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A Bulky Chiral N-Heterocyclic Carbene Palladium Catalyst Enables Highly Enantioselective Suzuki-Miyaura Cross-Coupling Reactions for the Synthesis of Biaryl Atropisomers

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ABSTRACT: Axially chiral biaryl scaffolds are essential structural units in chemistry. The asymmetric Pd-catalyzed Suzuki-Miyaura cross-coupling reaction has been widely recognized as one of the most practical methods for constructing atropisomers of biaryls. However, longstanding challenges remain in this field. For example, substrate scope is often narrow and specialized, functional groups and heterocycles can lead to reduced reactivity and selectivity, bulky *ortho*-substituents are usually needed, and reported methods are generally inapplicable to tetra-*ortho*-substituted biaryls. We have developed an unprecedented highly enantioselective N-heterocyclic carbene (NHC)-Pd catalyzed Suzuki-Miyaura cross-coupling reaction for the synthesis of atropisomeric biaryls. These reactions enable efficient coupling of aryl halides (Br, Cl) or aryl triflates with various types of aryl boron compounds ($B(OH)_2$, Bpin, Bneo, BF_3K), tolerate a remarkably broad scope of functional groups and heterocycles (>41 examples), employ low loading of catalyst (0.2-2 mol%), and proceed under mild conditions. The protocol provided general and efficient access to various atropisomeric biaryls and heterobiaryls in excellent enantioselectivities (up to >99% ee) with no need of using bulky *ortho*-substituted substrates and was effective for the synthesis of tetra-*ortho*-substituent biaryls. Moreover, the method was successfully applied to the diastereo- and enantioselective synthesis of atropisomeric ternaphthalenes. Critical to the success of the reaction is the development and application of an extremely bulky C_2-symmetric chiral NHC, (*R*,*R*,*R*,*R*)-DTB-SIPE, as the ligand for palladium. To the best of our knowledge, this is the first highly enantioselective (>90% ee) example of a chiral NHC-metal catalyzed $C(sp^2)$-$C(sp^2)$ cross-coupling reaction.

■ INTRODUCTION

The axially chiral biaryl skeletons represent key structural elements found in a wide variety of biologically active natural products and drugs.[1,2] These include gossypol, korupensamine A, and BI-224436, a quinoline-based biaryl serves as the allosteric HIV-1 integrase inhibitor.[3] Moreover, atropisomeric biaryls are widely present in many privileged ligands and catalysts such as BINOL, BINAP, and QUINAP, and have shown remarkable ability of stereoinduction in tremendous asymmetric reactions catalyzed by organometallics and organocatalysts (Figure 1).[4]

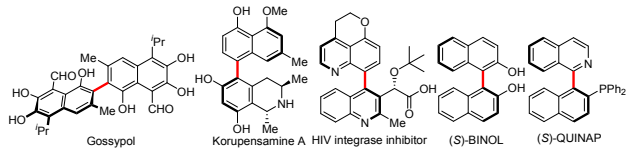
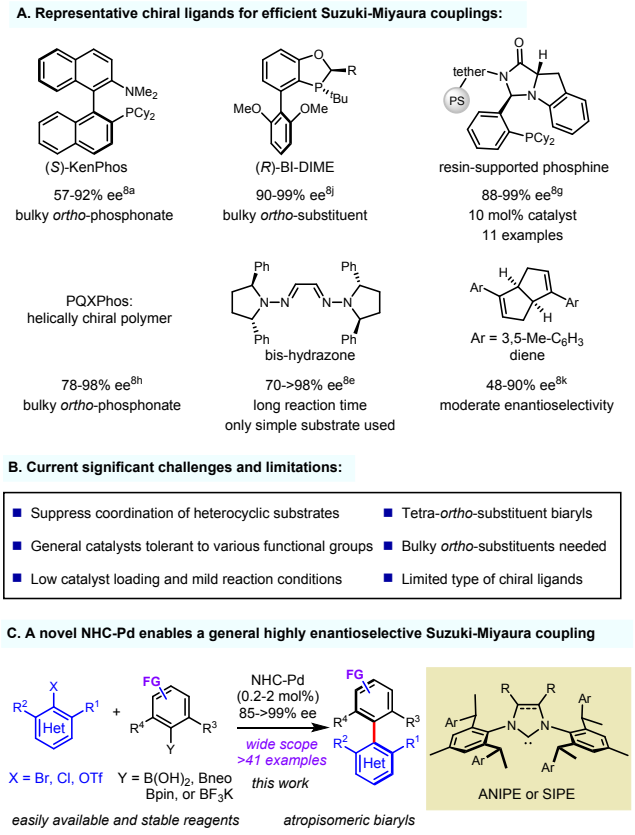


Figure 1. Examples of natural products and ligands bearing axially chiral biaryls.

Accordingly, extensive effort has been devoted to the synthesis of the axially chiral biaryl fragments in the past decades.[5,6] Among these reported methods, the Pd-catalyzed Suzuki-Miyaura cross-coupling reaction[7,8] has been recognized as one of the most practical methods for constructing the atropisomers because of the stability to moisture and oxygen and easy availability of both organo-boron and aryl halide coupling partners. Although Suzuki-Miyaura coupling is one of the most frequently utilized reactions in modern medicinal chemistry, the atroposelective variant of this Nobel prize-winning reaction has not been well-developed. In 2000, the pioneering studies on Pd-catalyzed asymmetric Suzuki-Miyaura reactions were disclosed by the groups of Buchwald[8a] and Cammidge[8c] using KenPhos and a chiral ferrocene ligand, respectively (Scheme 1A). Since then, important contributions in this realm have been made from the group of Fernandez and Lassaletta,[8e-f] Uozumi,[8g,u] Suginome,[8h] Senanayake,[8s] Tang,[8i-j] Lin,[8k] and others,[8m-t] through the development of chiral ligands including bishydrazones, a resin-supported phosphine, a helically chiral polymeric phosphine, biaryl monophosphines, and dienes. However, despite recent achievements, longstanding challenges and significant limitations remain in the field of enantioselective metal-catalyzed $C(sp^2)$-$C(sp^2)$ cross-couplings (Scheme 1B). First, the general construction of heterobiaryls represents an unmet challenge. The use of heterocyclic substrates poses additional challenges due to problems associated with their strong coordination ability,[9] weak reactivity or stability of reagents, and the reduced configurational stability of the products.[6a-d,r] Second, a general catalyst that allows the synthesis of atropisomeric biaryls with a wide array of functional groups and substitution patterns is highly desirable and remains unknown. Third, the preparation of tetra-*ortho*-substituted biaryls through an asymmetric Suzuki-Miyaura reaction is still challenging.[8s] Fourth, the high

enantioselectivity outcomes commonly relied on the use of substrates possessing a bulky *ortho*-substituent,[8] which led to limited variations of the *ortho*-substituents. Furthermore, reactions that performed with low catalyst loading under mild conditions are still rare. Finally, we noted that only a limited range of chiral phosphine ligands provide the products with good enantioselectivity, and limits the further development of enantioselective coupling reactions.

Scheme 1. Pd-Catalyzed Asymmetric Suzuki-Miyaura Cross-Coupling: Synthesis of Atropisomeric Biaryls

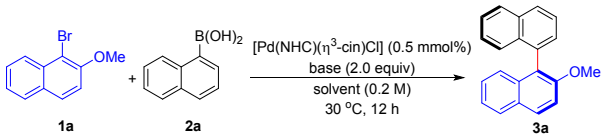


In this context, we felt that the development of new chiral ligand would be a fundamental strategy to address the abovementioned problems. In particular, we envision that the use of a highly electron-donating NHC ligand would form a robust palladium catalyst[10] to facilitate the oxidative addition of aryl halides and to suppress the deactivating coordination of substrates, thus resulting in the tolerance to various heterocycles and functional groups. However, the enantiocontrol of NHC-Pd-catalyzed C(sp^2)-C(sp^2) cross-coupling is notoriously difficult.[8p-r,11] Indeed, the best enantioselectivity so far obtained is 80% ee, despite several decades of effort from the chemical community to develop more selective ligand.[8p] In this regard, we recently developed a family of C_2-symmetric chiral NHC,[12] namely ANIPE and SIPE type ligands (Scheme 1C).[13] We envisage that the modular nature of our NHCs would allow the introduction of bulky and tunable C_2-symmetric substituents on nitrogen to enhance the level of enantiocontrol. Moreover, the sterically demanding property of these NHCs is expected to accelerate the critical elementary reductive elimination step. As part of our continuing efforts in NHC-metal catalysis, we disclose herein the development of a scalable route to a novel bulky chiral NHC ((*R*,*R*,*R*,*R*)-DTB-SIPE) and its successful application to a general, efficient, and highly enantioselective Pd-catalyzed Suzuki-Miyaura reaction for the synthesis of bi- and teraryl atropisomers with remarkably broad scope and tolerance for functional groups and heterocycles.

RESULTS AND DISCUSSION

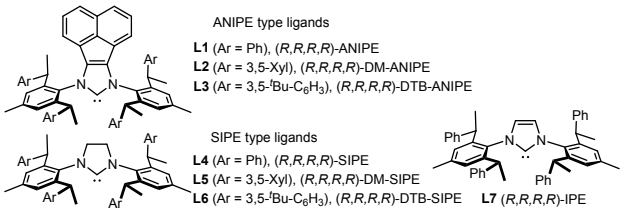
Reaction Optimization And Ligand Design. We thus commenced our study by using 1-bromo-2-methoxynaphthalene (**1a**) and naphthalen-1-ylboronic acid (**2a**) as model substrates for the synthesis of axially chiral biaryl (**3a**) in the presence of palladium-NHC pre-catalysts at ambient temperature. At first, the use of our previously reported ANIPE ligand (**L1**) gave product **3a** in nearly quantitative yield and 44% ee (Table 1, entry 1).

Table 1. Reaction Optimization[a]



1a 2a 3a

Entry	NHC	Solvent	Base	Yield (%)[b]	ee (%)[c]
1	**L1**	EtOH	K_2CO_3	99	44
2	**L2**	EtOH	K_2CO_3	89	74
3	**L3**	EtOH	K_2CO_3	70	80
4	**L4**	EtOH	K_2CO_3	98	54
5	**L5**	EtOH	K_2CO_3	72	84
6	**L6**	EtOH	K_2CO_3	66	96
7	**L7**	EtOH	K_2CO_3	99	40
8	**L6**	THF	K_2CO_3	<2	nd
9	**L6**	^{c}hexane	K_2CO_3	<2	nd
10	**L6**	toluene	K_2CO_3	59	90
11	**L6**	^{i}PrOH	K_2CO_3	73	94
12	**L6**	^{t}BuOH	K_2CO_3	76	97
13	**L6**	^{t}BuOH	NaOH	<2	nd
14	**L6**	^{t}BuOH	KO^{t}Bu	45	97
15	**L6**	^{t}BuOH	K_3PO_4	98	96
16	**L6**	^{t}BuOH	KOH	98	97

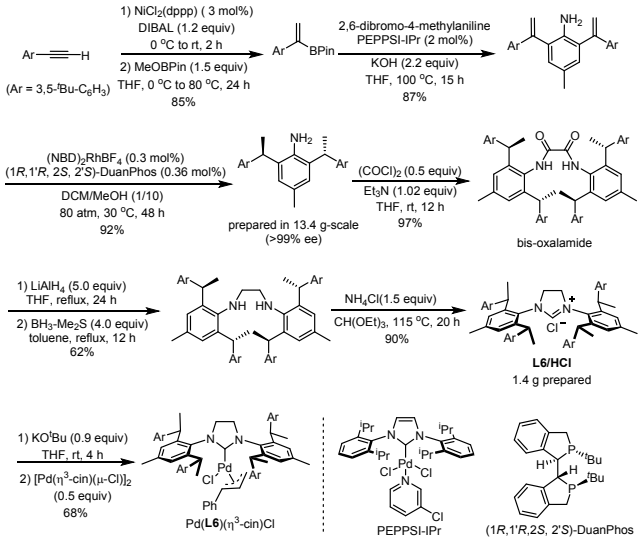


[a]Reactions were performed on a 0.1 mmol scale. [b]Determined by NMR analysis using crude samples. [c]Determined by HPLC analysis with a chiral stationary phase.

Using a bulkier DM-ANIPE ligand (**L2**) with 3,5-xylyl groups on the sidearm phenyl groups afford **3a** in 74% ee (entry 2).

Sterically more demanding DTB-ANIPE possessing 3,5-di-*tert*-butyl phenyl groups (**L3**) further improved the enantioselectivity to 80% (entry 3). Next, we examined our recently disclosed SIPE type ligand. The use of saturated SIPE (**L4**) having the same *N*-substituents with **L1** gave **3a** in quantitative yield and 54% ee (entry 4). Bulkier DM-SIPE ligand (**L5**) shown dramatically increased enantioselectivity of 84% (entry 5). Based on these observations, we concluded that SIPE type ligands were superior to the corresponding ANIPE type ligands in terms of enantioselectivity. The higher enantioselectivity stems from the incorporation of a bulkier flanking group to the ligands. Therefore, we anticipated that an extremely bulky DTB-SIPE ligand (**L6**) should be promising to improve the level of enantiocontrol. However, the preparation of **L6** turned out to be problematic (Scheme 2). Although we could prepare the corresponding chiral aniline[11j] in a 13.4 gram-scale employing very low loading of rhodium catalyst (0.3 mol%), a typical synthetic route to the carbene precursor (an imidazolium salt, **L6**/HCl) involving a diimine intermediate resulted in very low yield. Eventually, we were able to efficiently synthesize **L6**/HCl in gram-scale through a newly designed route using a bis-oxalamide intermediate.[14] As we expected, the use of **L6** did significantly improve the enantioselectivity to 96% ee, although the yield was moderate due to the formation of hydrodebromination byproduct (entry 6). Unsurprisingly, the less bulky unsaturated IPE ligand (**L7**) gave **3a** in very low enantioselectivity of 40% (entry 7). Importantly, a survey of solvents revealed that *t*BuOH was a superior solvent, as the hydrodebromination side reaction was completely suppressed in these cases (entries 8-12). Finally, through extensive screening of base effects, KOH was identified as the most effective base affording product **3a** in 97% ee and 98% yield (entries 13-16).

Scheme 2. Synthesis of a new NHC L6 and the pre-catalyst



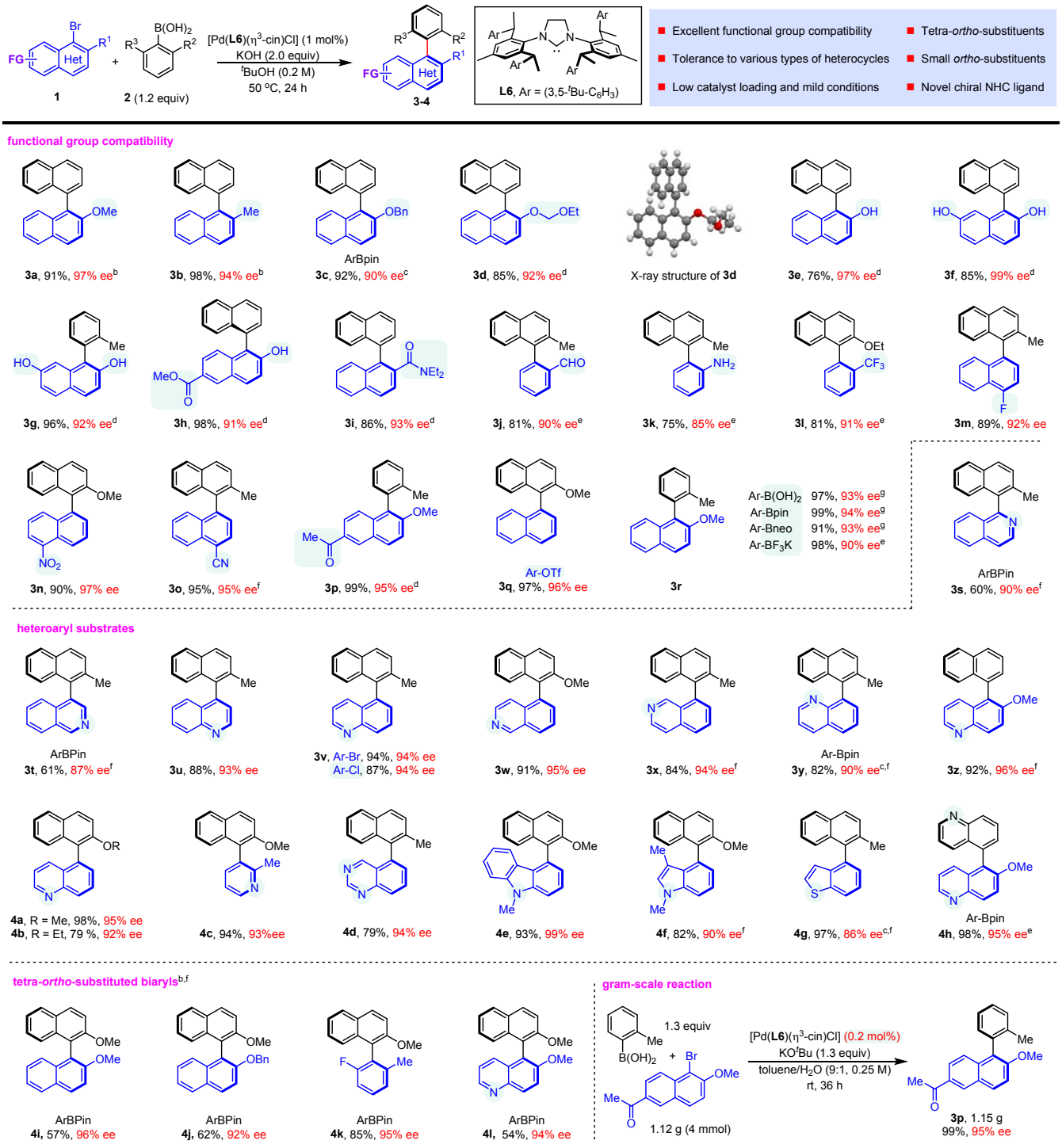
Reaction Scope. With the optimized reaction conditions in hand, we first examined the scope of this asymmetric cross-coupling using simple bromoarene substrates. As shown in Table 2, a wide variety of biaryl atropisomers were obtained with high yields and excellent enantioselectivities (**3a-3r**, 85-99% ee). Notably, large coordination groups at *ortho*-position of haloarenes such as phosphonate[8a,h,m-o], amide[8b], or carbonyl-benzooxazolidinone[8i-j] previously used for optimal stereoinduction are not necessary for our protocol. For example, the chiral *ortho*-hydroxyl biaryls, important structures commonly existed in numerous natural products, were obtained in high enantioselectivities without the assistance of a special bulky protection[8j], but using simple ether protecting groups (**3c**, **3d**) or non-protected substrates (**3e-3h**) even with lower loading of catalyst (0.5 mol%). Remarkably, these mild conditions tolerated a wide array of functional groups, including ethers (**3c**), hemiacetals (**3d**), esters (**3h**), amides (**3i**), aldehydes (**3j**), free anilines (**3k**), free phenols (**3e-3h**), ketones (**3p**), a trifluoromethyl (**3l**), nitro (**3n**), cyano (**3o**) group and fluoride (**3m**). In addition to aryl bromides, aryl chlorides (**3v**) and triflates (**3q**) were competent coupling partners. For the aryl-boron component, various bench-stable and commonly used organoboron sources, including the boronic acids, pinacol and neopentylglycol boronate esters (Bpin, Bneo), as well as the potassium organotrifluoroborates, all delivered products in excellent enantioselectivities and chemical yields (**3r**). These expansions further highlighted the generality of the current method.

Encouraged by the above outcomes, we next surveyed the scope of heteroaryl substrates. Due to their strong coordination to metals and lower configurational stability of products, it's much more challenging to achieve high levels of enantiocontrol. Quinolines, core structures in bioactive molecules and ligands, were chosen for evaluation. To our delight, high to excellent levels of enantiocontrol were obtained when we used bromo-quinoline and -isoquinoline substrates with nitrogen atoms at all possible positions (**3s-3y**, 87-95% ee). Moreover, bromoquinoline substrates were effective for coupling with several different arylboronic acids (**3z-4b**). Aside from quinoline and isoquinolines, other electron-deficient heterocycles such as pyridines (**4c**) and quinazolines (**4d**), and electron-rich heterocycles including carbazole (**4e**), indole (**4f**), and benzothiophene (**4g**), were all compatible, affording heterobiaryls in high yields and enantioselectivities. It bears mentioning that challenging heterobiaryls with lower rotation energy barriers, for example, **3y** and **4g** with less bulky 8-quinoline and benzothiophene fragments, respectively, could be generated in high enantioselectivities by conducting the reaction at ambient temperature. Interestingly, a heteroaryl bromide could be coupled with a heteroaryl boronate in excellent yield and enantioselectivity (**4h**). Importantly, this asymmetric coupling method could apply to the synthesis of challenging tetra-*ortho*-substituted biaryls from both aryl and heteroaryl bromides, furnishing products in excellent enantioselectivities (**4i-4l**). Furthermore, a gram-scale reaction (4 mmol) was successfully performed in the presence of very low loading of catalyst (0.2 mol%) to deliver the product (**3p**) in high yield and enantioselectivity as before, highlighting the practicality of this method. Finally, the absolute configuration of **3d** was determined to be the (*R*)-form by X-ray crystallographic diffraction analysis.

Synthesis Of Axially Chiral Ternaphthalenes. To further demonstrate the utility of our protocol, we applied it to the synthesis of atropisomeric ternaphthalenes (Scheme 3). Ternaphthalenes and oligonaphthalenes, which are higher homologs of binaphthalene, have played essential roles in supramolecular chemistry and materials science.[15] However, the asymmetric catalytic synthesis of these homologs has rarely been reported, presumably due to the difficulty in control of both diastereoselectivity and enantioselectivity.[16] To our

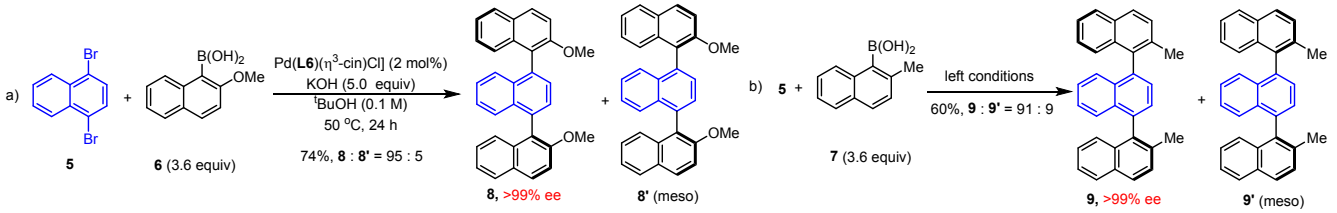
delight, the subjection of 1,4-dibromonaphthalene (**5**) and boronic acids (**6** or **7**) to our coupling conditions smoothly delivered the optically active ternaphthalenes (**8** or **9**) in excellent enantioselectivity (>99% ee) and in high to excellent ratio with their meso-isomers (**8'** or **9'**).

Table 2. Substrate Scope[a]



[a]Yields of isolated products on a 0.2 mmol scale. [b]40 °C. [c]30 °C. [d]0.5 mol% catalyst, KO^{t}Bu (1.3 equiv), toluene/H_2O (9:1), rt, 24 h. [e]2 mol% catalyst, Cs_2CO_3 (2.5 equiv), ^{t}BuOH/H_2O (9:1), 60 °C, 24 h. [f]2 mol% catalyst. [g]0.5 mol% catalyst.

Scheme 3. Synthesis of Axially Chiral Ternaphthalenes



Proposed Stereoinduction Models. To get insight into the origin of excellent stereoinduction of the newly designed ligand, we obtained the X-ray crystal structure of Pd(**L6**)(η^3-cin)Cl (Figure 2a).[17] The steric map of this complex shows a pronounced C_2-symmetric binding pocket with two accessible quadrants.[18] Based on the X-ray crystal structure, we proposed stereoinduction models for the oxidative addition and transmetalation intermediates of **L6**-Pd complex, as shown in Figure 2b. Notably, due to the steric repulsions between coupling partners and the bulky 3,5-di-*tert*-butyl phenyl group on the ligand, the reductive elimination would proceed through the favored transition state (TM_1), in which the two naphthyl substituents occupy the two vacant quadrants provided by **L6**-Pd complex, thereby furnishing biaryls **3d** in the (*R*)-configuration. These results are consistent with our initial hypothesis that the bulkier C_2-symmetric *N*-substituents on NHCs would lead to a more efficient enantiodiscrimination and facilitate the key reductive elimination step.

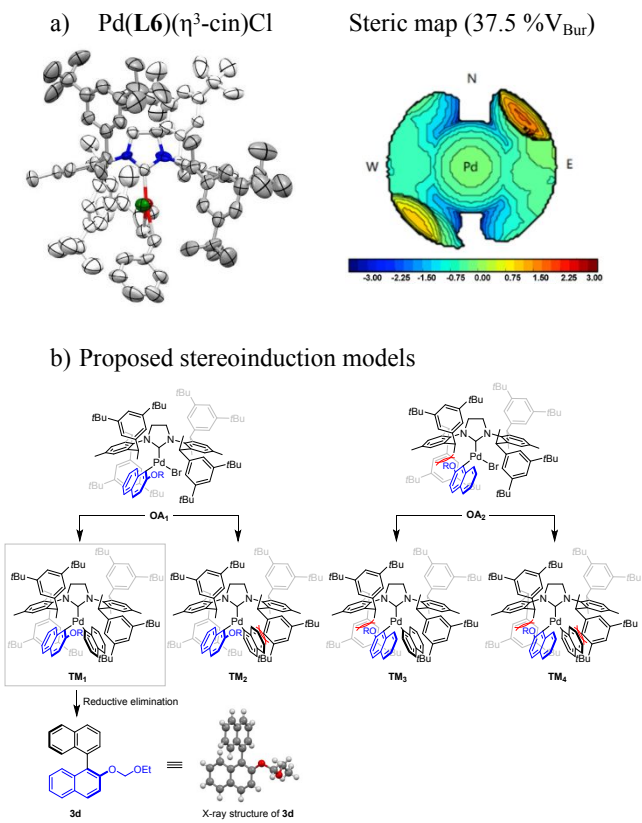


Figure 2. a) X-ray crystal structure and corresponding steric map of Pd(**L6**)(η^3-cin)Cl. b) Oxidative addition ($OA_{1\text{-}2}$) and transmetalation ($TM_{1\text{-}4}$) intermediates to binaphthyls (**3d**).

■ CONCLUSIONS

In conclusion, we have developed the first highly enantioselective NHC-Pd catalyzed (Suzuki-Miyaura) C(sp^2)-C(sp^2) cross-coupling reaction for the synthesis of atropisomeric biaryls. A diverse variety of axially chiral biaryls, heterobiaryls, tetra-*ortho*-substituted biaryls, and ternaphthalenes, were efficiently prepared in high yields with excellent levels of enantiocontrol from readily available and stable substrates. These reactions tolerate a remarkable scope of heterocycles and functional groups, employ low catalyst loading, and proceed under mild conditions. Key to the success of the reaction was the development and application of a very bulky C_2-symmetric chiral NHC for the Pd catalyst. Efforts to further explore this NHC-metal catalysis are underway in our laboratory.

■ ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.
Experimental procedures, spectroscopic data, and NMR spectra of all products (PDF)
Crystallographic data for **3d** (CCDC 1921079) (CIF)
Crystallographic data for Pd(**L4**)(η^3-cin)Cl (CCDC 1921080) (CIF)
Crystallographic data for Pd(**L6**)(η^3-cin)Cl (CCDC 1921081) (CIF)

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Notes
The authors declare the following financial interests: A patent (WO2019096209) for some of the ligands (including **L6**) in this Communication has been filed.

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■ REFERENCES

(1) (a) Kozlowski, M. C.; Morgan, B. J.; Linton, E. C. Total Synthesis of Chiral Biaryl Natural Products by Asymmetric Biaryl Coupling. *Chem. Soc. Rev.* **2009**, *38*, 3193. (b) Bringmann, G.; Gulder, T.; Gulder, T. A. M.; Breuning, M. Atroposelective Total Synthesis of Axially Chiral Biaryl Natural Products. *Chem. Rev.* **2011**, *111*, 563.

(2) (a) Clayden, J.; Moran, W. J.; Edwards, P. J.; LaPlante, S. R. The Challenge of Atropisomerism in Drug Discovery. *Angew. Chem. Int. Ed.* **2009**, *48*, 6398. (b) LaPlante, S. R.; Fader, L. D.; Fandrick, K. R.; Fandrick, D. R.; Hucke, O.; Kenper, R.; Miller, S. P. F.; Edwards, P. J.

Assessing Atropisomer Axial Chirality in Drug Discovery and Development. *J. Med. Chem.* **2011**, *54*, 7005. (c) Smyth, J. E.; Butler, N. M.; Keller, P. A. A. Twist of Nature – the Significance of Atropisomers in Biological Systems. *Nat. Prod. Rep*. **2015**, *32*, 1562.

(3) (a) Lu Y.-Z.; Wu, S.-C.; Yue, Y.; He, S.; Li, J.; Tang, J.; Wang, W.; Zhou, H.-B. Gossypol with Hydrophobic linear Esters Exhibits Enhanced Antitumor Activity as an Inhibitor of Antiapoptotic Proteins. *ACS Med. Chem. Lett*. **2016**, *7*, 1185. (b) Hallock, Y. F.; Manfredi, K. P.; Blunt, J. W.; Cardellina, J. H., II; Schaffer, M.; Gulden, K.-P.; Bringmann, G.; Lee, A. Y.; Clardy, J.; Francois, G.; Boyd, M. R. Korupensamines A-D, Novel Antimalarial Alkaloids from Ancistrocladus korupensis. *J. Org. Chem*. **1994**, *59*, 6349. (c) Fandrick, K. R.; Li, W.; Zhang, Y.; Tang, W.; Gao, J.; Rodriguez, S.; Patel, N. D.; Reeves, D. C.; Wu, J.-P.; Sanyal, S.; Gonnella, N.; Qu, B.; Haddad, N.; Lorenz, J. C.; Sidhu, K.; Wang, J.; Ma, S.; Grinberg, N.; Lee, H.; Tsantrizos, Y.; Poupart, M.-A.; Busacca, C. A.; Yee, N. K.; Lu, B. Z.; Senanayake, C. H. Concise and Practical Asymmetric Synthesis of a Challenging Atropisomeric HIV Integrase Inhibitor. *Angew. Chem., Int. Ed.* **2015**, 54, 7144.

(4) (a) Noyori, R.; Takaya, H. BINAP: An Efficient Chiral Element for Asymmetric Catalysis. *Acc. Chem. Res.* **1990**, *23*, 345. (b) Brunel, J. M. BINOL: A Versatile Chiral Reagent. *Chem. Rev.* **2005**, *105*, 857. (c) Carroll, M. P.; Guiry, P. J. P, N ligands in asymmetric catalysis. *Chem. Soc. Rev.* **2014**, 43, 819. For a book, see: (d) Privileged Chiral Ligands and Catalysts; Zhou, Q.-L., Ed.; Wiley-VCH: Weinheim, Germany, 2011.

(5) For selected reviews on the synthesis of axially chiral biaryls, see: (a) Bringmann, G.; Price-Mortimer, A. J.; Keller, P. A.; Gresser, M. J.; Garner, J.; Breuning, M. Atropselective Synthesis of Axially Chiral Biaryl Compounds. *Angew. Chem., Int. Ed*. **2005**, *44*, 5384. (b) Kumarasamy, E.; Raghunathan, R.; Sibi, M. P.; Sivaguru, J. Nonbiaryl and Heterobiaryl Atropisomers: Molecular Templates with Promise for Atropselective Chemical Transformations. *Chem. Rev.* **2015**, *115*, 11239. (c) Wencel-Delord, J.; Panossian, A.; Leroux, F. R.; Colobert, F. Recent Advances and New Concepts for the Synthesis of Axially Stereoenriched Biaryls. *Chem. Soc. Rev*. **2015**, *44*, 3418. (d) Yang, H.; Yang, X.; Tang, W. Transition-Metal Catalyzed Asymmetric Carbon-Carbon Cross-Coupling with Chiral Ligands. *Tetrahedron* **2016**, *72*, 6143. (e) Loxq, P.; Manoury, E.; Poli, R.; Deydier, E.; Labande, A. Synthesis of Axially Chiral Biaryl Compounds by Asymmetric Catalytic Reactions with Transition Metals. *Coord. Chem. Rev.* **2016**, *308*, 131. (f) Wang, Y.-B.; Tan, B. Construction of Axially Chiral Compounds via Asymmetric Organocatalysis. *Acc. Chem. Res.* **2018**, *51*, 534. (g) Zilate, B.; Castrogiovanni, A.; Sparr, C. Catalyst-Controlled Stereoselective Synthesis of Atropisomers. *ACS Catal.* **2018**, *8*, 2981. (h) Metrano, A. J.; Miller, S. J. Peptide-Based Catalysts Reach the Outer Sphere through Remote Desymmetrization and Atroposelectivity. *Acc. Chem. Res*. **2019**, *52*, 199.

(6) For selected recent examples: (a) Zheng, J.; Cui, W.-J.; Zheng, C.; You, S.-L. Synthesis and Application of Chiral Spiro Cp Ligands in Rhodium-Catalyzed Asymmetric Oxidative Coupling of Biaryl Compounds with Alkenes. *J. Am. Chem. Soc*. **2016**, *138*, 5242. (b) Wang, Q.; Cai, Z.-J.; Liu, C.-X.; Gu, Q.; You, S.-L. Rhodium-Catalyzed Atroposelective C-H Arylation: Efficient Synthesis of Axially Chiral Heterobiaryls. *J. Am. Chem. Soc.* **2019**,141, 9504. (c) Wang, J.; Chen, M.-W.; Ji, Y.; Hu, S.-B.; Zhou, Y.-G. Kinetic Resolution of Axially Chiral 5- or 8-Substituted Quinolines via Asymmetric Transfer Hydrogenation. *J Am. Chem. Soc.* **2016**, *138*, 10413. (d) Ros, A.; Estepa, B.; Ramírez-López, P.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. Dynamic Kinetic Cross-Coupling Strategy for the Asymmetric Synthesis of Axially Chiral Heterobiaryls. *J. Am. Chem. Soc.* **2013**, *135*, 15730. (e) Ramírez-López, P.; Ros, A.; Estepa, B.; Fernández, R.; Fiser, B.; Gómez-Bengoa, E.; Lassaletta, J. M. A Dynamic Kinetic C–P Cross-Coupling for the Asymmetric Synthesis of Axially Chiral P, N Ligands. *ACS Catal.* **2016**, *6*, 3955. (f) Hornillos, V.; Carmona, J. A.; Ros, A.; Iglesias-Siguenza, J.; Lopez-Serrano, J.; Fernandez, R.; Lassaletta, J. M. Dynamic Kinetic Resolution of Heterobiaryl Ketones by Zinc-Catalyzed Asymmetric Hydrosilylation. *Angew. Chem. Int. Ed.* **2018**, *57*, 3777. (g) Carmona, J. A.; Hornillos, V.; Ramírez-López, P.; Ros, A.; Iglesias-Sigüenza, J.; Gómez-Bengoa, E.; Fernández, R.; Lassaletta, J. M. Dynamic Kinetic Asymmetric Heck Reaction for the Simultaneous Generation of Central and Axial Chirality. *J. Am. Chem. Soc.* **2018**, *140*, 11067. (h) Narute, S.; Parnes, R.; Toste, F. D.; Pappo, D. Enantioselective Oxidative Homocoupling and Cross-Coupling of 2-Naphthols Catalyzed by Chiral Iron Phosphate Complexes. *J. Am. Chem. Soc*. **2016**, *138*, 16553. (i) Jolliffe, J. D.; Armstrong, R. J.; Smith, M. D. Catalytic Enantioselective Synthesis of Atropisomeric Biaryls by a Cation-Directed O-Alkylation. *Nat. Chem.* **2017**, *9*, 558. (j) Kwon, Y.; Chinn, A. J.; Kim, B.; Miller, S. J. Divergent Control of Point and Axial Stereogenicity: Catalytic Enantioselective C-N Bond-Forming Cross-Coupling and Catalyst-Controlled Atroposelective Cyclodehydration. *Angew. Chem. Int. Ed.* **2018**, *57*, 6251. (k) Kwon, Y.; Li, J.; Reid, J. P.; Crawford, J. M.; Jacob, R.; Sigman, M. S.; Toste, F. D.; Miller, S. J. Disparate Catalytic Scaffolds for Atroposelective Cyclodehydration. *J. Am. Chem. Soc.* **2019**, *141*, 6698. (l) Pan, C.; Zhu, Z.; Zhang, M.; Gu, Z. Palladium-Catalyzed Enantioselective Synthesis of 2-Aryl Cyclohex-2-enone Atropisomers: Platform Molecules for the Divergent Synthesis of Axially Chiral Biaryl Compounds. *Angew. Chem. Int. Ed.* **2017**, *56*, 4777. (m) Ding, L.; Sui, X.; Gu, Z. Enantioselective Synthesis of Biaryl Atropisomers via Pd/Norbornene-Catalyzed Three-Component Cross-Couplings. *ACS Catal.* **2018**, *8*, 5630. (n) Enantioselective Carbon-Carbon Bond Cleavage for Biaryl Atropisomers Synthesis, Deng, R.; Xi, J.; Li, Q.; Gu, Z. *Chem*, **2019**, *5*, 1. (o) Raut, V. S.; Jean, M.; Vanthuyne, N.; Roussel, C.; Constantieux, T.; Bressy, C.; Bugaut, X.; Bonne, D.; Rodriguez, J. Enantioselective Syntheses of Furan Atropisomers by an Oxidative Central-to-Axial Chirality Conversion Strategy. *J. Am. Chem. Soc.* **2017**, *139*, 2140. (p) Liao, G.; Li, B.; Chen, H.-M.; Yao, Q.-J.; Xia, Y.-N.; Luo, J.; Shi, B.-F. Pd-Catalyzed Atroposelective C–H Allylation through β-O Elimination: Diverse Synthesis of Axially Chiral Biaryls. *Angew. Chem. Int. Ed.* **2018**, *57*, 17151. (q) Liao, G.; Yao, Q.-J.; Zhang, Z.-Z.; Wu, Y.-J.; Huang, D.-Y.; Shi, B.-F. Scalable, Stereocontrolled Formal Syntheses of (+)-Isoschizandrin and (+)-Steganone: Development and Applications of Palladium(II)-Catalyzed Atroposelective C–H Alkynylation. *Angew. Chem. Int. Ed.* **2018**, *57*, 3661. (r) Luo, J.; Zhang, T.; Wang, L.; Liao, G.; Yao, Q.-J.; Wu, Y.-J.; Zhan, B.-B.; Lan, Y.; Lin, X.-F.; Shi, B.-F. Enantioselective Synthesis of Biaryl Atropisomers via Pd-Catalyzed C–H Olefination using Chiral Spiro Phosphoric Acid Ligands. *Angew. Chem. Int. Ed.* **2019**, *58*, 6708. (s) Luo, J.; Zhang, T.; Wang, L.; Liao, G.; Yao, Q.-J.; Wu, Y.-J.; Zhan, B.-B.; Lan, Y.; Lin, X.-F.; Shi, B.-F. Enantioselective Synthesis of Biaryl Atropisomers by Pd-Catalyzed C-H Olefination using Chiral Spiro Phosphoric Acid Ligands. *Angew. Chem., Int. Ed.* **2019**, *131*, 1. (t) Li, H.; Yan, X.; Zhang, J.; Guo, W.; Jiang, J.; Wang, J. Enantioselective Synthesis of C-N Axially Chiral N-Aryloxindoles by Asymmetric Rhodium-Catalyzed Dual C–H Activation. *Angew. Chem. Int. Ed.* **2019**, *58*, 6732. (u) Ma, C.; Jiang, F.; Sheng, F. T.; Jiao, Y.; Mei, G. J.; Shi, F. Design and Catalytic Asymmetric Construction of Axially Chiral 3,3'-Bisindole Skeletons. *Angew. Chem. Int. Ed.* **2019**, *58*, 3014. (v) Qi, L. W.; Mao, J. H.; Zhang, J.; Tan, B. Organocatalytic Asymmetric Arylation of Indoles Enabled by Azo Groups. *Nat. Chem.* **2018**, *10*, 58. (w) Qi, L.-W.; Li, S.; Xiang, S.-H.; Wang, J.; Tan, B. Asymmetric construction of atropisomeric biaryls via a redox neutral cross-coupling strategy. *Nat. Catal.* **2019**, *2*, 314. (x) Tian, J.-M.; Wang, A.-F.; Yang, J.-S.; Zhao, X.-J.; Tu, Y.; Zhang, S.-Y.; Chen, Z.-M. Cu-Complex Catalyzed Asymmetric Aerobic Oxidative Cross Coupling of 2-Naphthols: Enantioselective Synthesis of C1-symmetric BINOLs Bearing 3,3'-Disubstituents. *Angew. Chem. Int. Ed.* **2019**, *58*, 11023. (y) Tian, M.; Bai, D.; Zheng, G.; Chang J.; Li, X. Rh(III)-Catalyzed Asymmetric Synthesis of Axially Chiral Biindolyls by Merging C-H Activation and Nucleophilic Cyclization, *J. Am. Chem. Soc.* **2019**, *141*, 9527.

(7) For selected reviews on Pd-catalyzed Suzuki-Miyaura reactions: (a) Miyaura, N.; Suzuki, A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* **1995**, *95*, 2457. (b) Martin, R.; Buchwald, S. L. Palladium-Catalyzed Suzuki-Miyaura Cross-coupling Reactions Employing Dialkylbiaryl Phosphine Ligands. *Acc Chem Res*. **2008**, *41*, 1461. For reviews on asymmetric Suzuki-Miyaura reactions: (c) Baudoin, O. The Asymmetric Suzuki

Coupling Route to Axially Chiral Biaryls. *Eur. J. Org. Chem.* **2005**, 4223. (d) Zhang, D.; Wang, Q. Palladium catalyzed asymmetric Suzuki-Miyaura coupling reactions to axially chiral biaryl compounds: Chiral ligands and recent advances. *Coord. Chem. Rev.* **2015**, *286*, 1.

(8) For selected examples on asymmetric Suzuki-Miyaura reactions: (a) Yin, J. J.; Buchwald, S. L. A Catalytic Asymmetric Suzuki Coupling for the Synthesis of Axially Chiral Biaryl Compounds. *J. Am. Chem. Soc.* **2000**, *122*, 12051. (b) Shen, X.; Jones, G. O.; Watson, D. A.; Bhayana, B.; Buchwald, S. L. Enantioselective Synthesis of Axially Chiral Biaryls by the Pd-Catalyzed Suzuki-Miyaura Reaction: Substrate Scope and Quantum Mechanical Investigations. *J. Am. Chem. Soc.* **2010**, *132*, 11278. (c) Cammidge, A. N.; Crepy, K. V. L. The First Asymmetric Suzuki Cross-Coupling Reaction. *Chem. Commun.* **2000**, 1723. (d) Cammidge, A. N.; Crepy, K. V. L. Synthesis of Chiral Binaphthalenes using the Asymmetric Suzuki Reaction. *Tetrahedron*. **2004**, *60*, 4377. (e) Bermejo, A.; Ros, A.; Fernandez, R.; Lassaletta, J. M. C_2-Symmetric Bis-Hydrazones as Ligands in the Asymmetric Suzuki-Miyaura Cross-Coupling. *J. Am. Chem. Soc*. **2008**, *130*, 15798. (f) Ros, A.; Estepa, B.; Bermejo, A.; Alvarez, E.; Fernandez, R.; Lassaletta, J. M. Phosphino Hydrazones as Suitable Ligands in the Asymmetric Suzuki-Miyaura Cross-Coupling. *J. Org. Chem.* **2012**, *77*, 4740. (g) Uozumi, Y.; Matsuura, T.; Arakawa, T.; Yamada, Y. M. A. Asymmetric Suzuki-Miyaura Coupling in Water with a Chiral Palladium Catalyst Supported on an Amphiphilic Resin. *Angew. Chem., Int. Ed.* **2009**, *48*, 2708. (h) Yamamoto, T.; Akai, Y.; Nagata, Y.; Suginome, M. Highly Enantioselective synthesis of Axially Chiral biarylphosphonates: Asymmetric Suzuki-Miyaura Coupling Using High-Molecular-Weight, Helically Chiral Polyquinoxaline-Based Phosphines. *Angew. Chem., Int. Ed.* **2011**, *50*, 8844. (i) Tang, W.; Patel, N. D.; Xu, G.; Xu, X.; Savoie, J.; Ma, S.; Hao, M.-H.; Keshipeddy, S.; Capacci, A. G.; Wei, X.; Zhang, Y.; Gao, J.; Li, W.; Rodriguez, S.; Lu, B. Z.; Yee, N. K.; Senanayake, C. H. Efficient Chiral Monophosphorous Ligands for Asymmetric Suzuki-Miyaura Coupling Reactions. *Org. Lett*. **2012**, *14*, 2258. (j) Xu, G.; Fu, W.; Liu, G.; Senanayake, C. H.; Tang, W. Efficient Syntheses of Korupensamines A, B and Michellamine B by Asymmetric Suzuki-Miyaura Coupling Reactions. *J. Am. Chem. Soc*. **2014**, *136*, 570. (k) Zhang, S.-S.; Wang, Z. Q.; Xu, M.-H.; Lin, G.-Q. Chiral Diene as the Ligand for the Synthesis of Axially chiral Compounds via the Palladium-Catalyzed Suzuki-Miyaura Coupling Reaction. *Org. Lett.* **2010**, *12*, 5546. (l) Sawai, K.; Tatumi, R.; Nakahodo, T.; Fujihara, H. Asymmetric Suzuki-Miyaura Coupling Reactions Catalyzed by Chiral Palladium Nanoparticles at Room Temperature. *Angew. Chem., Int. Ed.* **2008**, *47*, 6917. (m) Wang, S.; Li, J.; Miao, T.; Wu, W.; Li, Q.; Zhuang, Y.; Zhou, Z.; Qiu, L.-Q. Highly Efficient Synthesis of a Class of Novel Chiral-Bridged Atropisomeric Monophosphine Ligands via Simple Desymmetrization and Their Applications in Asymmetric Suzuki-Miyaura Coupling Reaction. *Org. Lett*. **2012**, *14*, 1966. (n) Zhou, Y.; Zhang, X.; Liang, H.; Cao, Z.; Zhao, X.; He, Y.; Wang, S.; Pang, J.; Zhou, Z.; Ke, Z.; Qiu, L.-Q. Enantioselective Synthesis of Axially Chiral Biaryl Monophosphine Oxides via Direct Asymmetric Suzuki Coupling and DFT Investigations of the Enantioselectivity. *ACS Catal.* **2014**, *4*, 1390. (o) Xia, W.; Li, Y.; Zhou, Z.; Chen, H.; Liang, H.; Yu, S.; He, X.; Zhang, Y.; Pang, J.; Zhou, Z.; Qiu, L.-Q. Synthesis of Chiral-Bridged Atropisomeric Monophosphine Ligands with Tunable Dihedral Angles and their Applications in Asymmetric Suzuki-Miyaura Coupling Reactions. *Adv. Synth. Catal.* **2017**, *359*, 1656. (p) Benhamou, L.; Besnard, C.; Kundig, E. P. Chiral PEPPSI Complexes: Synthesis, Characterization, and Application in Asymmetric Suzuki-Miyaura Coupling Reactions. *Organometallics.* **2014**, *33*, 260. (q) Li, Y.; Tang, J.; Gu, J.; Wang, Q.; Sun, P.; Zhang, D. Chiral 1,2-CyclohexaneBridged Bis-NHC Palladium Catalysts for Asymmetric Suzuki-Miyaura Coupling: Synthesis, Characterization, and Steric Effects on Enantiocontrol. *Organometallics*. **2014**, *33*, 876. (r) Wu, L.-L.; Salvador, A.; Ou, A.; Shi, M.-W.; Skelton, B. W.; Dorta, R. Monodentate Chiral N-Heterocyclic Carbene-Palladium-Catalyzed Asymmetric Suzuki-Miyaura and Kumada Coupling. *Synlett* **2013**, *24*, 1215. (s) Patel, N. D.; Sieber, J. D.; Tcyrulnikov, S.; Simmons, B. J.; Rivalti, D.; Duvvuri, K.; Zhang, Y.; Gao, D. A.; Fandrick, K. R.; Haddad, N.; Lao, K. S.; Mangunuru, H. P. R.; Biswas, S.; Qu, B.; Grinberg, N.; Pennino, S.; Lee, H.; Song, J. J.; Gupton, B. F.; Garg, N. K.; Kozlowski, M. C.; Senanayake, C. H. Computationally Assisted Mechanistic Investigation and Development of Pd-Catalyzed Asymmetric Suzuki-Miyaura and Negishi Cross-Coupling Reactions for Tetra-*ortho*-Substituted Biaryl Synthesis. *ACS Catal.* **2018**, *8*, 10190. (t) Genov, M.; Almorin, A.; Espinet, P. Efficient Synthesis of Chiral 1,1'-Binaphthalenes by the Asymmetric Suzuki-Miyaura Reactions: Dramatic Synthetic Improvement by Simple Purification of Naphthylboronic Acids. *Chem. -Eur. J.* **2006**, *12*, 9346. (u) Uozumi, Y.; Matsuura, Y.; Suzuka, T.; Arakawa, T.; Yamada, Y. M. A. Palladium-Catalyzed Asymmetric Suzuki-Miyaura Cross Coupling with Homochiral Phosphine Ligands Having Tetrahydro-1H-imidazo[1,5-a]indole Backbone. *Synthesis*. **2017**, *49*, 59.

(9) Liu, Y.-J.; Xu, H.; Kong, W.J.; Shang, M.; Dai, H.-X.; Yu, J.-Q. Overcoming the limitations of directed C-H functionalizations of heterocycles. *Nature*, **2014**, *155*, 389.

(10) (a) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. Palladium Complexes of N-Heterocyclic Carbenes as Catalysts for Cross-Coupling Reactions—A Synthetic Chemist-s Perspective. *Angew. Chem. Int. Ed*. **2007**, *46*, 2768. (b) Valente, C.; Calimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. The Development of Bulky Palladium NHC Complexes for the Most-Challenging Cross-Coupling Reactions. *Angew. Chem. Int. Ed*. **2012**, *51*, 3314. (c) Fortman, G. C.; Nolan, S. P. N-Heterocyclic carbene (NHC) ligands and palladium in homogeneous cross-coupling catalysis: a perfect union. *Chem. Soc. Rev.*, **2011**, *40*, 5151.

(11) For selected examples on highly enantioselective (>90% ee) NHC-metal catalysis in $C(sp^3)$-C bond-forming reactions, see: (a) Larsen, A. O.; Leu, W.; Oberhuber, C. N.; Campbell, J. E.; Hoveyda, A. H.; Bidentate NHC-Based Chiral Ligands for Efficient Cu-Catalyzed Enantioselective Allylic Alkylations: Structure and Activity of an Air-Stable Chiral Cu Complex. *J. Am. Chem. Soc*. **2004**, *126*, 11130. (b) Sato, Y.; Hinata, Y.; Seki, R.; Oonishi, Y.; Saito, N. Nickel-Catalyzed Enantio- and Diastereoselective Three-Component Coupling of 1,3-Dienes, Aldehydes, and Silanes Using Chiral N-Heterocyclic Carbenes as Ligands. *Org. Lett*. **2007**, *9*, 5597. (c) Zhang, T.; Shi, M. Chiral Bidentate Bis(N-Heterocyclic Carbene)-Based Palladium Complexes Bearing Carboxylate Ligands: Highly Effective Catalysts for the Enantioselective Conjugate Addition of Arylboronic Acids to Cyclic Enones. *Chem. Eur. J.* **2008**, *14*, 3759. (d) Wurtz, S.; Lohre, C.; Frohlich, R.; Bergander, K.; Glorius, F. IBiox[(-)-menthyl]: A Sterically Demanding Chiral NHC Ligand. *J. Am. Chem. Soc*. **2009**, *131*, 8344. (e) Nakanishi, M.; Katayev, D.; Besnard, C.; Kundig, E. P. Fused Indolines by Palladium-Catalyzed Asymmetric C-C Coupling Involving an Unactivated Methylene Group. *Angew. Chem., Int. Ed.* **2011**, *50*, 7438. (f) Ho, C.-Y.; Chan, C.-W.; He, L. S. Catalytic Asymmetric Hydroalkenylation of Vinylarenes: Electronic Effects of Substrates and Chiral N-Heterocyclic Carbene Ligands. *Angew. Chem., Int. Ed.* **2015**, *54*, 4512. (g) Kumar, R.; Hoshimoto, Y.; Tamai, E.; Ohashi, M.; Ogoshi, S. Two-step Synthesis of Chiral Fused Tricyclic Scaffolds from Phenols via Desymmetrization on Nickel. *Nat. Commun*. **2017**, *8*, 32. (h) Wang, H.; Lu, G.; Sormunen, G. J.; Malik, H. A.; Liu, P.; Montgomery, J. NHC Ligands Tailored for Simultaneous Regio- and Enantiocontrol in Nickel-Catalyzed Reductive Couplings. *J. Am. Chem. Soc.* **2017**, *139*, 9317. (i) Loup, J.; Zell, D.; Oliveira, J. C. A.; Keil, H.; Stalke, D.; Ackermann, L. Asymmetric Iron-Catalyzed C-H Alkylation Enabled by Remote Ligand meta-Substitution. *Angew. Chem., Int. Ed.* **2017**, *56*, 14197. (j) Diesel, J.; Finogenova, A. M.; Cramer, N. Nickel-Catalyzed Enantioselective Pyridone C–H Functionalizations Enabled by a Bulky N-Heterocyclic Carbene Ligand. *J. Am. Chem. Soc*. **2018**, *140*, 4489.

(12) (a) Wang, F.; Liu, L.-J.; Wang, W.; Li, S.; Shi, M. Chiral NHC–Metal-Based Asymmetric Catalysis. *Coord. Chem. Rev*. **2012**, *256*, 804. (b) Janssen-Muller, D.; Schlepphorst, C.; Glorius, F. Privileged chiral N-heterocyclic carbene ligands for asymmetric transition-metal catalysis. *Chem. Soc. Rev*. **2017**, *46*, 4845.

(13) (a) Cai, Y.; Yang, X.-T.; Zhang, S.-Q.; Li, F.; Li, Y.-Q.; Ruan, L.-X.; Hong, X.; Shi, S.-L. Copper Catalyzed Enantioselective Markovnikov Protoboration of α-Olefins Enabled by a Buttressed N-

Heterocyclic Carbene Ligand. *Angew. Chem., Int. Ed.* **2018**, *57*, 1376. (b) Cai, Y.; Zhang, J.-W.; Li, F.; Liu, J.-M.; Shi, S.-L. Nickel/N-Heterocyclic Carbene Complex-Catalyzed Enantioselective Redox-Neutral Coupling of Benzyl Alcohols and Alkynes to Allylic Alcohols. *ACS Catal*. **2019**, *9*, 1. (c) Zhang, W.-B.; Yang, X.-T.; Ma, J.-B.; Su, Z.-M.; Shi, S.-L. Regio- and Enantioselective C-H Cyclization of Pyridines with Alkenes Enabled by a Nickel/N-Heterocyclic Carbene Catalysis. *J. Am. Chem. Soc*. **2019**, *141*, 5628. (d) Cai, Y.; Ye, X.; Liu, S.; Shi, S.-L. Nickel/NHC-Catalyzed Asymmetric C–H Alkylation of Fluoroarenes with Alkenes: Synthesis of Enantioenriched Fluorotetralins. *Angew. Chem., Int. Ed.* **2019**, 10.1002/anie.201907387. (e) Independently, similar ligands were reported by the Cramer group, see 11j. The design of ligands inspired by Gawley's carbene (**L7**), see: (f) Albright, A.; Gawley, R. E. Application of a C_2-Symmetric Copper Carbenoid in the Enantioselective Hydrosilylation of Dialkyl and Aryl-Alkyl Ketones. *J. Am. Chem. Soc*. **2011**, *133*, 19680.

(14) **L6** was included in our patent, see: (a) Shi, S.-L.; Cai, Y.; Yang, X.-T.; Li, F. WO2019096209 (publication date: May 23rd, **2019**). (b) During the preparation of this manuscript, a Ni-catalysis using **L6** appeared: Diesel, J.; Grosheva, D.; Kodama, S.; Cramer, N. A Bulky Chiral N-Heterocyclic Carbene Nickel Catalyst Enables Enantioselective C–H Functionalizations of Indoles and Pyrroles. *Angew. Chem. Int. Ed*. **2019**, *58*, 11044.

(15) (a) Lin, P. Fluorescence of Organic Molecules in Chiral Recognition. *Chem. Rev*. **2004**, *104*, 1687. (b) Yashima, E.; Ousaka, N.; Taura, D.; Shimomura, K.; Ikai, T.; Maeda, K. Supramolecular Helical Systems: Helical Assemblies of Small Molecules, Foldamers, and Polymers with Chiral Amplification and Their Functions. *Chem. Rev*. **2016**, *116*, 13752.

(16) Hayashi, T.; Hayashizaki, K.; Ito, Y. Asymmetric Synthesis of Axially Chiral 1,1':5',1' - and 1,1':4',1' -Ternaphthalenes by Asymmetric Cross-Coupling with a Chiral Ferrocenylphosphine-Nickel Catalyst. *Tetrahedron Lett.* **1989**, *30*, 215.

(17) The X-ray crystal structure of Pd(**L4**)(η^3-cin)Cl (CCDC 1921080) was also obtained, see SI for details.

(18) (a) Falivene, L.; Credendino, R.; Poater, A.; Petta, A.; Serra, L.; Oliva, R.; Scarano, V.; Cavallo, L. SambVca 2. A Web Tool for Analyzing Catalytic Pockets with Topographic Steric Maps. *Organometallics* **2016**, *35*, 2286. (b) https://www.molnac.unisa.it/OMtools/sambvca2.0/

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