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Pyrrolidines and piperidines bearing chiral tertiary alcohols by nickel-catalyzed enantioselective reductive cyclization of *N*-alkynones

Guodu Liu^{1,2}, Wenzhen Fu¹, Xingye Mu¹, Ting Wu¹, Ming Nie¹, Kaidi Li¹, Xiaodong Xu¹ & Wenjun Tang¹

Pyrrolidines and piperidines are important building blocks in organic synthesis. Numerous methods exist for constructing substituted pyrrolidines and piperidines. However, efficient syntheses of pyrrolidines and piperidines bearing chiral tertiary alcohols are limited. Here we report an efficient enantioselective nickel-catalyzed intramolecular reductive cyclization of *N*-alkynones. A P-chiral bisphosphorus ligand DI-BIDIME is designed and applied in the synthesis of tertiary allylic siloxanes bearing pyrrolidine and piperidine rings in high yields and excellent enantioselectivities, with triethylsilane as reducing reagent. The highest turn over number achieved is 1000 (0.1 mol% catalyst loading) with > 99:1 er. This reaction provides a practical way to synthesize pyrrolidine and piperidine derivatives with chiral tertiary alcohols from easily accessible starting materials under mild conditions. The products can be scaled up and transformed to various useful chiral intermediates. The P-chiral bisphosphorus ligand developed in this study represents one of the few ligands for highly enantioselective cyclization of alkynones.

¹ State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Ling Ling Road, Shanghai 200032, China. ² Department of Chemistry and Chemical Engineering, Inner Mongolia University, 235 Da Xue West Road, Hohhot 010021, China. Correspondence and requests for materials should be addressed to W.T. (email: tangwenjun@sioc.ac.cn)

Transition metal-catalyzed coupling of alkynals/alkynones has become a powerful method for efficient construction of allylic alcohol derivatives in current organic chemistry^{1–3}. Recent development by employing various transition metal catalysts such as Ti⁴, Ni^{5–18}, Rh^{19–24}, Ir²⁵, Ru^{26–28}, and Pd^{29,30} in combination with a variety of coupling components and reducing/alkylative agents has greatly expanded its scope and applications. Among them, the nickel-catalyzed coupling of π systems pioneered by Mori^{5,8}, Montgomery^{6,7,10}, and Jamison^{9,15}, is particularly attractive and offers a broad substrate scope and good functional group compatibility. However, the enantioselective cyclization of these substrates, especially for constructing chiral tertiary alcohols is limited¹⁶. The chiral tertiary alcohols construction is synthetically more difficult as the asymmetric addition to ketones (tetrasubstituted carbon synthesis) is generally more challenging than addition to aldehydes. Furthermore, the nickel-catalyzed reactions usually demonstrated in considerably high catalytic loadings (5 to 30 mol% of Ni catalyst), which is not “green” enough for the practicality of nickel-catalyzed synthesis. Thus, the development of efficient enantioselective nickel-catalyzed reactions remains a major challenge for synthetic chemists.

Herein, we report an efficient regiospecific and enantioselective nickel-catalyzed intramolecular reductive cyclization of *N*-alkynones with up to 1000 TON (0.1 mol% catalyst loading) and > 99:1 er under mild conditions.

Results

Ligand design. Despite the recent progress in nickel-catalyzed reactions, few reports are available on ligand engineering in seeking for a more robust and active nickel catalyst. Based on our previous experience on ligand design, we proposed this objective

could be achieved by the development of our privileged ligand BIDIME^{31–34}. We intuitively designed DI-BIDIME in hope to develop a more efficient enantioselective nickel-catalyzed reaction (Fig. 1a). Our design in DI-BIDIME are in two strategies: (1) DI-BIDIME is free of H7, not only avoiding the potential C–H functionalization at H7 position^{35–37} but also making the adjacent C–O bond more hindered and resistant to cleave in the presence of a nickel metal^{38,39}; (2) both phosphorus atoms in DI-BIDIME should function independently with a reduced ligand entropy by half. This could be helpful for increasing the longevity of nickel catalyst. We herein report the development of DI-BIDIME (L4) by using this strategy.

Reaction discovery. Multi-substituted pyrrolidines and piperidines are widely present in the structures of bioactive natural products and drugs^{40–43} (Fig. 1b). In general, their optical active version led to enhanced bio-activities^{44,45}. However, methods for efficient construction of chiral substituted pyrrolidines and piperidines were limited⁴⁶. In the past two decades, many metal-catalyzed cyclizations were developed for constructing functionalized pyrrolidines and piperidines (Fig. 1c–h). From 2000s, Montgomery group have first studied Ni-catalyzed regioselective cyclization of tethered *N*-alkynals without investigated their enantioselectivity^{6,7,11} (Fig. 1c). Krische and Tanaka then developed the rhodium-catalyzed enantioselective cyclizations of *N*-alkynals to form pyrrolidines with chiral secondary alcohols/ethers^{20,22,23} (Fig. 1d). In 2007, Zhou and colleagues²¹ first reported one enantioselective rhodium-catalyzed hydrosilylation/cyclization of 1,6-enynes (Fig. 1e) and followed by a enantioselective Ni-catalyzed intramolecular hydroalkenylation of *N*-1,6-dienes to synthesize chiral functionalized pyrrolidines and piperidines¹⁸ (Fig. 1f). In 2013, the first regioselective cyclization

Fig. 1 Ligand design and reaction discovery of nickel-catalyzed regiospecific asymmetric reductive cyclization of *N*-alkynones. **a** Design of a more robust ligand for Ni-catalyzed reductive coupling. **b** Several therapeutic agents and bioactive molecules bearing a multi-substituted pyrrolidine/piperidine moiety. **c–h** Previous work of constructing functionalized multi-substituted pyrrolidines/piperidines via metal-catalyzed cyclizations. **i** This work: efficient nickel-catalyzed regiospecific asymmetric reductive cyclization of *N*-alkynones to synthesize pyrrolidines/piperidines with chiral tertiary alcohol silyl ether

Fig. 2 Reaction optimization. Nickel-catalyzed regiospecific asymmetric reductive cyclization of *N*-alkynones (**1a**) applying different ligands. Full screening conditions are reported in Table 1

of *N*-alkynones was reported by Lu and colleagues³⁰, which is catalyzed by a Pd precursor to construct a series of pyrrolidines with tertiary alcohols (Fig. 1g). Then Li and Xu²⁴ reported an asymmetric rhodium-catalyzed cyclization for chiral tertiary allylic alcohols (Fig. 1h). To the best of our knowledge, there is no efficient Ni-catalyzed cyclization with high TONs (> 100), which can provide pyrrolidines and piperidines with chiral tertiary alcohols. We herein describe a highly efficient and practical nickel-catalyzed intramolecular reductive cyclization of *N*-alkynones for the first time with the nickel loading as low as 0.1 mol %, by employing the newly developed chiral bisphosphorus ligand DI-BIDIME through ligand engineering. A variety of pyrrolidine/piperidine derivatives bearing a chiral tertiary alcohol silyl ether moiety are prepared in high yields and excellent enantioselectivities (Fig. 1i). Further transformations of the silyl ether to alcohol and related derivatives were demonstrated. The applications of this method to the synthesis of key intermediates of prodine and (–)-peroxetene were also accomplished. We believed that this asymmetric Ni-catalyzed intramolecular reductive cyclization of *N*-alkynones would provide an efficient access to many useful building blocks of bioactive pyrrolidine and piperidine molecules.

Ligand effects and catalyst loading optimization. We began this study by choosing *N*-alkynone (**1a**) as the standard substrate to investigate the nickel-catalyzed intramolecular reductive cyclization of *N*-alkynones with triethylsilane (Et_3SiH) as the reducing reagent (Fig. 2). The reactions were performed under nitrogen in dioxane at 25 °C for 12 h in the presence of a nickel catalyst prepared in situ from 10 mol % $\text{Ni}(\text{cod})_2$, 10 mol% monophosphorus ligand/5 mol% bisphosphorus ligand, and 3 equiv. Et_3SiH . First, we evaluated various commercial available mono-, bis-phosphorus ligands and ligands developed in our laboratory^{47,48}. As shown in Table 1, monophosphorus ligands: PPh_3 , PCy_3 , Ru-Phos, S-Phos, and X-Phos provided the desired product **2a** in racemic form with high to excellent yields (PPh_3 : 98%; PCy_3 : 82%; Ru-Phos: 95%; S-Phos: 98%; X-Phos: 85%, entries 1–5). Chiral ligands (*R*)-MONOPHOS, (*R*)-Me-DuPhos, (*R*)-Binapine, and **L1** showed no reactivity for this cyclization, whereas (*R*)-BINAP, (*R*)-(S)-JosiPhos, and (*R*)-DTBM-SEGPhos only give trace (< 5%) cyclized product (entries 6–12). Surprisingly, our ligands (*S*)-Me-BIDIME (**L2**), (*S*)-BIDIME (**L3**), and (*S*, *S*)-DI-BIDIME [**L4**, see details in Supplementary Information (SI) for the synthesis] were applicable to the cyclization to obtain tertiary allylic alcohol silyl ethers **2a** in good to excellent yields and enantioselectivities at 10 mol % nickel loading [**L2**: 68% yield, 89:11 er; **L3**: 98% yield, 97:3 er; **L4**: 98% yield, 99:1 er; entries 13–15]. We are excited to explore the potential of new ligand **L4** in consideration of its excellent yield and enantioselectivity,

Table 1 Ligand effects and catalyst loading optimization of nickel-catalyzed intramolecular reductive coupling of *N*-alkynone (**1a**)

Entries ^a	Ligand	X (mol %)	Y (mol %)	T (°C)	Solvent	Yield (%) ^b	er (%) ^c
1	PPh₃	10	10	25	Dioxane	98	0
2	PCy₃	10	10	25	Dioxane	82	0
3	Ru-Phos	10	10	25	Dioxane	95	0
4	S-Phos	10	10	25	Dioxane	98	0
5	X-Phos	10	10	25	Dioxane	85	0
6	(R)-MONOPHOS	10	10	25	Dioxane	0	ND
7	(R)-BINAP	10	5	25	Dioxane	< 5	ND
8	(R)-(S)-JosiPhos	10	5	25	Dioxane	< 5	ND
9	(R)-Me-DuPhos	10	5	25	Dioxane	0	ND
10	(R)-Binapine	10	5	25	Dioxane	0	ND
11	(R)-DTBM-SEGPhos	10	5	25	Dioxane	< 5	ND
12	L1	10	10	25	Dioxane	0	ND
13	L2	10	10	25	Dioxane	68	89:11
14	L3	10	10	25	Dioxane	98	97:3
15	L4	10	5	25	Dioxane	98	99:1
16	L3	1	1	25	Dioxane	40	97:3
17	L4	1	0.5	25	Dioxane	98	99:1
18	L4	0.1	0.05	25	Dioxane	45 ^d	99:1
19	L4	0.1	0.05	60	Dioxane	98 ^d	99:1

The reaction scheme is shown in Fig. 2

^a Unless otherwise specified, the reactions were performed under nitrogen in dioxane (0.5 mL) for 12 h with **1a** (0.2 mmol), $\text{Ni}(\text{cod})_2$ (X mol %), ligand (Y mol %), and triethylsilane (0.6 mmol); product **2a** was the only observed product. The *R* absolute configuration of **2a** was assigned on the basis of the absolute configuration of **3a** determined by X-ray crystallography

^b Isolated yields

^c The enantiomeric excess was determined by chiral HPLC on a Chiralcel AD-H column

^d The reactions were performed under nitrogen in dioxane (2.5 mL) for 12 h with **1a** (2 mmol), $\text{Ni}(\text{cod})_2$ (2 μmol, 0.1 mol%), **L4** (1 μmol, 0.05 mol%), and triethylsilane (6 mmol). Text in italics (entry 19) indicates optimised conditions

especially for its catalyst loading with $\text{Ni}(\text{cod})_2$. To our delight, decreasing the nickel loading to 1 mol%, the highest yield and enantioselectivity (98% yield, 99:1 er) remained with **L4** (entry 17), but only partial conversions were observed for **L3** (40% yield), although the high er was maintained (97:3 er, entry 16) under standard conditions. We further reduced the catalyst loading to 0.1 mol% (TON = 1000); excellent enantioselectivity (99:1 er) was achieved for **L4** with a full conversion at 60 °C (entry 19), but a partial conversion at 25 °C (45% yield, entry 18). Thus, fortunately we find that substrate **1a** was completely converted to the product **2a** with excellent yield and enantioselectivity at 60 °C for 12 h in the presence of 0.1 mol% $\text{Ni}(\text{cod})_2$ and

Fig. 3 Substrate scope of asymmetric nickel-catalyzed reductive cyclization of *N*-alkynones. **a** Unless otherwise specified, the reactions were performed under nitrogen in dioxane (0.5 mL) at 25 °C for 12 h with **1** (0.2 mmol) in the presence of $\text{Ni}(\text{cod})_2$ (1 mol%), **L4** (0.5 mol%), and triethylsilane (0.6 mmol); **b** 0.5 mol% $\text{Ni}(\text{cod})_2$, 0.25 mol% **L4**; **c** $T = 60^\circ\text{C}$; **d** 2 mol% $\text{Ni}(\text{cod})_2$, 1 mol% **L4**, $T = 80^\circ\text{C}$; **e** 4 mol% $\text{Ni}(\text{cod})_2$, 2 mol% **L4**; **f** **3o** was the corresponding product after the desilylation of **2o**, the absolute configuration of **2n–2q** was assigned on the basis of the absolute configuration of **3o** determined by X-ray crystallography, the absolute configuration of **2b–2l** was assigned the same as **2a**

0.05 mol% (*S,S*)-DI-BI-DIME when scaled up to 2 mol substrate scale. The absolute configuration of **2a** was assigned as *R* on the basis of the absolute configuration of desilylation product **3a** determined by X-ray crystallography (see details in SI).

Substrate scope. The high activity of **L4** encouraged us to look into the substrate scope of the Ni-catalyzed intramolecular reductive coupling of *N*-alkynones. For this investigation, we adopted catalyst **L4** and the conditions of entry 17 rather than those of entry 19 (Table 1) due to efficiency for convenience. As shown in Fig. 3, a series of aromatic *N*-alkynones with various substitution patterns and electronic properties were utilized to form products **2b–h** in excellent yields (76–98%) and enantioselectivities (98:2 – > 99:1 er). Substrates with either electron-donating (**2b**, **2f**, **2g**) or electron-withdrawing (**2c**, **2d**) substituents were all affordable to this asymmetric cyclization. Different substitution pattern with different electronic properties may have effects on the reactivity (especially for the yields), as both of **2e** and **2f** have better yields than **2b–2d** even with lower catalyst loading [0.5 mol% compared with 1 mol% $\text{Ni}(\text{cod})_2$]. *o*-OMe substituted **2g** was obtained under higher temperature (60 °C) with the full conversion of the substrate. A substrate containing an indole moiety **1h** was also applicable for this transformation to obtain product **2h** in an excellent yield and er (80% yield, 99:1 er) at 80 °C with 2 mol% $\text{Ni}(\text{cod})_2$ and 1 mol% **L4**. To our delight, under the same conditions as **2h** (80 °C, 2 mol% $\text{Ni}(\text{cod})_2$, 1 mol% **L4**), aliphatic ketone **1i** was also converted to the cyclization product **2i** in 94% yield and > 99:1 er; an aliphatic alkyne was also transformed to a pyrrolidine product **2j** in 84% yield and 92:8 er besides aromatic alkynes. The different *N*-

protecting group also had a significant influence on its reactivity. Substrates with an *N*-Tf group and *N*-Bn group were less reactive, and products **2k** and **2l** were obtained in 19% yield and 10% yield, respectively, albeit with excellent er (98:2, > 99:1 separately). No formation of **2m** was observed when an *N*-Boc group was employed for the substrate. The vastly different reactivity could be due to the conformational difference of the substrates exerted by various *N*-protecting groups. The bulky *N*-sulfonamides could have allowed the alkyne and ketone moieties to a close proximity, facilitating the cycloaddition mediated by a nickel catalyst to occur. We were curious about the size of the ring closure of this cyclization. Six-membered heterocycle were also synthesized from the accessible substrates **1n–1q**. Piperidine products **2n–2q** also gave in excellent yields and good enantioselectivities (95–98% yields, 90:10–89:11 er), albeit with the requirement of more $\text{Ni}(\text{cod})_2$ and ligand (5 mol% and 2.5 mol%, respectively). The diminished enantioselectivity of six-membered heterocycles in comparison with that of five-membered ones is possibly due to the conformational difference of the substrate. Six-membered cyclization could be more facile and efficient by development of a suitable new ligands. The absolute configuration of **2n–2q** was confirmed as *R* on the basis of the X-ray crystallographic analysis of **3o**, which is the desilylation product of **2o**.

Mechanistic considerations. The high enantioselectivities and yields prompted us to study the mechanism of this catalytic reaction and develop a stereochemical model. To understand whether the cycloaddition of **1a** with the nickel complex takes place before the action of Et_3SiH , a stoichiometric amount of $[\text{Ni}(\text{cod})_2]$ was mixed with ligand **L4** with stirring in dioxane at room

temperature. The solution was turned dark brown quickly after the addition of substrate **1a**. This process was monitored by React-IR; the three-dimensional spectra and trend chart of peak variation were shown in Fig. 4 and Fig. 5 separately. An absorption peak at 1701cm^{-1} of ketone functional group appeared after the addition of **1a** and persisted before the addition of phosphorus ligand **L4**, indicating the cycloaddition of the carbonyl group did not proceed without the phosphorus ligand.

Fig. 4 Reaction monitoring. Three-dimensional spectra of stoichiometric reaction of $[\text{Ni}(\text{cod})_2]$, **1a**, and **L4** monitored by React-IR

Fig. 5 Kinetics of consumption of **1a**. Trend chart of peak variation at 1701cm^{-1} of stoichiometric reaction of $[\text{Ni}(\text{cod})_2]$, **1a**, and **L4** monitored by React-IR

However, the absorption peak slowly disappeared after the addition of a stoichiometric amount of **L4**, indicating that the cycloaddition of **1a** with a nickel species bearing a bisphosphorus ligand **L4** has occurred, which generate the key intermediate for the following reduction with Et_3SiH .

Based on these results and previous mechanistic study by Baxter and Montgomery⁴⁹, and computational studies by Houk and colleagues^{47,48} on nickel-catalyzed intermolecular or intramolecular ynal reductive cyclizations, we proposed the catalytic cycle of this intramolecular asymmetric reductive cyclization of *N*-alkynones as dimeric metallacyclic model, which was depicted in Fig. 6. Bisphosphorus ligand **L4** reacted with $\text{Ni}(\text{cod})_2$ to form the Ni^0 species **I**, then addition of *N*-alkynone **1a** generated the cyclization process through the stage **II** and provided dimer Ni^{II} metallacycle **III**. This is followed by coordination and σ -bond metathesis with triethylsilane to produce Ni^{II} hydride species **IV**. Final reductive elimination of **IV** provided the desired product **2a** and regenerated the Ni^0 catalyst, which completed the catalytic circulation of this trend. The enantioselectivity and stereoselectivity are apparently controlled by the cycloaddition stage **III**, two equivalent of Ni source elegantly coordinated to one equivalent of the unique bisphosphorus ligand **L4** and two equivalent of *N*-alkynone **1a** by the ketone and alkyne formed the cyclized intermediate **III** in high enantioselectivity and regioselectivity. Conformational analysis of metallacycle **III** with **L4** as the ligand indicates that the steric interactions between the phenyl group on the metallacycle ring and the 2, 6-dimethoxy phenyl moiety and *P*-chiral *t*-Bu group of **L4** are rigid, which favored the *R* configuration of the following stages to the cyclization product **1a**. The reason for the enantioselectivity enhancement of DI-BIDIME (**L4**) than BIDIME (**L2**) is possibly due to the greater steric hindrance of the stage **III**. The absolute configuration of product **3a** determined by X-ray crystallography confirmed this hypothesis for the asymmetric control cycle.

Synthetic utility of cyclization product. The highly enantioselective transformation allowed us to synthesize pyrrolidines with chiral tertiary alcohols and related derivatives. A gram-scale cyclization of **1a** was carried out in dioxane at 60°C in the presence of 0.1 mol% $\text{Ni}(\text{cod})_2$ and 0.05 mol% **L4**, and the product **2a** (1.26 g) was obtained in 98% yield and 99:1 er (Fig. 7). Direct

Fig. 6 Proposed mechanistic pathway. The proposed mechanism involves a dimeric metallacyclic model of asymmetric reductive cyclization of *N*-alkynones with nickel⁰ and bisphosphorus ligand **L4**

hydrogenation of the double bond in **2a** over 10% Pd/C and H₂ took place stereo specifically at the opposite side to the OSiEt₃ group, forming compound **4a** quantitatively with diastereoselectivity of 7:1 dr. After desilylation with TBAF (tetrabutylammonium fluoride), the two separable diastereoisomers with tertiary alcohol can be produced in 84% yield (**5a**) and 12% yield (**5a'**). To investigate the stereo effects of chirality and hindrance of OSiEt₃ to the adjacent double bond reactions, we are curious to hydrogenate the free tertiary allylic alcohol **3a** under the same condition as **4a**, the isolated products **5a** and **5a'** were provided in 39% yield and 60% yield separately. These results showed that the more bulky group at C3 position induced the major product as **5a** with good diastereoselectivity (7:1 dr), but less diastereoselectivity (3:2 dr) with the other diastereoisomer **5a'** as major product. The results showed that the bulkiness of OH relating group has significant impact for the diastereoselectivity of hydrogenated product. This information may give suggestions for the synthesis of more complicated molecules with more than one chiral center. The double bond in **2a** could be easily treated with ozone (O₃) to give the ketone intermediate **6a** in 90% yield, which is one versatile building block for many useful reactions, such as reductive aminations, Wittig reactions, and so on. For example, the olefin **8a** can be obtained in 85% yield with CH₃PPh₃Br as the Wittig reagent from ketone **6a**. By the way, deprotection of **6a** could easily prepare chiral α-tertiary alcohol ketone **7a** in 96% yield. The derivatives **6a**, **7a**, **8a**, **9a**, and **10a** were anticipated to find wider applications in organic synthesis, which expanded the synthetic utility of this methodology.

Synthetic application to drug intermediates. To further demonstrate the synthetic utility of this methodology, we then focused on the synthesis of intermediates of the important drugs from available cyclized products. As showed in Fig. 8a, the chiral cyclization product **2o** was converted to ketone compound **11** by ozonolysis reaction with 90% yield, followed by Wittig reaction utilizing CH₃PPh₃Br as the reagent to give the olefin **12** in 88% yield, then deprotection of silyl group with TBAF to afford the desired tertiary alcohol olefins **13** (96% yield), which could be transformed to the drug prodine (analgesic) by procedures^{16,18,44} reported in literature. The key intermediate of antidepressant (–)-paroxetine **16** was also achieved through similar steps (Fig. 8b). Ozonolysis of **2q** provided ketone **14** in 90% yield and then delivered to olefin **15** with 86% yield, which underwent deprotection of trimethylsilyl group to give the desired tertiary alcohol olefins **16** in 96% yield. This intermediate could be converted to (–)-paroxetine through the similar procedures reported by Tang and colleagues¹⁶, and Zhou and colleagues¹⁸.

Discussion

In summary, we have developed a highly efficient regioselective and enantioselective nickel-catalyzed intramolecular reductive cyclization of *N*-alkynones mediated by a nickel catalyst bearing P-chiral diphosphorus ligand with triethylsilane as the reducing reagent. A variety of pyrrolidine/piperidine derivatives bearing a chiral tertiary allylic alcohol silyl ether moiety were synthesized in high yields (up to 98% isolated yield) and excellent enantio-

Fig. 7 Synthetic utility of cyclization products. Gram-scale reaction and further transformation of cyclization product **2a**

Fig. 8 Synthetic application to drug intermediates. **a** Synthetic application to intermediates of prodine from **2o**. **b** Synthetic application to intermediates of (–)-paroxetine from **2q**

electivities (> 99:1 er). The highest TON of Ni-catalyzed reactions was reported as 1000 [0.1 mol% catalyst loading of Ni(cod)₂] with developed unique ligand (S, S)-DI-BIDIME (**L4**), which is designed by ligand engineering through C7-bicoupling of privileged monophosphorus ligand (S)-BIDIME (**L2**). This method has proved to be a practical process for concise synthesis of pyrrolidines/piperidines with a chiral tertiary alcohol group. Mechanistic studies showed that the cycloaddition stage dimer Ni^{II} metallacycle **III** is the enantioselectivity-determining step, whereas the ligand **L4** had an important role for providing a large π -conjugated system or steric interactions. A gram-scale preparation and a number of transformations of the cyclization product were conducted to show the capability and scalability of this methodology. The efficient synthesis of key intermediates of prodine and (–)-paroxetine has also been demonstrated for its applications in drug synthesis. Ligand design and engineering has proved to be an effective strategy for developing practical efficient asymmetric nickel-catalyzed transformations. The catalyst developed in this study has potential for application in other cyclization reactions. Further exploration on more efficient nickel catalyst, its detailed mechanistic study, and development of various efficient nickel-catalyzed asymmetric reactions are under investigation in our laboratory.

Methods

General procedure for asymmetric nickel-catalyzed intramolecular reductive cyclization of N-alkynes. Ni(cod)₂ (2 μ mol, 1 mol%), (S,S)-DI-BIDIME (**L4**, 1 μ mol, 0.5 mol%), and dioxane (0.5 mL) were added to a 5 mL screw-cap vial equipped with a magnetic stirring bar in the glove box. Substrate **1** (0.2 mmol, 1.00 equiv.) was added to the solution in one portion, stirred for 5 min, followed by the addition of triethylsilane (Et₃SiH, 0.6 mmol, 3.00 equiv.). The vial was closed with a screw cap and the resulting mixture was stirred at 25 °C for 12 h. Quenched with saturated sodium bicarbonate (NaHCO₃), extracted with ethyl acetate (EtOAc), washed with saturated NaCl, dried over anhydrous sodium sulfate (Na₂SO₄), filtered, and concentrated under vacuum. The residue was purified by column chromatography (10% petroleum ether/EtOAc) to afford compound **2**.

Synthesis and characterization. Full synthetic procedures and characterization for ligand DI-BIDIME and substrates **1a–1q** are available in the Supplementary Methods and Supplementary Figures 1–9. High-performance liquid chromatography charts for racemic and chiral products **2a–2q** are available in Supplementary Figures 10, 12–22, and 24–25. Full procedures for synthetic transformations to compounds **3a–16** are available in Supplementary Figures 26 and 27. ¹H, ¹³C, ³¹P, and ¹⁹F NMR spectra of purified compounds are available in Supplementary Figures 28–83.

Crystallography. X-ray crystallographic CIF files, RFT files, and checkcif files for compounds **3a** and **3o** are available in Supplementary Data 1–6. X-ray-derived ORTEP representations of **3a** and **3o** are available in Supplementary Figures 11 and 23

Data availability

The authors declare that all other data supporting the findings of this study are available within the article and Supplementary Information files, and also are available from the corresponding author upon reasonable request. The X-ray crystallographic coordinates for structures that support the findings of this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC) with the accession code CCDC1532676 (**3a**) and CCDC1532677 (**3o**). These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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Author contributions

W.T. and G.L. conceived and designed the experiments. G.L. and W.F. performed the experiments and prepared the Supplementary Information. X.M. and T.W. helped in substrates synthesis. M.N. helped in ligand synthesis. K.L. and X.X. helped in isolating and analyzing the data. W.T. and G.L. wrote the paper. All authors discussed the results and commented on the manuscript.

Additional information

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