).

12 Takeda, T. & Terada, M. Development of a Chiral Bis(guanidino)iminophosphorane as an Uncharged Organosuperbase for the Enantioselective Amination of Ketones. *J. Am. Chem. Soc.* **135**, 15306-15309 (2013).

13 Xu, B., Zhu, S. F., Zuo, X. D., Zhang, Z. C. & Zhou, Q. L. Enantioselective N-H Insertion Reaction of α‐Aryl α‐Diazoketones: An Efficient Route to Chiral α‐Aminoketones. *Angew. Chem. Int. Ed.* **53**, 3913-3916 (2014).

14 Miles, D. H., Guasch, J. & Toste, F. D. A Nucleophilic Strategy for Enantioselective Intermolecular α-Amination: Access to Enantioenriched α-Arylamino Ketones. *J. Am. Chem. Soc.* **137**, 7632-7635 (2015).

15 Yang, X. & Toste, F. D. Direct Asymmetric Amination of α-Branched Cyclic Ketones Catalyzed by a Chiral Phosphoric Acid. *J. Am. Chem. Soc.* **137**, 3205-3208 (2015).

16 Lamb, R. A., Aberle, N. S., Lucas, N. T., Lessene, G. & Hawkins, B. C. Total Synthesis of (−)‐Spiroleucettadine. *Angew. Chem. Int. Ed.* **56**, 14663-14666 (2017).

17 Saied, E. M., Le, T. L.-S., Hornemann, T. & Arenz, C. Synthesis and characterization of some atypical sphingoid bases. *Bioorg. Med. Chem. Lett.* **26**, 4047-4057 (2018).

18 Gomes, R. d. S. & Corey, E. J. A Method for the Catalytic Enantioselective Synthesis of Chiral α-Azido and α-Amino Ketones from Racemic α-Bromo Ketones, and Its Generalization to the Formation of Bonds to C, O, and S. *J. Am. Chem. Soc.* **141**, 20058-20061 (2019).

19 Guo, W. *et al.* Chiral Phosphoric Acid Catalyzed Enantioselective Synthesis of α-Tertiary Amino Ketones from Sulfonium Ylides. *J. Am. Chem. Soc.* **142**, 14384-14390 (2020).

20 Gandolfo, E., Tang, X., Raha Roy, S. & Melchiorre, P. Photochemical Asymmetric Nickel‐Catalyzed Acyl Cross‐

Coupling. *Angew. Chem. Int. Ed.* **58**, 16854-16858 (2019).
21 Shu, X., Huan, L., Huang, Q. & Huo, H. Direct Enantioselective C(sp(3))-H Acylation for the Synthesis of alpha-Amino Ketones. *J. Am. Chem. Soc.* **142**, 19058-19064 (2020).
22 Gao, Y. & Baran, P. S. Nickel‐Catalyzed Enantioselective Decarboxylative Acylation: Rapid, Modular Access to α‐Amino Ketones**. *Angew. Chem. Int. Ed.* **62**, e202315203 (2023).
23 Chen, J. & Zhu, S. Nickel-Catalyzed Multicomponent Coupling: Synthesis of α-Chiral Ketones by Reductive Hydrocarbonylation of Alkenes. *J. Am. Chem. Soc.* **143**, 14089-14096 (2021).
24 Cherney, A. H., Kadunce, N. T. & Reisman, S. E. Catalytic Asymmetric Reductive Acyl Cross-Coupling: Synthesis of Enantioenriched Acyclic α,α-Disubstituted Ketones. *J. Am. Chem. Soc.* **135**, 7442-7445 (2013).
25 Poremba, K. E., Dibrell, S. E. & Reisman, S. E. Nickel-Catalyzed Enantioselective Reductive Cross-Coupling Reactions. *ACS. Catal.* **10**, 8237-8246 (2020).
26 Chen, L.-M. & Reisman, S. E. Enantioselective C(sp2)–C(sp3) Bond Construction by Ni Catalysis. *Acc. Chem. Res.* **57**, 751-762 (2024).
27 Merino, E. & Nevado, C. Addition of CF3 across unsaturated moieties: a powerful functionalization tool. *Chem. Soc. Rev.* **43**, 6598-6608 (2014).
28 Dhungana, R. K., KC, S., Basnet, P. & Giri, R. Transition Metal-Catalyzed Dicarbofunctionalization of Unactivated Olefins. *Chem. Rec.* **18**, 1314-1340 (2018).
29 Giri, R. & KC, S. Strategies toward Dicarbofunctionalization of Unactivated Olefins by Combined Heck Carbometalation and Cross-Coupling. *J. Org. Chem.* **83**, 3013-3022 (2018).
30 Lin, J., Song, R. J., Hu, M. & Li, J. H. Recent Advances in the Intermolecular Oxidative Difunctionalization of Alkenes. *Chem. Rec.* **19**, 440-451 (2018).
31 Zhang, J.-S., Liu, L., Chen, T. & Han, L.-B. Transition-Metal-Catalyzed Three-Component Difunctionalizations of Alkenes. *Chem.−Asian J.* **13**, 2277-22291 (2018).
32 Badir, S. O. & Molander, G. A. Developments in Photoredox/Nickel Dual-Catalyzed 1,2-Difunctionalizations. *Chem* **6**, 1327-1339 (2020).
33 Derosa, J., Apolinar, O., Kang, T., Tran, V. T. & Engle, K. M. Recent developments in nickel-catalyzed intermolecular dicarbofunctionalization of alkenes. *Chem. Sci.* **11**, 4287-4296 (2020).
34 Qi, X. & Diao, T. Nickel-Catalyzed Dicarbofunctionalization of Alkenes. *ACS Catal.* **10**, 8542-8556 (2020).
35 Wickham, L. M. & Giri, R. Transition Metal (Ni, Cu, Pd)-Catalyzed Alkene Dicarbofunctionalization Reactions. *Acc. Chem. Res.* **54**, 3415-3437 (2021).
36 Zhu, S., Zhao, X., Li, H. & Chu, L. Catalytic three-component dicarbofunctionalization reactions involving radical capture by nickel. *Chem. Soc. Rev.* **50**, 10836-10856 (2021).
37 Anthony, D., Lin, Q., Baudet, J. & Diao, T. Nickel‐Catalyzed Asymmetric Reductive Diarylation of Vinylarenes. *Angew. Chem. Int. Ed.* **58**, 3198-3202 (2019).
38 Guo, L. *et al.* General Method for Enantioselective Three-Component Carboarylation of Alkenes Enabled by Visible-Light Dual Photoredox/Nickel Catalysis. *J. Am. Chem. Soc.*, 20390−20399 (2020).
39 Tu, H. Y. *et al.* Enantioselective Three-Component Fluoroalkylarylation of Unactivated Olefins through Nickel-Catalyzed Cross-Electrophile Coupling. *J. Am. Chem. Soc.* **142**, 9604-9611 (2020).
40 Wei, X., Shu, W., García-Domínguez, A., Merino, E. & Nevado, C. Asymmetric Ni-Catalyzed Radical Relayed Reductive Coupling. *J. Am. Chem. Soc.* **142**, 13515-13522 (2020).
41 Qian, P. *et al.* Catalytic enantioselective reductive domino alkyl arylation of acrylates via nickel/photoredox catalysis. *Nat. Commun.* **12**, 6613 (2021).
42 Wang, Y.-Z. *et al.* Enantioselective Reductive Cross-Couplings of Olefins by Merging Electrochemistry with Nickel Catalysis. *J. Am. Chem. Soc.* **145**, 23910-23917 (2023).
43 Hu, X., Cheng-Sánchez, I., Kong, W., Molander, G. A. & Nevado, C. Nickel-catalysed enantioselective alkene dicarbofunctionalization enabled by photochemical aliphatic C–H bond activation. *Nat. Catal.* (2024).
44 Li, Y.-Z. *et al.* Enantioselective nickel-catalyzed dicarbofunctionalization of 3,3,3-trifluoropropene. *Nat. Commun.* **13**, 5539 (2022).
45 Wang, F., Pan, S., Zhu, S. & Chu, L. Selective Three-Component Reductive Alkylalkenylation of Unbiased Alkenes via Carbonyl-Directed Nickel Catalysis. *ACS Catal.* **12**, 9779-9789 (2022).
46 Li, X. *et al.* Three-component enantioselective alkenylation of organophosphonates via nickel metallaphotoredox catalysis. *Chem* **9**, 154-169 (2023).

47 Dong, Z. *et al.* Enantioselective Directed Nickel-Catalyzed Three-Component Reductive Arylalkylation of Alkenes via the Carbometalation/Radical Cross-Coupling Sequence. *ACS Catal.* **14**, 4395-4406 (2024).
48 Du, X. Y., Cheng-Sánchez, I. & Nevado, C. Dual Nickel/Photoredox-Catalyzed Asymmetric Carbosulfonylation of Alkenes. *J. Am. Chem. Soc.* **145**, 12532-12540 (2023).
49 Liu, M.-S. & Shu, W. Rapid Synthesis of β-Chiral Sulfones by Ni-Organophotocatalyzed Enantioselective Sulfonylalkenylation of Alkenes. *JACS Au* **3**, 1321-1327 (2023).
50 Huang, H., Lin, Y. M. & Gong, L. Recent Advances in Photochemical Asymmetric Three‐Component Reactions. *Chem. Rec.* **23** (2023).
51 Dong, Z., Song, L. & Chen, L.-A. Enantioselective Ni-Catalyzed Three-Component Dicarbofunctionalization of Alkenes. *ChemCatChem.* **15**, 4395-4406 (2023).
52 Fan, P., Lan, Y., Zhang, C. & Wang, C. Nickel/Photo-Cocatalyzed Asymmetric Acyl-Carbamoylation of Alkenes. *J. Am. Chem. Soc.* **142**, 2180-2186 (2020).
53 Lan, Y. & Wang, C. Nickel-catalyzed enantioselective reductive carbo-acylation of alkenes. *Commun. Chem.* **3**, 45 (2020).
54 Li, Y. *et al.* Carbamoyl Fluoride-Enabled Enantioselective Ni-Catalyzed Carbocarbamoylation of Unactivated Alkenes. *J. Am. Chem. Soc.* **142**, 19844-19849 (2020).
55 Marchese, A. D. *et al.* Nickel-Catalyzed Enantioselective Carbamoyl Iodination: A Surrogate for Carbamoyl Iodides. *ACS Catal.* **10**, 4780-4785 (2020).
56 Wu, X., Qu, J. & Chen, Y. Quinim: A New Ligand Scaffold Enables Nickel-Catalyzed Enantioselective Synthesis of α-Alkylated γ-Lactam. *J. Am. Chem. Soc.* **142**, 15654-15660 (2020).
57 Wu, J. & Wang, C. Nickel-Catalyzed Asymmetric Reductive Dicarbamoylation of Alkenes. *Org. Lett.* **23**, 6407-6411 (2021).
58 Wu, X. *et al.* Catalytic Desymmetric Dicarbofunctionalization of Unactivated Alkenes. *Angew. Chem. Int. Ed.* **61**, e202111598 (2022).
59 Wu, X. *et al.* Nickel‐Catalyzed Enantioselective Reductive Alkyl‐Carbamoylation of Internal Alkenes. *Angew. Chem. Int. Ed.* **61**, e202207536 (2022).
60 Zhang, C., Wu, X., Xia, T., Qu, J. & Chen, Y. Ni-catalyzed carbamoylation of unactivated alkenes for stereoselective construction of six-membered lactams. *Nat. Commun.* **13**, 5964 (2022).
61 He, F. *et al.* Enantioselective Synthesis of α-Alkenylated γ-Lactam Enabled by Ni-Catalyzed 1,4-Arylcarbamoylation of 1,3-Dienes. *CCS Chem.* **5**, 341-349 (2023).
62 Jin, Y., Fan, P. & Wang, C. Nickel-Catalyzed Reductive Asymmetric Aryl-Acylation and Aryl-Carbamoylation of Unactivated Alkenes. *CCS Chem.* **4**, 1510-1518 (2022).
63 Zhao, X. *et al.* Intermolecular selective carboacylation of alkenes via nickel-catalyzed reductive radical relay. *Nat. Commun.* **9**, 3488 (2018).
64 Kadam, A. A., Metz, T. L., Qian, Y. & Stanley, L. M. Ni-Catalyzed Three-Component Alkene Carboacylation Initiated by Amide C–N Bond Activation. *ACS Catal.* **9**, 5651-5656 (2019).
65 Wang, L. & Wang, C. Nickel-Catalyzed Three-Component Reductive Alkylacylation of Electron-Deficient Activated Alkenes. *Org. Lett.* **22**, 8829-8835 (2020).
66 Xi, X., Chen, Y. & Yuan, W. Nickel-Catalyzed Three-Component Alkylacylation of Alkenes Enabled by a Photoactive Electron Donor–Acceptor Complex. *Org. Lett.* **24**, 3938-3943 (2022).
67 Oguma, K., Miura, M., Satoh, T. & Nomura, M. Rhodium-catalyzed coupling of sodium tetraphenylborate with acid anhydrides in the presence or absence of norbornene. *J. Organomet. Chem.* **648**, 297–301 (2002).
68 Ishii, T., Ota, K., Nagao, K. & Ohmiya, H. N-Heterocyclic Carbene-Catalyzed Radical Relay Enabling Vicinal Alkylacylation of Alkenes. *J. Am. Chem. Soc.* **141**, 14073-14077 (2019).
69 Li, J. L. *et al.* Radical Acylfluoroalkylation of Olefins through N‐Heterocyclic Carbene Organocatalysis. *Angew. Chem. Int. Ed.* **59**, 1863-1870 (2019).
70 Zhou, M., Zhao, H. Y., Zhang, S., Zhang, Y. & Zhang, X. Nickel-Catalyzed Four-Component Carbocarbonylation of Alkenes under 1 atm of CO. *J. Am. Chem. Soc.* **142**, 18191-18199 (2020).
71 Wang, C., Liu, N., Wu, X., Qu, J. & Chen, Y. Nickel‐Catalyzed Regiodivergent Acylzincation of Styrenes with Organozincs and CO†. *Chin. J. Chem.* **42**, 599-604 (2023).
72 Sibi, M. P., Manyem, S. & Zimmerman, J. Enantioselective Radical Processes. *Chem. Rev.* **103**, 3263−3295 (2003).
73 Lipp, A., Badir, S. O. & Molander, G. A. Stereoinduction in Metallaphotoredox Catalysis. *Angew. Chem. Int. Ed.* **60**,

1714-1726 (2020).
74 Proctor, R. S. J., Colgan, A. C. & Phipps, R. J. Exploiting attractive non-covalent interactions for the enantioselective catalysis of reactions involving radical intermediates. *Nat. Chem.* **12**, 990-1004 (2020).
75 Zhao, C., Jia, X., Wang, X. & Gong, H. Ni-Catalyzed Reductive Coupling of Alkyl Acids with Unactivated Tertiary Alkyl and Glycosyl Halides. *J. Am. Chem. Soc.* **136**, 17645-17651 (2014).
76 Ni, S. *et al.* A Radical Approach to Anionic Chemistry: Synthesis of Ketones, Alcohols, and Amines. *J. Am. Chem. Soc.* **141**, 6726-6739 (2019).
77 He, Y., Song, H., Chen, J. & Zhu, S. NiH-catalyzed asymmetric hydroarylation of N-acyl enamines to chiral benzylamines. *Nat. Commun.* **12**, 638 (2021).

Table of Contents Graphic (required)