ORGANIC CHEMISTRY FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal

Check for updates

Cite this: DOI: 10.1039/d5qo00590f

Enantioselective construction of cycloalkyl amines *via* nickel-catalysed alkene desymmetrization†

Ludi Li,‡[a] Bo Chen,‡[a] Wenxu Cao,[b,c] G. V. Surendra Babu,[b] Weike Liao,[a] Pengli Zhang*[b] and Guoqin Xia *[a,b,c]

Received 1st April 2025,
Accepted 29th April 2025

DOI: 10.1039/d5qo00590f

rsc.li/frontiers-organic

Three-dimensional chiral cyclic frameworks containing multiple stereocenters are prevalent skeletons in natural products and bioactive molecules. Nevertheless, the synthetic methods for these architectures are limited to date. In this study, an efficient synthetic route for cyclic chiral amines with two adjacent stereocenters was developed by employing symmetric cyclopentenylamine derivatives as starting materials. This reaction demonstrates a broad substrate scope with various functional groups, resulting in excellent yields and stereoselectivities. The proposed mechanism involves a sophisticated sequence of NiH species-mediated transformations, including NiH insertion, β-hydride elimination, reversed NiH insertion and alkylation steps, which collectively enable the precise construction of these complex chiral architectures.

Introduction

The prevalence of flat molecular architectures in traditional pharmaceuticals largely stems from the ready availability and synthetic flexibility of benzene rings sourced from petrochemicals.[1] However, recent scientific advancements have revealed that increasing molecular saturation significantly enhances drug-like properties. This enhancement primarily arises from improved three-dimensional spatial selectivity during target protein engagement, resulting in stronger molecular interactions and reduced dissociation rates. Moreover, elevated saturation levels promote superior solubility profiles, facilitating the creation of clinically effective drug formulations.[2] These advantages emphasize the strategic value of reducing sp^2 carbons while augmenting sp^3 carbons in drug development processes. Furthermore, the enantiomeric variants of a single molecule frequently exhibit distinct pharmacological and pharmacokinetic behaviours, highlighting the critical need for stereoselective synthetic methods in creating saturated hydrocarbon compounds.[3] Given the widespread availability of unsaturated hydrocarbons as chemical precursors, we propose that utilizing alkenes or alkynes as foundational reaction platforms to establish novel sp^3 carbon chiral centres could offer a robust strategy for constructing three-dimensional chiral molecular structures with promising pharmaceutical applications.

Transition metal catalysis with chiral ligands represents one of the most thoroughly investigated domains in asymmetric synthesis.[4] Among these catalysts, nickel has emerged as a particularly noteworthy element due to its abundance on earth and its variable valence state between +1, +2 and +3. In the past two decades, nickel catalysts have been widely used in $C(sp^3)$–$C(sp^3)$ bond formation reactions *via* single electron transfer processes.[5] In 2004, Vicic *et al.* hypothesized that the Ni-catalysed $C(sp^3)$–$C(sp^3)$ bond coupling might occur *via* a radical coupling mechanism during their investigation of the Negishi reaction.[6] This was followed by a significant breakthrough in 2005, when Fu's group reported the first example of Ni-catalysed asymmetric $C(sp^3)$–$C(sp^3)$ bond coupling.[7] In 2006, Fu's group systematically investigated the mechanism behind these Ni-catalysed $C(sp^3)$–$C(sp^3)$ bond coupling reactions and provided compelling evidence for the formation of alkyl radical intermediates in such reactions.[8] Since the primary work of Fu's group, a series of Ni-catalysed enantioselective $C(sp^3)$–$C(sp^3)$ bond coupling reactions have been reported using organometallic reagents and alkyl halides as the substrates.[9] In recent years, transition metal hydrides were also used as a reactive intermediate for alkene functionalization. The first remarkable breakthrough was made by Buchwald's group, who developed a series of CuH-catalysed hydroamination and carbonyl addition reactions utilizing alkenes as starting materials.[10] Beyond the well-established catalytic systems, researchers have identified a range of transition metals, including Mn, Fe, and Co, as effective catalysts

[a]State Key Laboratory of Discovery and Utilization of Functional Components in Traditional Chinese Medicine, School of Pharmaceutical Sciences, Guizhou Medical University, Guiyang 550014, China. E-mail: xiaguoqin@simm.ac.cn
[b]Zhongshan Institute for Drug Discovery, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Zhongshan 528400, China. E-mail: zhangpengli@zidd.ac.cn
[c]University of Chinese Academy of Sciences, Beijing 101408, China

†Electronic supplementary information (ESI) available. CCDC 2435261. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d5qo00590f

‡These authors contributed equally.

for olefin hydrofunctionalization processes.[11] In parallel developments, nickel hydride complexes have also emerged as versatile catalysts, demonstrating remarkable efficacy in hydrofunctionalization reactions of alkene substrates.[12] The primary work for Ni-catalyzed hydroalkylation of alkene was reported by Hu's group in 2012, utilizing a pincer nickel catalyst with diethoxymethylsilane as the hydrogen donor.[13] Significant progress was achieved in 2016 when Fu and Liu introduced a methodology for terminal alkene hydrocarbonation, employing 4,4′-di-*tert*-butyl-2,2′-bipyridine as ligand.[14] In 2017, Zhu's group demonstrated the capability of NiH species to facilitate remote C(sp^3)–H arylation through NiH migration.[15] Their subsequent investigations revealed the prevalence of chain-walking mechanisms in NiH-catalyzed reductive alkene functionalization.[16] The field witnessed another milestone when G. C. Fu's laboratory pioneered enantioselective NiH-catalyzed hydroalkylation, utilizing a chiral nickel-bis(oxazoline) catalyst to achieve stereochemical control.[17] Despite these advancements, the scientific community continues to grapple with the persistent challenge of regioselectivity control in nickel species insertion into non-activated alkenes. To address this challenge, researchers have developed various directing groups that coordinate with nickel catalysts to facilitate controlled insertion reactions. Engle's laboratory has pioneered a series of nickel-catalyzed regioselective difunctionalization reactions involving unactivated alkenes, utilizing aminoquinoline as an effective bidentate directing group.[18] This approach has been further developed by Shu's research team and Fu's group, who successfully applied similar methodologies to achieve nickel hydride-catalyzed enantioselective hydrocarbonation of diverse substrates, including acrylamides, acyl enamines, and unactivated alkenes.[19]

Cycloalkanes with multiple chiral centers are frequently encountered in bioactive small molecules, underscoring the significance of developing efficient methods for synthesizing these architectures from readily available starting materials (Fig. 1a). In 2021, Brown group demonstrated that amide group could direct the arylboration of cyclopentenes utilizing nickel catalyst for the preparation of 1,3,4-trisubstituted cycloalkanes.[20] Recent work by Zhu's group and our group also revealed that esters and amides were able to direct the hydroalkylation of cycloalkenes *via* NiH catalysis[21] (Fig. 1b). Notably, these transformations consistently produce 1,2-disubstituted products through five-membered nickel metallacycle intermediates, which benefit from thermodynamic stability. A significant unanswered question remains regarding the applicability of this strategy to cyclopentenyl amine substrates. In such cases, amide-directed NiH insertion would generate six-membered nickel intermediates, traditionally considered less stable than their five-membered counterparts.[22] Motivated by these considerations, we sought to develop a hydroalkylation protocol for cyclopentenyl amines that could efficiently produce diverse chiral 1,2-disubstituted cycloalkyl amines, which are potentially valuable for bioactive molecule synthesis.

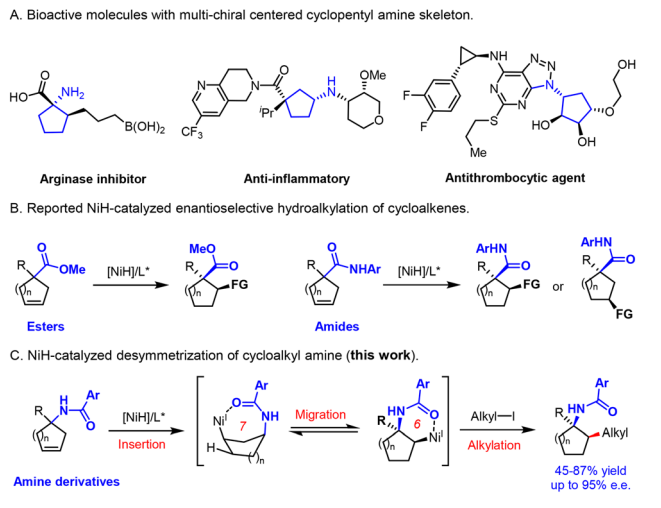


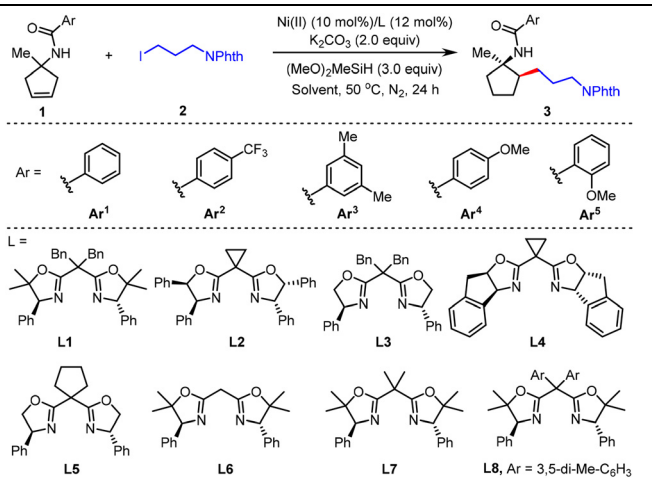
Fig. 1 Cyclopentyl amine skeletons and their synthetic approaches.

Results and discussion

We initiated this reaction by evaluating various amide directing groups on cyclopentenyl amine substrates. The reaction system employed alkyl iodide **2** as the coupling partner, nickel acetate as the catalyst, bis(oxazoline) **L1** as the ligand, dimethoxymethylsilane as the hydrogen source, and potassium carbonate as the base in THF. Our initial screening revealed promising results when benzamide served as the directing group, yielding the hydroalkylation product in 32% yield with 72% ee and an 8 : 1 dr (Table 1, entry 1). However, directing groups bearing electron-withdrawing or sterically bulky substituents proved ineffective (Table 1, entries 2 and 3). Further optimization showed that 4-methoxybenzamide was viable, while 2-methoxybenzamide delivered superior performance, achieving 76% yield, 74% ee, and a dr exceeding 20 : 1 (Table 1, entries 4 and 5). Subsequent ligand screening identified bis(oxazoline) **L8** as optimal, significantly enhancing the enantioselectivity (Table 1, entries 6–12). Further refinement of nickel catalysts and solvents revealed that $Ni(OBs)_2$ in 1,4-dioxane, combined with **L8**, provided the best outcome. Lowering the temperature to 40 °C further improved the yield to 65%, with 92% ee and a dr > 20 : 1. Finally, increasing $(MeO)_2MeSiH$ to 4.0 equivalents established the optimal reaction conditions, which provided a yield of 70%, with 91% ee and a dr value exceeding 20 : 1 (entries 13–15).

Having established the optimal reaction conditions, we proceeded to explore the substrate scope of this transformation. Using compound **1a** as our model substrate, we first evaluated various alkyl iodide coupling partners (Fig. 2). The reaction demonstrated remarkable versatility, successfully accommodating a range of linear and branched alkyl iodides including 1-iodobutane, 1-iodohexane, 1-iodo-3-methylbutane, (2-iodoethyl)cyclopropane, and 1-iodo-3-phenylpropane, all of which afforded products (**3a–3e**) in high yields with outstanding enantioselectivity and diastereoselectivity. The method-

Table 1 Conditions optimization[a]



Entry	Ar	L	Ni(II)	Solvent	Yield	ee	dr
1	**Ar^1**	**L1**	$Ni(OAc)_2$	THF	32%	72%	8 : 1
2	**Ar^2**	**L1**	$Ni(OAc)_2$	THF	n.d.	—	—
3	**Ar^3**	**L1**	$Ni(OAc)_2$	THF	Trace	—	—
4	**Ar^4**	**L1**	$Ni(OAc)_2$	THF	33%	71%	6 : 1
5	**Ar^5**	**L1**	$Ni(OAc)_2$	THF	76%	74%	>20 : 1
6	**Ar^5**	**L2**	$Ni(OAc)_2$	THF	66%	45%	>20 : 1
7	**Ar^5**	**L3**	$Ni(OAc)_2$	THF	42%	32%	7 : 1
8	**Ar^5**	**L4**	$Ni(OAc)_2$	THF	Trace	—	—
9	**Ar^5**	**L5**	$Ni(OAc)_2$	THF	70%	54%	>20 : 1
10	**Ar^5**	**L6**	$Ni(OAc)_2$	THF	11%	30%	2 : 1
11	**Ar^5**	**L7**	$Ni(OAc)_2$	THF	58%	70%	8 : 1
12	**Ar^5**	**L8**	$Ni(OAc)_2$	THF	60%	80%	11 : 1
13	**Ar^5**	**L8**	$Ni(OBs)_2$	Dioxane	61%	90%	>20 : 1
14[b]	**Ar^5**	**L8**	$Ni(OBs)_2$	Dioxane	65%	92%	>20 : 1
15[c]	**Ar^5**	**L8**	**$Ni(OBs)_2$**	**Dioxane**	**70%**	**91%**	**>20 : 1**

[a] The reaction was conducted with **1** (0.1 mmol), **2** (0.25 mmol), Ni(II) (10 mol%), **L** (12 mol%), $(MeO)_2MeSiH$ (3.0 equiv.), K_2CO_3 (2.0 equiv.) in appropriate solvent under N_2 atmosphere for 24 h. $Ni(OBs)_2$: nickel(II) 2-AMino-5-methylbenzenesulfonate. The dr value was determined by crude ^1H NMR analysis. [b] The reaction was conducted at 40 °C. [c] The reaction was conducted at 40 °C, $(MeO)_2MeSiH$ (4.0 equiv.).

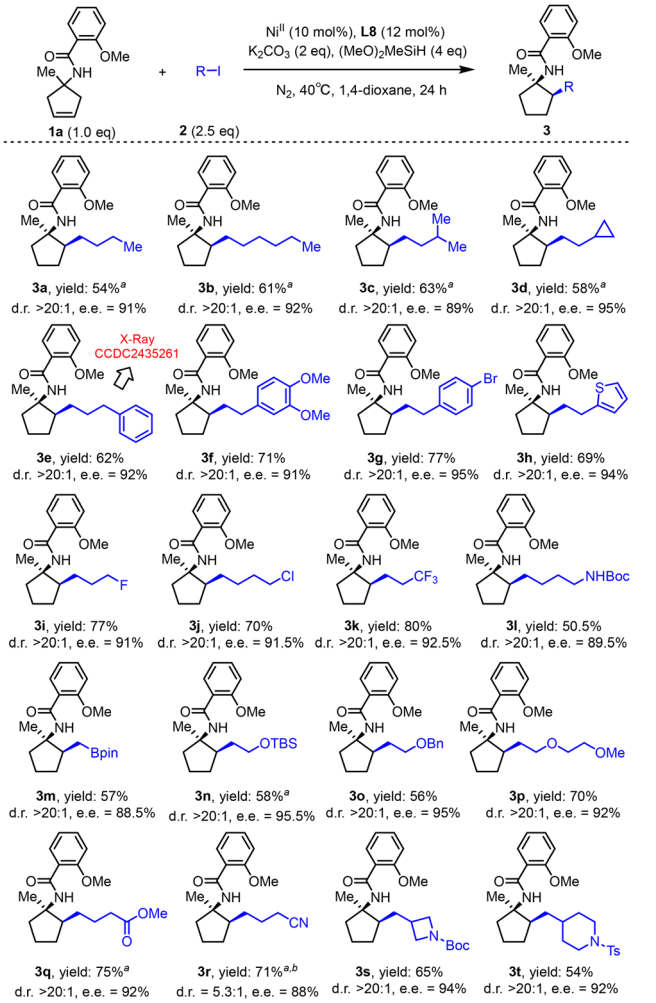


Fig. 2 Substrate scope of alkyl iodide. [a] 4.0 equiv. of alkyl iodide was used. [b] The dr value was determined by ^1H NMR spectroscopy analysis.

ology proved equally effective with substituted homobenzylic iodides bearing methoxy, bromo, and thiophene groups (**3f–3h**), maintaining both excellent yields and stereoselectivity. Notably, the reaction showed excellent functional group tolerance, accommodating halogen substituents (fluoride, chloride) and trifluoromethyl groups (**3i–3k**) without compromising the high stereoselectivity. Further demonstrating its synthetic utility, the protocol successfully incorporated various heteroatoms including nitrogen, boron, and oxygen (**3l–3p**). Particularly noteworthy was the stability of the alkyl boron group (**3m**), which remained intact without undergoing transmetallation with the nickel catalyst. The system also tolerated carboxylate group (**3q**), delivering hydroalkylation products with maintained efficiency. An exception was observed for substrate containing a cyano group, where the diastereoselectivity of the product decreased (**3r**). We hypothesize that the cyano group may compete with the directing group for coordination to the nickel catalyst. Finally, we extended the methodology to aza-heterocyclic substrates, which reacted smoothly under the optimized conditions, further highlighting the broad applicability of this transformation (**3s**, **3t**).

A variety of substituted cyclopentyl amines were also investigated utilizing 2-(3-iodopropyl)isoindoline-1,3-dione as the coupling partner under the optimal conditions (Fig. 3). We found that all the alkyl substituents could provide good yields, with the ee ranged from 80% to 91% (**3u–3z**). The benzyl substituted substrate only gave 25% yield with a ee of 83% (**3aa**). We speculated that the steric effect of the benzyl group could decrease the coordination of the amide directing group with nickel catalyst. Cycloalkyl substituents also gave the moderate yields and excellent stereoselectivity (**3ac**, **3ad**). Unfortunately, substituents with methoxy and trifluoromethyl groups only gave moderate yields and moderate stereoselectivities (**3ae**, **3af**).

Our investigation also encompassed unsubstituted cycloalkyl substrates at the α-position of the amine (Fig. 4). The cyclopentenyl amine (**4**) demonstrated limited reactivity, achieving only 31% yield despite extensive ligand screening

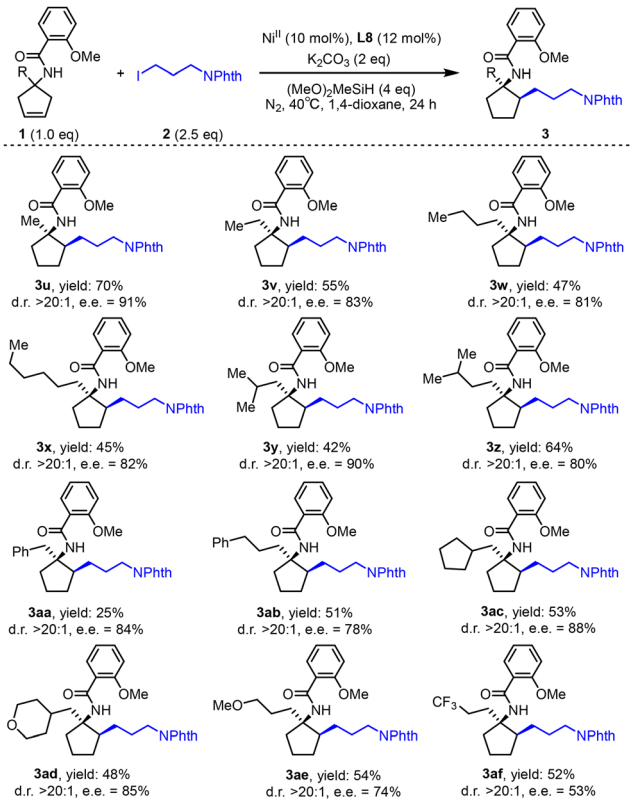


Fig. 3 Substrate scope of substituted cyclopentyl amine.

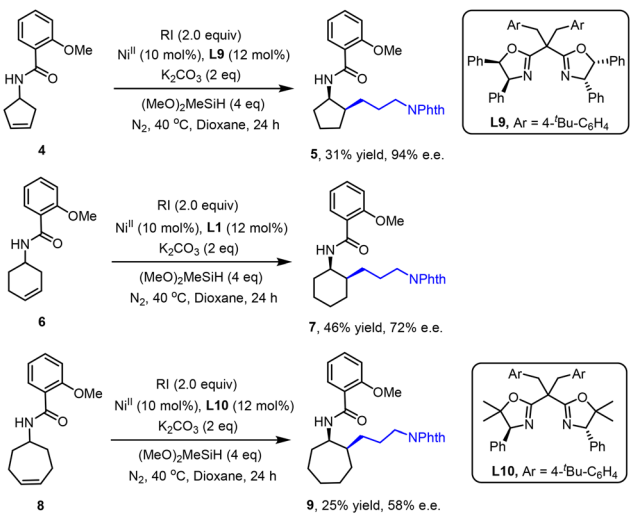


Fig. 4 Cycloalkyl substrates without substituent at α-position of amine.

(with **L9** emerging as optimal), though it exhibited excellent enantioselectivity (94% ee). This diminished yield likely stems from the absence of Thorpe–Ingold effect at the amide directing group's α-position, restricting conformational flexibility necessary for effective transannular direction. The racemic cyclohexenyl amine (**6**) showed improved performance, affording 46% yield with **L1** as ligand while maintaining moderate enantioselectivity (72% ee). We propose that the observed stereoselectivity may arise through a dynamic kinetic asymmetric transformation mechanism, analogous to previous reports by Zhu's group.[21a] Notably, the cycloheptenyl amine substrate (**8**) proved particularly challenging, delivering merely 25% yield and 58% ee when employing **L10** as the optimal ligand.

To elucidate the mechanism underlying this reaction, we performed a series of control experiments. Notably, the addition of 2.0 equivalents of TEMPO completely suppressed the reaction, suggesting a possible radical pathway for the alkylation step of this reaction (Fig. 5A). We also analyzed the products distribution of this reaction in THF utilizing compound **4** as the substrate. Besides the hydroalkylation product **5**, an alkene isomerization side product (**10**) was also isolated with a ee of 66%, providing an evidence of NiH migration process in this reaction (Fig. 5B). In addition, product **5** can be also generated using racemic **10** as the substrate, giving a yield of 25% and ee of 75%, suggesting that the final product was derived from intermediate **10**. We hypothesized that employing racemic substrate **10** would lead to the formation of a racemic 6-membered metallacycle in the initial step. This intermediate could potentially yield both racemic hydroalkylation products and undergo dynamic kinetic asymmetric transformation, leading to a lower enantioselectivity of product. At last, we also synthesized compound **11** using this method in 87% yield with a 95% ee value, which was further transformed into a aza-bicyclic product **12** in 98% yield while maintaining the ee value.

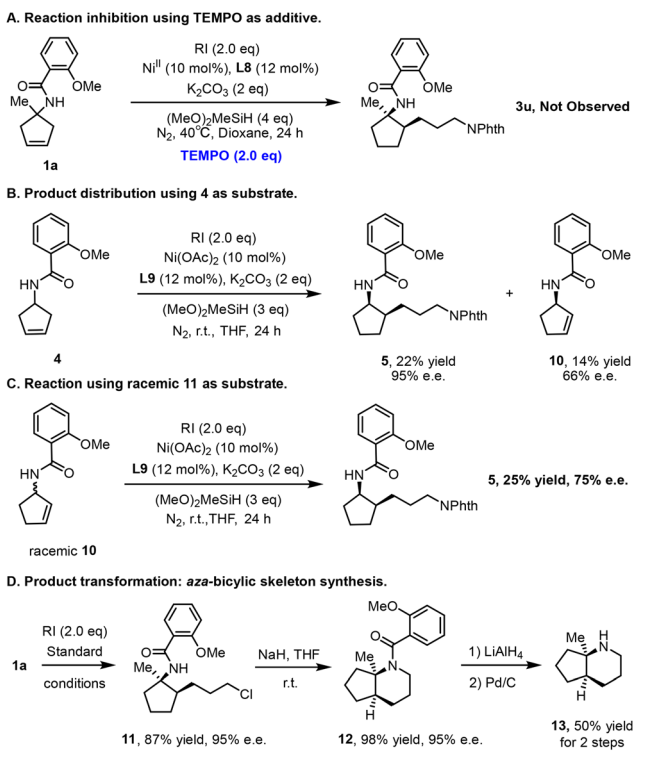


Fig. 5 Control experiments and synthetic applications.

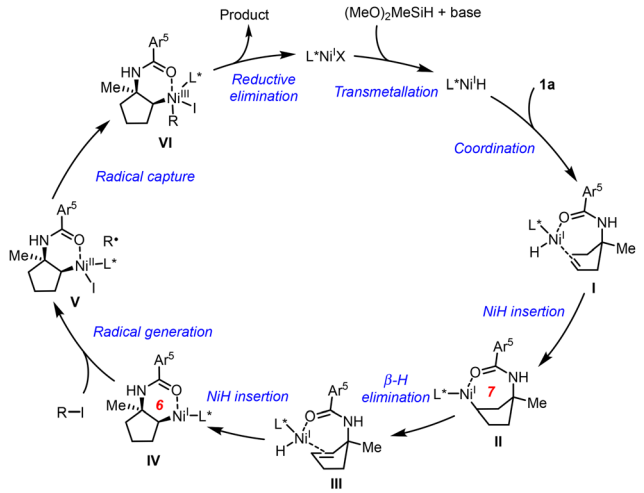


Fig. 6 Proposed mechanism.

The 2-methoxy benzoyl directing group on compound **12** could be removed efficiently by a sequential reduction and hydrogenation to provide a [5,6]-bicyclic amine skeleton **13** in 50% total yield.

Finally, we present a proposed mechanism for this reaction illustrated in Fig. 6. The catalytic cycle initiates with transmetallation between the nickel catalyst and silane reagent, yielding an active nickel hydride species. This NiH complex subsequently coordinates with substrate **1a**, undergoing hydride insertion to form a seven-membered organonickel intermediate (**II**). Following β-hydride elimination, intermediate **III** is generated, which then experiences a second NiH insertion to produce a six-membered organonickel species (**IV**). This intermediate engages with the alkyl iodide through a single-electron transfer process, ultimately forming a reactive Ni(III) species. The catalytic cycle concludes with reductive elimination from this high-valent nickel complex (**VI**), affording the final hydroalkylation product.

Conclusions

In conclusion, we have established a robust synthetic protocol for constructing cyclic chiral amine frameworks featuring two contiguous stereocenters, utilizing readily accessible cycloalkene precursors. This transformation exhibits remarkable functional group tolerance across a diverse range of substrates, delivering 5-membered ring products with exceptional yields and stereo-control. The method described here could also be used for the construction of multi-chiral centred 6-membered and 7-membered ring systems, albeit with lower efficiency. Mechanistic investigations reveal an intricate cascade of NiH-mediated processes, encompassing sequential insertion, β-hydride elimination, reverse insertion, and alkylation events. The directing group approach implemented in this work offers valuable insights for developing other controlled alkene functionalization methodologies.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the financial support from National Natural Science Foundation of China (22271297), Program for Talented Young Investigators of Guangdong Province (2021QN020533) and Zhongshan Science and Technology Bureau (CXTD2023009).

References

1 (*a*) M. A. M. Subbaiah and N. A. Meanwell, Bioisosteres of the Phenyl Ring: Recent Strategic Applications in Lead Optimization and Drug Design, *J. Med. Chem.*, 2021, **64**, 14046–14128; (*b*) T. J. Ritchie and S. J. F. Macdonald, The impact of aromatic ring count on compound developability – are too many aromatic rings a liability in drug design, *Drug Discovery Today*, 2009, **14**, 1011–1020.

2 (*a*) J. Tsien, C. Hu, R. R. Merchant and T. Qin, Three-dimensional saturated C(sp^3)-rich bioisosteres for benzene, *Nat. Rev. Chem.*, 2024, **8**, 605–627; (*b*) F. Lovering, J. Bikker and C. Humblet, Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success, *J. Med. Chem.*, 2009, **52**, 6752–6756.

3 (*a*) W. H. Brooks, W. C. Guida and K. G. Daniel, The significance of chirality in drug design and development, *Curr. Top. Med. Chem.*, 2011, **11**, 760–770; (*b*) B. Kasprzyk-Hordern, Pharmacologically active compounds in the environment and their chirality, *Chem. Soc. Rev.*, 2010, **39**, 4466–4503.

4 (*a*) R. Jana, T. P. Pathak and M. S. Sigman, Advances in transition metal (Pd, Ni, Fe)-catalysed cross-coupling reactions using alkyl-organometallics as reaction partners, *Chem. Rev.*, 2011, **111**, 1417–1492; (*b*) C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot and V. Snieckus, Palladium-Catalysed Cross-Coupling: A Historical Contextual Perspective to the 2010 Nobel Prize, *Angew. Chem., Int. Ed.*, 2012, **51**, 5062–5085.

5 (*a*) G. A. Dawson, E. H. Spielvogel and T. Diao, Nickel-Catalysed Radical Mechanisms: Informing Cross-Coupling for Synthesizing Non-Canonical Biomolecules, *Acc. Chem. Res.*, 2023, **56**, 3640–3653; (*b*) S. Z. Tasker, E. A. Standley and T. F. Jamison, Recent advances in homogeneous nickel catalysis, *Nature*, 2014, **509**, 299–309.

6 T. J. Anderson, G. D. Jones and D. A. Vicic, Evidence for a NiI Active Species in the Catalytic Cross-Coupling of Alkyl Electrophiles, *J. Am. Chem. Soc.*, 2004, **126**, 8100–8101.

7 C. Fischer and G. C. Fu, Asymmetric Nickel-Catalysed Negishi Cross-Couplings of Secondary α-Bromo Amides with Organozinc Reagents, *J. Am. Chem. Soc.*, 2005, **127**, 4594–4595.

8 F. GonzaÂlez-Bobes and G. C. Fu, Amino Alcohols as Ligands for Nickel-Catalysed Suzuki Reactions of Unactivated Alkyl Halides, Including Secondary Alkyl Chlorides, with Arylboronic Acids, *J. Am. Chem. Soc.*, 2006, **128**, 5360–5361.

9 (*a*) Z. Wang, H. Yin and G. C. Fu, Catalytic enantioconvergent coupling of secondary and tertiary electrophiles with olefins, *Nature*, 2018, **563**, 379–383; (*b*) H. Huo, B. J. Gorsline and G. C. Fu, Catalyst-controlled doubly enantioconvergent coupling of racemic alkyl nucleophiles and electrophiles, *Science*, 2020, **367**, 559–564; (*c*) Y. Gao, B. Zhang, J. He and P. S. Baran, Ni-electrocatalytic enantioselective doubly decarboxylative $C(sp^3)$–$C(sp^3)$ cross coupling, *J. Am. Chem. Soc.*, 2023, **145**, 11518–11523; (*d*) B. Zhang, J. He, Y. Gao, L. Levy, M. S. Oderinde, M. D. Palkowitz, T. G. Murali Dhar, M. D. Mandler, M. R. Collins, D. C. Schmitt, P. N. Bolduc, T. Chen, S. Clementson, N. N. Petersen, G. Laudadio, C. Bi, Y. Kawamata and P. S. Baran, Complex molecule synthesis by electrocatalytic decarboxylative cross-coupling, *Nature*, 2023, **623**, 745–751; (*e*) B. Zhang, Y. Gao, Y. Hioki, M. S. Oderinde, J. X. Qiao, K. X. Rodriguez, H.-J. Zhang, Y. Kawamata and P. S. Baran, *Nature*, 2022, **606**, 313–318; (*f*) K. Kang and D. J. Weix, Nickel-catalysed $C(sp^3)$–$C(sp^3)$ cross electrophile coupling of in situ generated NHP esters with unactivated alkyl bromides, *Org. Lett.*, 2022, **24**, 2853–2857; (*g*) D. Sun and A. G. Doyle, Ni/Photoredox-catalysed $C(sp^3)$–$C(sp^3)$ coupling between aziridines and acetals as alcohol-derived alkyl radical precursors, *J. Am. Chem. Soc.*, 2022, **144**, 20067–20077; (*h*) D. Lin, Y. Chen, Z. Dong, P. Pei, H. Ji, L. Tai and L.-A. Chen, General and modular access to enantioenriched α-trifluoromethyl ketones via nickel-catalysed reductive trifluoroalkylation, *CCS Chem.*, 2023, **5**, 1386–1397; (*i*) Z. Dong, Q. Tang, C. Xu, L. Chen, H. Ji, S. Zhou, L. Song and L.-A. Chen, Directed Asymmetric Nickel-Catalyzed Reductive 1,2-Diarylation of Electronically Unactivated Alkenes, *Angew. Chem., Int. Ed.*, 2023, **62**, e202218286.

10 (*a*) R. Y. Liu and S. L. Buchwald, CuH-Catalysed Olefin Functionalization: From Hydroamination to Carbonyl Addition, *Acc. Chem. Res.*, 2020, **53**, 1229–1243; (*b*) S. Zhu, N. Niljianskul and S. L. Buchwald, Enantio- and Regioselective CuH-Catalysed Hydroamination of Alkenes, *J. Am. Chem. Soc.*, 2013, **135**, 15746–15749; (*c*) Y. Dong, K. Shin, B. K. Mai, P. Liu and S. L. Buchwald, Copper Hydride-Catalysed Enantioselective Olefin Hydromethylation, *J. Am. Chem. Soc.*, 2022, **144**, 16303–16309; (*d*) C. Li, K. Shin, R. Y. Liu and S. L. Buchwald, Engaging Aldehydes in CuH-Catalysed Reductive Coupling Reactions: Stereoselective Allylation with Unactivated 1,3-Diene Pronucleophiles, *Angew. Chem., Int. Ed.*, 2019, **58**, 17074–17080; (*e*) Y. Zhou, O. D. Engl, J. S. Bandar, E. D. Chant and S. L. Buchwald, CuH-Catalysed Asymmetric Hydroamidation of Vinylarenes, *Angew. Chem., Int. Ed.*, 2018, **57**, 6672–6675; (*f*) G. Lu, R. Y. Liu, Y. Yang, C. Fang, D. S. Lambrecht, S. L. Buchwald and P. Liu, Ligand–Substrate Dispersion Facilitates the Copper-Catalysed Hydroamination of Unactivated Olefins, *J. Am. Chem. Soc.*, 2017, **139**, 16548–16555; (*g*) Y. Yang, I. B. Perry, G. Lu, P. Liu and S. L. Buchwald, Copper-catalysed asymmetric addition of olefin-derived nucleophiles to ketones, *Science*, 2016, **353**, 144–150; (*h*) S. Zhu, N. Niljianskul and S. L. Buchwald, A direct approach to amines with remote stereocentres by enantioselective CuH-catalysed reductive relay hydroamination, *Nat. Chem.*, 2016, **8**, 144–150; (*i*) D. Niu and S. L. Buchwald, Design of Modified Amine Transfer Reagents Allows the Synthesis of α-Chiral Secondary Amines via CuH-Catalysed Hydroamination, *J. Am. Chem. Soc.*, 2015, **137**, 9716–9721.

11 (*a*) S. W. M. Crossley, C. Obradors, R. M. Martinez and R. A. Shenvi, Mn, Fe, Co-Catalysed Radical Hydrofunctionalizations of Olefins, *Chem. Rev.*, 2016, **116**, 8912–9000; (*b*) L. D. Luca, A. Passera and A. Mezzetti, Asymmetric Transfer Hydrogenation with a Bifunctional Iron(II) Hydride: Experiment Meets Computation, *J. Am. Chem. Soc.*, 2019, **141**, 2545–2556; (*c*) E. Bergamaschi, V. J. Mayerhofer and C. J. Teskey, *ACS Catal.*, 2022, **12**, 14806–14811.

12 (*a*) Z. Zhang, S. Bera, C. Fan and X. Hu, Streamlined Alkylation via Nickel-Hydride-Catalysed Hydrocarbonation of Alkenes, *J. Am. Chem. Soc.*, 2022, **144**, 7015–7029; (*b*) Y. He, R. Tao and S. Zhu, Nickel Hydride Catalysed Remote Hydroarylation of Olefins, *Synlett*, 2022, 224–230.

13 J. Breitenfeld, R. Scopelliti and X. Hu, Synthesis, Reactivity, and Catalytic Application of a Nickel Pincer Hydride Complex, *Organometallics*, 2012, **31**, 2128–2136.

14 X. Lu, B. Xiao, Z. Zhang, T. Gong, W. Su, J. Yi, Y. Fu and L. Liu, Practical carbon-carbon bond formation from olefins through nickel-catalysed reductive olefin hydrocarbonation, *Nat. Commun.*, 2016, **7**, 11129.

15 Y. He, Y. Cai and S. Zhu, Mild and Regioselective Benzylic C-H Functionalization: Ni-Catalysed Reductive Arylation of Remote and Proximal Olefins, *J. Am. Chem. Soc.*, 2017, **139**, 1061–1064.

16 (*a*) F. Zhou, J. Zhu, Y. Zhang and S. Zhu, NiH-Catalysed Reductive Relay Hydroalkylation: A Strategy for the Remote C(sp3)–H Alkylation of Alkenes, *Angew. Chem., Int. Ed.*, 2018, **57**, 4058–4062; (*b*) Y. Zhang, B. Han and S. Zhu, Rapid Access to Highly Functionalized Alkyl Boronates by NiH-Catalysed Remote Hydroarylation of Boron-Containing Alkenes, *Angew. Chem., Int. Ed.*, 2019, **58**, 13860–13864; (*c*) Y. He, C. Liu, L. Yu and S. Zhu, Ligand-Enabled Nickel-Catalysed Redox-Relay Migratory Hydroarylation of Alkenes with Arylborons, *Angew. Chem., Int. Ed.*, 2020, **59**, 9186–9191; (*d*) Y. Wang, Y. He and S. Zhu, NiH-Catalysed

Functionalization of Remote and Proximal Olefins: New Reactions and Innovative Strategies, *Acc. Chem. Res.*, 2022, **55**, 3519–3536; (*e*) X. Jiang, F. T. Sheng, Y. Zhang, G. Deng and S. Zhu, Ligand Relay Catalysis Enables Asymmetric Migratory Reductive Acylation of Olefins or Alkyl Halides, *J. Am. Chem. Soc.*, 2022, **144**, 21448–21456.

17 (*a*) Z. Wang, H. Yin and G. C. Fu, Catalytic enantioconvergent coupling of secondary and tertiary electrophiles with olefins, *Nature*, 2018, **563**, 379–383; (*b*) F. Zhou, Y. Zhang, X. Xu and S. Zhu, NiH-Catalysed Remote Asymmetric Hydroalkylation of Alkenes with Racemic α-Bromo Amides, *Angew. Chem., Int. Ed.*, 2019, **58**, 1754–1758; (*c*) Z. P. Yang and G. C. Fu, Convergent Catalytic Asymmetric Synthesis of Esters of Chiral Dialkyl Carbinols, *J. Am. Chem. Soc.*, 2020, **142**, 5870–5875; (*d*) S. J. He, J. W. Wang, Y. Li, Z. Y. Xu, X. X. Wang, X. Lu and Y. Fu, Nickel-Catalysed Enantioconvergent Reductive Hydroalkylation of Olefins with α-Heteroatom Phosphorus or Sulfur Alkyl Electrophiles, *J. Am. Chem. Soc.*, 2020, **142**, 214–221; (*e*) S. Bera, R. Z. Mao and X. Hu, Enantioselective C(sp^3)–C(sp^3) cross-coupling of non-activated alkyl electrophiles via nickel hydride catalysis, *Nat. Chem.*, 2021, **13**, 270–277.

18 (*a*) J. Derosa, V. T. Tran, M. N. Boulous, J. S. Chen and K. M. Engle, Nickel-Catalysed β,γ-Dicarbofunctionalization of Alkenyl Carbonyl Compounds via Conjunctive Cross-Coupling, *J. Am. Chem. Soc.*, 2017, **139**, 10657–10660; (*b*) J. Derosa, R. Kleinmans, V. T. Tran, M. K. Karunananda, S. R. Wisniewski, M. D. Eastgate and K. M. Engle, Nickel-Catalysed 1,2-Diarylation of Simple Alkenyl Amides, *J. Am. Chem. Soc.*, 2018, **140**, 17878–17883; (*c*) Z.-Q. Li, Y. Fu, R. Deng, V. T. Tran, Y. Gao, P. Liu and K. M. Engle, Ligand-Controlled Regiodivergence in Nickel-Catalysed Hydroarylation and Hydroalkenylation of Alkenyl Carboxylic Acids, *Angew. Chem., Int. Ed.*, 2020, **59**, 23306–23312.

19 (*a*) S. Wang, L. Shi, X.-Y. Chen and W. Shu, Catalyst-Controlled Regiodivergent and Enantioselective Formal Hydroamination of N,N-Disubstituted Acrylamides to α-Tertiary-α-Aminolactam and β-Aminoamide Derivatives, *Angew. Chem., Int. Ed.*, 2023, **62**, e202303795; (*b*) P.-F. Yang and W. Shu, Orthogonal Access to α-/β-Branched/Linear Aliphatic Amines by Catalyst-Tuned Regiodivergent Hydroalkylations, *Angew. Chem., Int. Ed.*, 2022, **61**, e202208018; (*c*) L. Shi, L.-L. Xing, W.-B. Hu and W. Shu, *Angew. Chem., Int. Ed.*, 2021, **60**, 1599–1604; (*d*) X.-X. Wang, Y.-T. Xu, Z.-L. Zhang, X. Lu and Y. Fu, NiH-catalysed proximal-selective hydroalkylation of unactivated alkenes and the ligand effects on regioselectivity, *Nat. Commun.*, 2022, **13**, 1890; (*e*) J. W. Wang, Y. Li, W. Nie, Z. Chang, Z. A. Yu, Y. F. Zhao, X. Lu and Y. Fu, Catalytic asymmetric reductive hydroalkylation of enamides and enecarbamates to chiral aliphatic amines, *Nat. Commun.*, 2021, **12**, 1313.

20 A. L. Lambright, Y. Liu, I. A. Joyner, K. M. Logan and M. K. Brown, Mechanism-Based Design of an Amide-Directed Ni-Catalyzed Arylboration of Cyclopentene Derivatives, *Org. Lett.*, 2021, **23**, 612–616.

21 (*a*) C. Chen, W. Guo, D. Qiao and S. Zhu, Synthesis of Enantioenriched 1,2-cis Disubstituted Cycloalkanes by Convergent NiH Catalysis, *Angew. Chem., Int. Ed.*, 2023, **62**, e202308320; (*b*) K. Zeng, L. Li, X. Luo, Y. Wang, X. Song, P. Zhang and G. Xia, Ligand-Controlled Enantioselective and Regiodivergent Construction of 1,2- and 1,3-Disubstituted Alicycles, *Org. Lett.*, 2024, **26**, 7938–7943.

22 (*a*) G. Xia, J. Weng, L. Liu, P. Verma, Z. Li and J.-Q. Yu, Reversing conventional site-selectivity in C(sp^3)–H bond activation, *Nat. Chem.*, 2019, **11**, 571–577; (*b*) G. Xia, Z. Zhuang, L.-Y. Liu, S. L. Schreiber, B. Melillo and J.-Q. Yu, Ligand enabled b-methylene C(sp^3)-H arylation of masked aliphatic alcohols, *Angew. Chem., Int. Ed.*, 2020, **59**, 7783–7787.