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Low-Temperature Ni-Catalyzed C−N Cross-Coupling via Kinetic Resolution Enabled by a Bulky yet Flexible, Chiral *N*-Heterocyclic Carbene

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Abstract: The transition-metal-catalyzed C−N cross-coupling has revolutionized the construction of amines. Despite the innovations of multiple generations of ligands to modulate the reactivity of the metal center, ligands for the low-temperature enantioselective amination of aryl halides remain a coveted target of catalyst engineering. Designs that promote one elementary reaction often create bottlenecks at other steps. We here report an unprecedented low-temperature (as low as -50 ℃), enantioselective Ni-catalyzed C−N cross-coupling of aryl chlorides with sterically hindered secondary amines via a kinetic resolution process (s factor up to >300). A bulky yet flexible chiral N-heterocyclic carbene (NHC) ligand is leveraged to drive both oxidative addition and reductive elimination with low barriers and control the enantioselectivity. Computational studies indicate that the rotations of multiple σ-bonds on the C_2-symmetric chiral ligand adapt to the changing needs of catalytic processes. We expect this design would be widely applicable to diverse transition states to achieve other challenging metal-catalyzed asymmetric cross-coupling reactions.

Introduction

Transition-metal-catalyzed C−N cross-coupling reactions serve as a critical platform to prepare aniline derivatives, a common structural element found in bioactive natural products, active pharmaceutical agents, and advanced functional materials.[1,2] Over the past few decades, the amination reactions have moved forward through the iterative discovery and optimization of multiple generations of ligands to tune the behavior of the metal center.[1,3] For example, the discovery of biarylphosphine ligands by Buchwald[3a] and oxalic diamide ligands by Ma[1d] has remarkably accelerated the evolution of Pd- and Cu-catalyzed aryl amination, respectively (Figure 1A). Most of these reactions, however, require elevated temperatures due to the respective rate-limiting elementary steps. Alternatively, earth-abundant nickel[4] has emerged as a "spirited horse" for cross-coupling reactions because of its unique reactivity towards less reactive electrophiles.[5-7] The reductive elimination of Ni(II)-amido complexes have usually needed heat conditions.[5] Several elegant strategies, including rational ligand design,[5,6] photo-induced pathway,[8] and electrochemically-driven method,[9] have recently been developed to enable more mild and efficient Ni-catalyzed aryl aminations. However, despite tremendous progress in the past decades, the reaction temperature for this historically significant transformation is still high; a low-temperature (< 0 ℃) metal-catalyzed C−N cross-coupling has not been reported.

Low-temperature C−N cross-coupling is highly attractive because it represents a longstanding unmet challenge and serves as a desired target for ligand design and development. It may allow for good functional group compatibility, high levels of enantiocontrol, and further mechanistic understanding. The achievement of stereochemical control is particularly noteworthy, as asymmetric variants of aryl amination have been rarely reported[10], although chiral amines are of high value found in a wide array of research areas. Moreover, a strategy developed for low-temperature amination would potentially enable other challenging cross-couplings. The obstacle to developing low-temperature amination is due to the intrinsic contradiction of elementary catalytic steps of C−N cross-coupling, which also is a common issue for cross-coupling chemistry as a whole.[11] In general, an electron-rich ligand needs *small* enough to facilitate the metal-coordination, oxidative addition (OA), and transmetalation (TM) steps, especially for sterically hindered substrates, while a *bulky* ligand assists monoligation of metal and promotes reductive elimination (RE).[12] Thus, classical rigid ligands often promote one elementary step at the cost of the others. Consequently, the improvement in the overall kinetic profile is usually modest, and favorable reactivity is only observed for certain subclasses of substrates, necessitating the use of high temperatures to achieve reasonable rates of catalyst turnover. Furthermore, the requirement for bulky groups on ligands or substrates to induce stereoselectivity further adds to the challenge of achieving a favorable kinetic profile. Therefore, the development of a general strategy to simultaneously facilitate the three elementary steps of C−N cross-coupling, as well as to achieve stereocontrol, is highly desirable yet remains elusive.

We felt that the identification of suitable bulky yet flexible chiral NHC ligands would permit an elusive, general low-temperature enantioselective C-N cross-coupling reaction.[13,14] In 2003, Glorius and coworkers first proposed a concept of "flexible steric bulk" and developed tricyclic NHCs possessing three different conformers that interconvert through cyclohexane chair-flips.[15] These bulky but conformationally flexible NHC allow room-temperature Suzuki-Miyaura coupling of sterically hindered aryl chlorides through favoring three elementary steps.[12a] While the "flexible steric bulk" strategy has been widely applied in ligand

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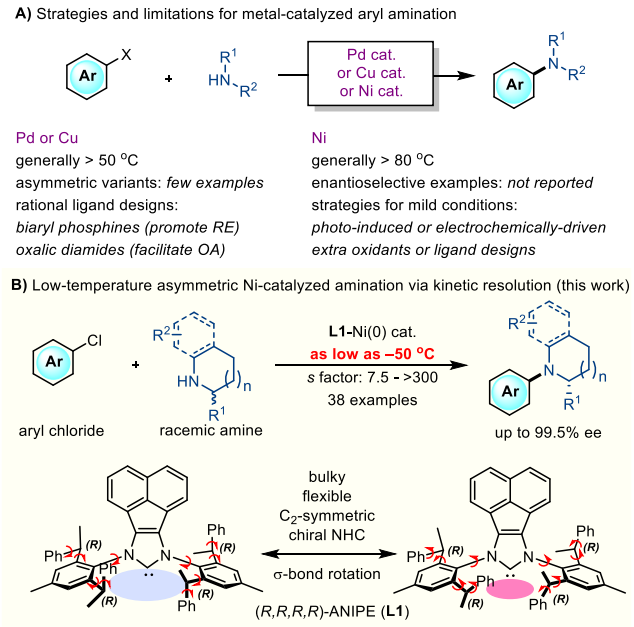


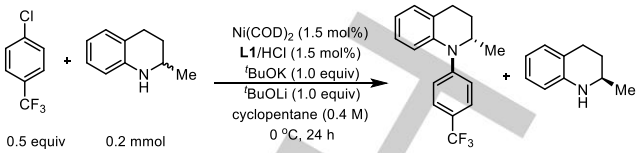
Figure 1. Metal-catalyzed C−N cross-couplings.

design for cross-coupling reactions, *chiral* ligands with a bulky yet flexible property are rarely developed.[14, 15c]

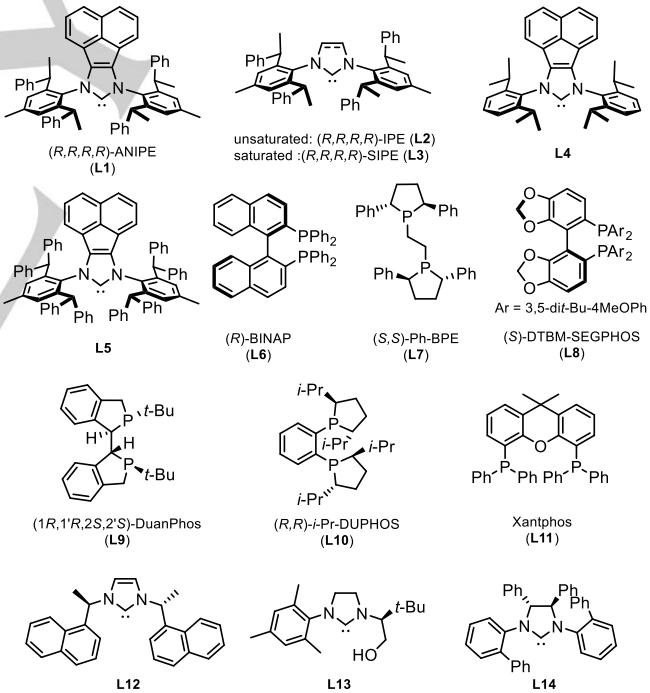
In this regard, we have recently developed a family of sterically demanding C_2-symmetric chiral NHC, namely, ANIPE- and SIPE-type ligands, and successfully applied them to various metal-catalyzed asymmetric transformations.[16] These reactions include the first highly enantioselective chiral NHC-metal-catalyzed Suzuki-Miyaura cross-coupling,[16c] C-H activation,[16d-f] hydrofunctionalization,[16a-b] and carbonyl addition[16g]. On the basis of X-ray crystal structures of several metal/NHC complexes,[16] we were aware that the conformational flexibility of our ligands through the rotation of single bonds might be applicable to flexible docking of substrates and subsequent C–N bond formation. In particular, we envisaged that the rotation of multiple C−C and C−N single bonds on the flexible C_2-symmetric chiral aniline fragments on the ligands (Figure 1B) would make space to allow for rapid OA and TM, especially for sterically hindered substrates; the subsequent conformation recovery would promote the crucial RE step. Notably, the presence of C_2-symmetric chiral axes in the NHCs renders them capable of excellent enantiocontrol ability during the rotation events of catalysis processes. Herein, we describe an unprecedented low-temperature (as low as -50 ℃), highly enantioselective Ni-catalyzed C−N bond-forming kinetic resolution of sterically hindered α-branched secondary amines with aryl chlorides to afford chiral amine products (Figure 1B). Computational studies suggest that our bulky yet flexible chiral NHC would drive low barriers for both OA and RE and control the stereoselectivity. DFT calculations reveal that the rotations of multiple σ-bonds on the C_2-symmetric chiral NHC are leveraged to enable the dynamic fit of catalyst pockets with substrates. We expect this bulky yet flexible chiral NHC design based on σ-bond rotations would be broadly applicable to adapt to distinct transition states to promote many asymmetric metal-catalyzed cross-coupling reactions.

Results and Discussion

Table 1. Reaction Optimization



Entry	variation from standard conditions	Conv. (%)[a]	ee (%)[b] of product	s factor[a]
1	**none**	**43**	**92**	**49.9**
2	**L2**/HCl instead of **L1**/HCl	<2	-	-
3	**L3**/HCl instead of **L1**/HCl	0	-	-
4	0.5 equiv ^{t}BuOK instead of 1.0 equiv ^{t}BuOK	33	93	43.0
5	1.5 equiv ^{t}BuOK instead of 1.0 equiv ^{t}BuOK	35	85	19.2
6	0.5 equiv ^{t}BuOLi instead of 1.0 equiv ^{t}BuOLi	37	83	17.7
7	1.5 equiv ^{t}BuOLi instead of 1.0 equiv ^{t}BuOLi	43	91	44.9
8	THF instead of cyclopentane	23	90	26.9
9	toluene instead of cyclopentane	30	88	24.2
10	DMF instead of cyclopentane	0	-	-
11	30 °C	50	84	31.2
12	**L6-L11** instead of **L1**/HCl	0	-	-
13	**L12-L14**/HCl instead of **L1**/HCl	0	-	-
14	**L4-L5**/HCl instead of **L1**/HCl	<2	-	-
15	w/o Ni(COD)$_2$ or **L1**/HCl	0	-	-



[a] Calculated conversions (Conv.) and s factors were calculated from ee values, Conv. = $ee_{SM}/(ee_{SM} + ee_{PR})$, s = ln[(1−C(1+$ee_{PR}$)] / ln[(1−C(1−$ee_{PR}$)]; [b] ee values were determined by chiral HPLC analysis.

Reaction Optimization. Although the enzymatic kinetic resolution and classical resolution by crystallization of chiral salts are often used for chiral amine synthesis,[17] kinetic resolution of amines *via* a Ni-catalyzed *N*-arylation remains an elusive but attractive strategy. We commenced our studies with a model coupling reaction of 4-chlorobenzotrifluoride with racemic 2-methyl-1,2,3,4-tetrahydroquinoline. After intensive investigation of the reaction parameters, we found that the desired chiral

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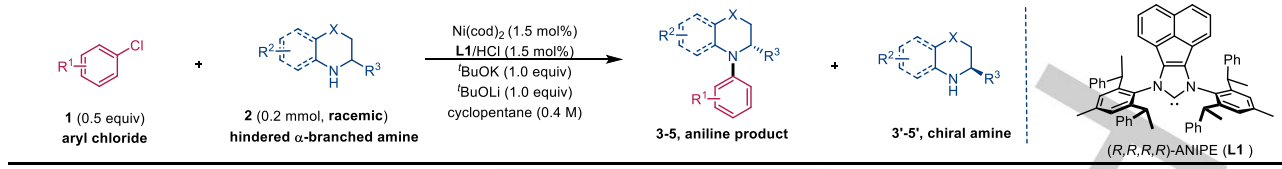
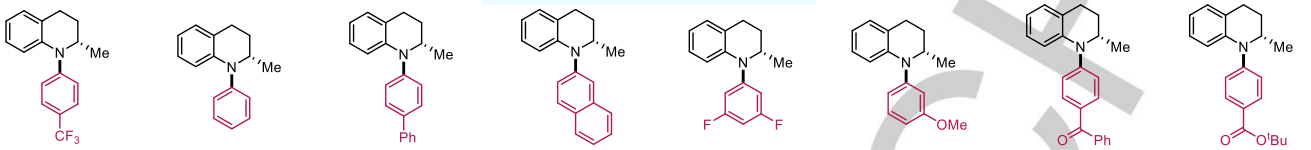
Table 2. Substrate Scope[a]



aryl chloride coupling partners



3a (0 °C, 24 h) 92% ee, s = 49.9, 43% (43%) **3a'**, 69% ee

3b (30 °C, 48 h) 93% ee, s = 41.6, 31% (26%) **3b'**, 42% ee

3c (10 °C, 36 h) 89% ee, s = 30.5, 40% (36%) **3c'**, 58% ee

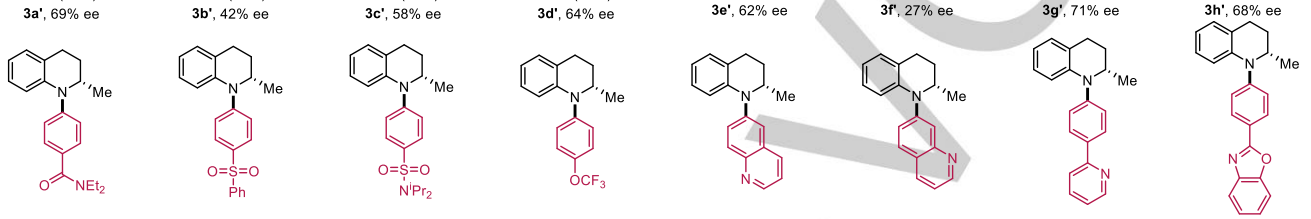
3d (10 °C, 36 h) 89% ee, s = 33.4, 42% (37%) **3d'**, 64% ee

3e (10 °C, 24 h) 90% ee, s = 36.1, 41% (35%) **3e'**, 62% ee

3f (30 °C, 48 h) 91% ee, s = 28.9, 23% (22%) **3f'**, 27% ee

3g (0 °C, 48 h) 88% ee, s = 33.7, 45% (41%) **3g'**, 71% ee

3h (0 °C, 24 h) 91% ee, s = 43.6, 43% (40%) **3h'**, 68% ee



3i (0 °C, 24 h) 90% ee, s = 28.8, 32% (30%) **3i'**, 42% ee

3j (0 °C, 48 h) 87% ee, s = 30.7, 45% (43%) **3j'**, 71% ee

3k (0 °C, 36 h) 99.5% ee, s = 76.6, 39% (36%) **3k'**, 64% ee

3l (30 °C, 48 h) 93% ee, s = 37.3, 25% (25%) **3l'**, 31% ee

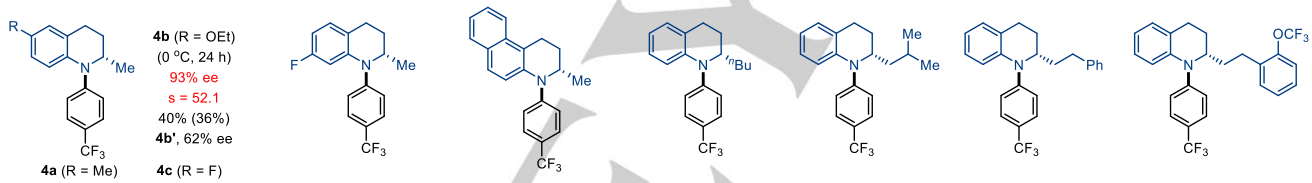
3m (10 °C, 36 h) 87% ee, s = 29.4, 44% (44%) **3m'**, 68% ee

3n (10 °C, 36 h) 85% ee, s = 31.0, 49% (46%) **3n'**, 83% ee

3o (0 °C, 48 h) 89% ee, s = 34.6, 43% (40%) **3o'**, 67% ee

3p (-10 °C, 48 h) 81% ee, s = 22.3, 49% (45%) **3p'**, 77% ee

amine coupling partners



4a (R = Me) (0 °C, 24 h) 91% ee, s = 47.5, 45% (42%) **4a'**, 74% ee

4b (R = OEt) (0 °C, 24 h) 93% ee, s = 52.1, 40% (36%) **4b'**, 62% ee

4c (R = F) (0 °C, 24 h) 91% ee, s = 47.5, 45% (41%) **4c'**, 75% ee

4d (10 °C, 24 h) 92% ee, s = 36.0, 31% (30%) **4d'**, 42% ee

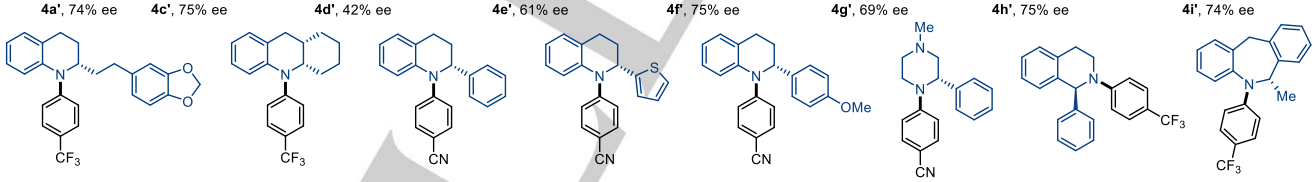
4e (0 °C, 24 h) 90% ee, s = 35.7, 40% (36%) **4e'**, 61% ee

4f (10 °C, 24 h) 93% ee, s = 63.4, 45% (43%) **4f'**, 75% ee

4g (10 °C, 24 h) 86% ee, s = 27.9, 45% (40%) **4g'**, 69% ee

4h (10 °C, 24 h) 95% ee, s = 87.9, 44% (43%) **4h'**, 75% ee

4i (10 °C, 24 h) 92% ee, s = 54.4, 45% (42%) **4i'**, 74% ee



4j (10 °C, 24 h) 89% ee, s = 28.5, 36% (35%) **4j'**, 50% ee

4k (10 °C, 36 h) 96% ee, s = 95.0, 40% (35%) **4k'**, 65% ee

4l (10 °C, 24 h) 97% ee, s = 170.3, 46% (40%) **4l'**, 81% ee

4m (10 °C, 24 h) 92% ee, s = 44.9, 40% (36%) **4m'**, 62% ee

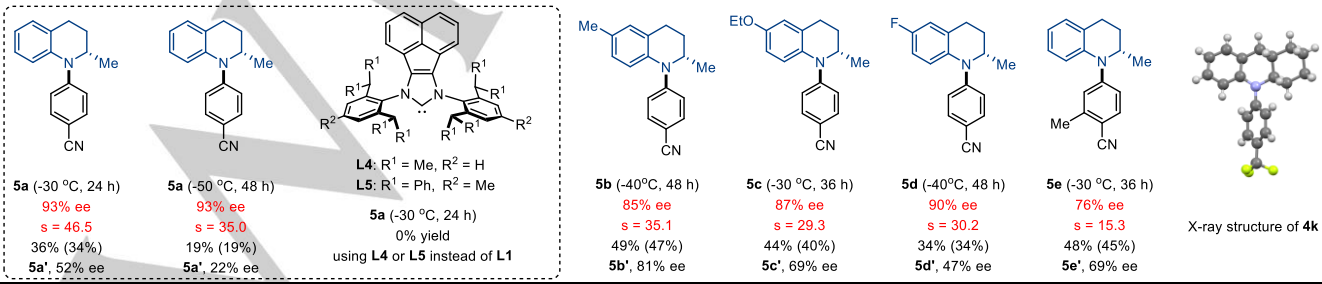
4n (10 °C, 24 h) 99% ee, s >300, 48% (45%) **4n'**, 90% ee

4o (0 °C, 48 h) 89% ee, s = 32.3, 41% (40%) **4o'**, 62% ee

4p (30 °C, 24 h) 74% ee, s = 11.6, 43% (40%) **4p'**, 55% ee

4q (30 °C, 24 h) 70% ee, s = 7.5, 29% (29%) **4q'**, 28% ee

C–N coupling at -30 °C ~ -50 °C



5a (-30 °C, 24 h) 93% ee, s = 46.5, 36% (34%) **5a'**, 52% ee

5a (-50 °C, 48 h) 93% ee, s = 35.0, 19% (19%) **5a'**, 22% ee

L4: R^1 = Me, R^2 = H
L5: R^1 = Ph, R^2 = Me

5a (-30 °C, 24 h) 0% yield using **L4** or **L5** instead of **L1**

5b (-40°C, 48 h) 85% ee, s = 35.1, 49% (47%) **5b'**, 81% ee

5c (-30 °C, 36 h) 87% ee, s = 29.3, 44% (40%) **5c'**, 69% ee

5d (-40°C, 48 h) 90% ee, s = 30.2, 34% (34%) **5d'**, 47% ee

5e (-30 °C, 36 h) 76% ee, s = 15.3, 48% (45%) **5e'**, 69% ee

X-ray structure of **4k**

[a]Yields of isolated products on 0.2 mmol scale. Data are reported as isolated yield in parentheses and calculated conversion outside of parentheses; isolated yields were determined by isolation after chromatographic purification; calculated conversions (C = $ee_{SM}/(ee_{SM} + ee_{PR})$) and s factors were calculated from enantiomeric excesses (ee) values, s = $\ln[(1- C(1+ee_{PR})] / \ln[(1-C(1-ee_{PR})]$; ee values were determined by chiral HPLC analysis.

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N-arylated product **3a** could be obtained in high conversion (43% conv., the theoretical conversion is 50%) and excellent enantioselectivity (92% ee) in the presence of a low loading of $Ni(cod)_2$ catalyst (1.5 mol%), an air-stable NHC precursor (**L1**/HCl, 1.5 mol%), and 1.0 equivalent of both Li*O*^{t}Bu and K*O*^{t}Bu in cyclopentane at 0 ^{o}C for 24 h (Table 1, entry 1). Interestingly, the large acenaphthoimidazolylidene framework of **L1** (ANIPE) was found to be necessary, as the use of less bulky ligands such as **L2** or **L3** resulted in almost no conversions (entries 2-3). We believe that the acenaphthyl backbone of **L1** would buttress the four 1-phenethyl groups on the NHC closer to the reactive center, thus further accentuate the steric effect.[16a,18] In addition, the amount and ratio of Li*O*^{t}Bu and K*O*^{t}Bu (1/1) were crucial to maintaining a nearly homogenous reaction mixture under low temperatures (entries 4-7). Use of THF (entry 8) or toluene (entry 9) as solvent resulted in a lower s value. Conducting the reaction at 30 °C led to a slightly higher yield but moderate enantioselectivity (entry 11). We found that other commonly used chiral NHC or phosphine ligands did not provide the product (entries 12-14). Finally, control experiments revealed the critical role of both nickel and **L1** for this efficient amination reaction, as no desired product was detected in the absence of either nickel or NHC ligand (entry 15). It bears mentioning that a Ni-catalyzed arylation of α-branched secondary amines has previously unexplored.[19]

Reaction Scope. With the optimized reaction conditions in hand, we next set out to survey the generality of aryl chlorides for this asymmetric amination protocol. As shown in Table 2, electron-neutral and electron-deficient aryl chlorides were successfully transformed into the corresponding chiral amines in high yields and enantioselectivities (81-99.5% ee). Aryl chlorides bearing a wide range of functional groups, such as trifluoromethyl (**3a**) and trifluoromethoxy groups (**3l**), fluoride (**3e**), ethers (**3f**), ketones (**3g**), esters (**3h**), amides (**3i**), sulfones (**3j**), and sulfonamides (**3k**), were all well-tolerated under the reaction conditions. Importantly, potentially deleterious oxidative additions of nickel catalysts into ethers, ketones, esters, or amides were not detectable, probably due to the mild reaction conditions. Moreover, heteroaryl chlorides possessing quinolines (**3m**, **3n**), pyridines (**3o**), and benzoxazole (**3p**) were all competent coupling partners. However, an electron-rich aryl chloride was found less reactive under the mild reaction conditions, affording products in moderate yield and high enantioselectivity (91% ee) (**3f**).

Subsequently, we examined the scope of amine coupling components. An array of enantioenriched *N*-arylated tetrahydroquinoline products with different substituents were obtained in high to excellent yields and enantioselectivities (86-99% ee) (**4a**-**4n**). Regardless of the presence of a methyl group (**4a**-**4e**) or long aliphatic chains such as butyl, isobutyl, phenethyl groups at the adjoining stereocenter (**4f**-**4j**), the products were generated in high yields and enantioselectivities. Surprisingly, the use of sterically demanding 2-aryl substituted tetrahydroquinoline substrates (**4l**-**4n**) did not reduce the reaction efficacy but gave increased s factor (up to >300, **4n**); the unproductive reduction of electrophiles through competitive β-H elimination was not observed. We attribute this success to a highly efficient and well-controlled reductive elimination process. Besides, a tricyclic amine with two adjacent stereocenters was successfully arylated under the kinetic resolution condition (**4k**); the absolute stereochemistry of the product **4k** was determined by single-crystal X-ray diffraction. In addition to tetrahydroquinolines, other cyclic amines including piperidine (**4o**), tetrahydroisoquinoline (**4p**), and dihydrobenzoazepines (**4q**) also served as suitable substrates, providing related products in good yields and enantioselectivities. Furthermore, a 4-mmol-scale reaction was successfully performed, delivering product **3a** with similar efficiency and selectivity (see SI for details). The chiral amine architectures obtained by our protocol are all highly appealing, given their prevalence in medicinally relevant compounds.[20]

Low Temperature Aryl Amination. An important breakthrough of current enantioselective C−N cross-coupling is its ability to run at very low temperatures. To demonstrate this point, we conducted the amination reactions at -30 ℃, and even -50 ℃ (Table 2). We were able to couple a series of tetrahydroquinolines with 4-CN-substituted aryl chlorides (**5a**-**5e**), delivering products in good yields and enantioselectivities (76-93% ee). Interestingly, the use of electronically similar but less bulky NHC (**L4**, with 2,6-diisopropylaniline fragments) or more hindered NHC (**L5**, with 2,6-dibenzhydrylaniline fragments) instead of **L1** both resulted in no desired conversions at -30 ℃. We attribute the lack of reactivity to ineffective RE in **L4** and inefficient OA, TM, or coordination in the case of **L5** due to unfavorable steric environments at different catalysis stages. To the best of our knowledge, this is the first time for a C(sp^2)−N cross-coupling reaction to run at such low temperature (< -30 ℃). These facts indicate that elementary catalytic steps of this challenging Ni-catalyzed C−N cross-coupling of aryl chlorides with sterically hindered secondary amines are well-balanced, highlighting the advantages of the suitable "flexible steric bulk" of our chiral NHC ligand.

Computational studies. We next performed density functional theory (DFT) calculations to investigate the origins of the high reactivity of this unexpected low-temperature aryl amination. The DFT-computed free energy profile of the overall catalytic cycle is shown in Figure 2A. From the substrate-coordinated complex, OA occurs smoothly with a low barrier of 8.9 kcal/mol. The ligand exchange of OA intermediate **8** occurs through an association-dissociation mechanism. The coordination of tetrahydroquinoline anion is exergonic by 14.0 kcal/mol, generating the anionic tetracoordinated species **9**. Subsequent dissociation of chlorine anion produces the pre-reductive elimination intermediate **10**. The subsequent rate-determining RE step proceeds with only a 14.7 kcal/mol barrier, consistent with the ability to carry out the reaction under low-temperature conditions. The calculated free energy profiles for the corresponding potassium or lithium cation processes are found very close to that of the anionic pathway, which confirmed the mechanistic information from the anionic pathway (see SI, Figure S3-4). Besides, our computations indicate that the Ni(I/III) mechanism has a high barrier for OA and thus unlikely to occur (see SI, Figure S1).[21]

We ascribe the low barrier of RE to the large steric hindrance of **L1**. The low barrier of OA probably due to the conformational flexibility and strong electron-donating ability of the ligand. We calculated the buried volume (%V Buried)[22] to quantify the difference in steric encumbrance of **L1** (with 2,6-diphenethylaniline fragments) and **L4'** (with 2,6-diisopropylaniline fragments) as shown in Figure 2B. **L1** with a buried volume of 58.0 % is found far bulkier than (51.0 %V Buried) and thus expected to undergo far more difficult OA step than the electronically similar **L4'**. However, the OA barrier of catalyst

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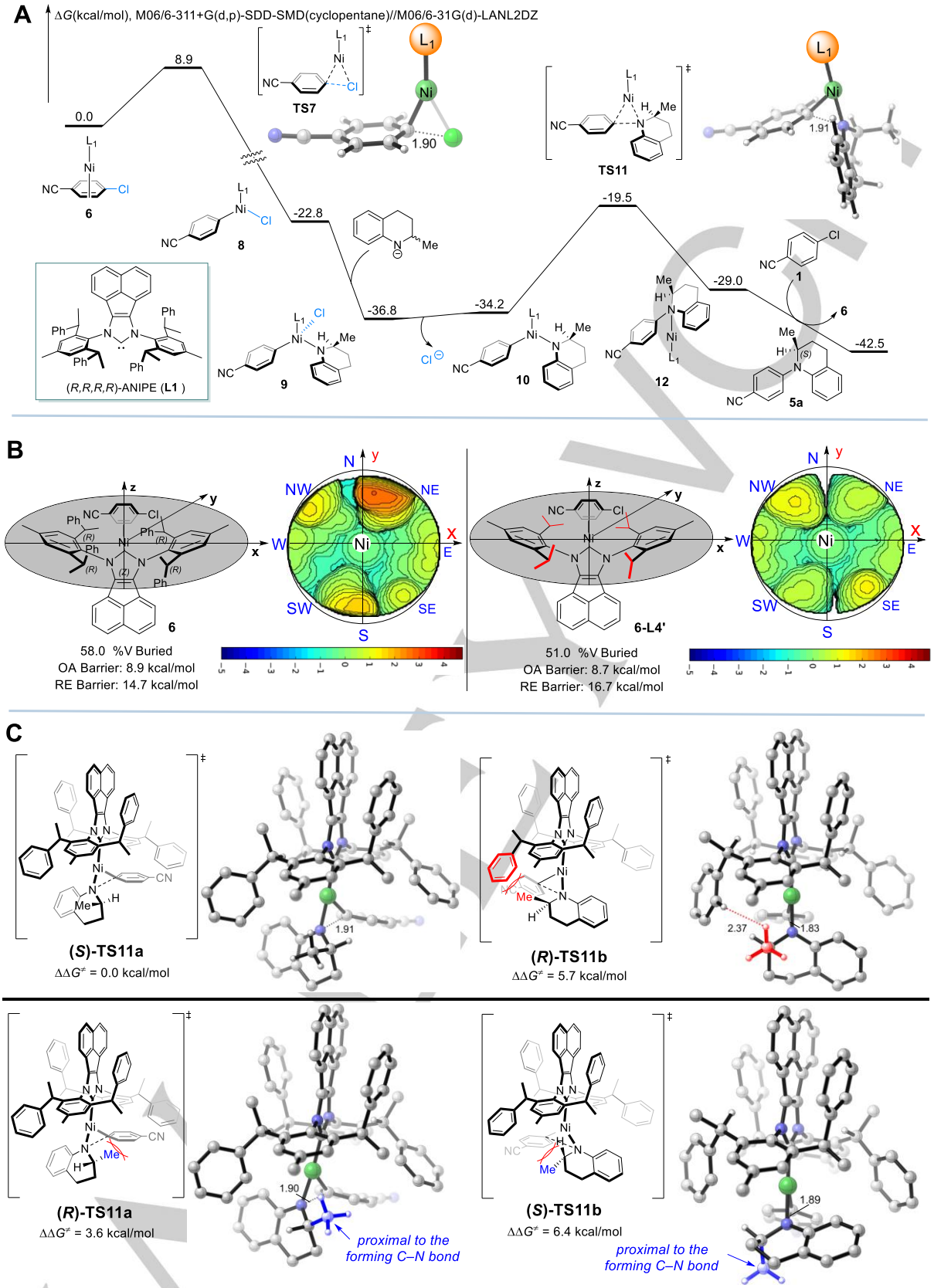

Figure 2. DFT calculations. (**A**) DFT-computed Gibbs free energies changes. (**B**) Comparisons of buried volume and OA barrier of **L1** and **L4'** derived catalysts. (**C**) Transition-state structures of the enantioselectivity-determining RE step.

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derived from **L1** (8.9 kcal/mol) is very close to **L4'** (8.7 kcal/mol). These results suggest that the conformational flexibility of **L1** compensates for the unfavorable steric effect in the OA step. In addition, the RE barrier of catalyst derived from **L4'** is significantly higher than **L1** (16.7 kcal/mol *vs.* 14.7 kcal/mol), which indicates the importance of ligand steric hindrance.

Further calculation verified that the amine coordination step is reversible, and the RE step is the enantio-determining step (see SI, Figure S2). To understand the origin of the high enantiocontrol, we studied the RE transition states that produce both enantiomers of amine products (Figure 2C). **In (*S*)-TS11a** and **(*R*)-TS11b**, the methyl group of amine substrate is distal to the forming C−N bond, while in **(*R*)-TS11a** and **(*S*)-TS11b**, the same methyl groups are proximal to the forming C−N bonds. Due to the increased steric repulsions, the latter two cases' free energies are less favorable than **(*S*)-TS11a** by 3.6 and 6.4 kcal/mol. In **(*S*)-TS11a**, the unfavorable repulsion between the phenyl group of phenethyl moiety on **L1** and the methyl group of amine substrate is avoided, thereby leading to the preferential formation of the (*S*)-aminated product **5a**, with an activation free energy that is 5.7 kcal/mol lower than that of the disfavored transition state **(*R*)-TS11b**.

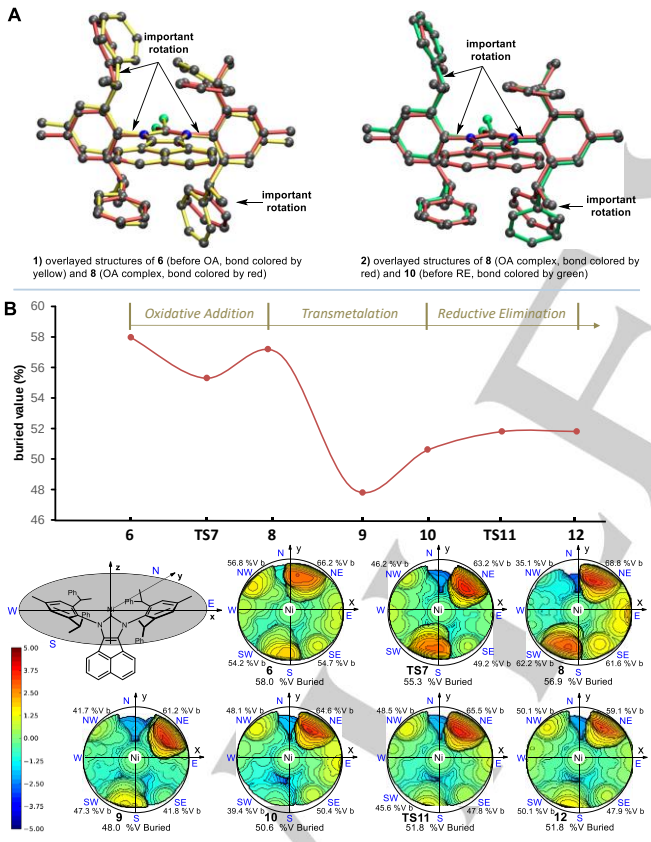

Figure 3. (**A**) Overlay of catalyst structures of involved intermediates. (**B**) Change of buried volume of nickel catalyst throughout the catalytic cycle.

To demonstrate the proposed conformational flexibility of our ligand through the rotation of single bonds, we calculated the dihedron angle changes of aniline fragments during the catalysis process (see SI, Figure S6-8). Substantial rotations of C−C_{Ph} bonds of stereogenic centers and C−N bonds of the aniline group are observed throughout the catalytic process. In particular, two phenyl groups of phenylethyl moieties close to the nickel center are found to rotate dramatically (from 124.9° to 64.7°; from 127.3° to 105.6°). These rotations are clearly confirmed by comparisons on the orientations of aniline fragments on the overlaid ligand structures in the three key optimized transition states (i.e., before OA (**6**), OA complex (**8**), before RE (**10**), Figure 3A). These rotations are likely critical to accommodate each substrate to fit the changing steric environments at various catalysis stages. Furthermore, we quantified the dynamic change of ligand's buried volume during the catalytic process.[22] As shown in Figure 3B, the ligand's buried volume decreases substantially during OA (from 58.0% (**6**) to 55.3% (**TS7**)) and TS (from 56.9% (**8**) to 50.6% (**10**)) processes, while increases in the course of RE (from 50.6% (**10**) to 51.8% (**TS11**)). These results suggest that more space in the binding pocket is induced by the ligand-substrate repulsions to allow for rapid OA and TS processes. Subsequent conformation recovery of the ligand makes the catalyst pocket getting smaller to promote the RE process. Taken together, these computational findings and experimental outcomes under low temperature (Figure 2) are consistent with our initial hypothesis that our bulky but flexible C_2-symmetric chiral ligand through rotations of multiple σ-bonds during the catalysis event would balance operations to achieve an overall favorable kinetic profile, and enable high levels of stereocontrol simultaneously.

Conclusion

In summary, we have developed an unprecedented low-temperature asymmetric Ni-catalyzed C−N cross-coupling of aryl chlorides with sterically hindered α-branched secondary amines, delivering chiral amine products in a highly selective kinetic resolution manner. The key to the success of the transformation is the use of our ANIPE, a bulky but flexible chiral NHC ligand, to drive low barrier elementary catalytic steps and control the enantioselectivity. More broad applications of these ligands in other challenging yet important enantioselective cross-coupling reactions are currently underway in our laboratory and will be reported in due course.

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Keywords: low-temperature • asymmetric catalysis • C-N coupling • NHC ligand • nickel

[1] a) P. Ruiz-Castillo, S. L. Buchwald, *Chem. Rev.* **2016**, *116*, 12564–12649; b) J. F. Hartwig, *Acc. Chem. Res*. **2008**, *41*, 1534–1544; c) R. Dorel, C. P. Grugel, A. Haydl, *Angew. Chem., Int. Ed*. **2019**, *58*, 17118–

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17129; d) S. Bhunia, G. G. Pawar, S. V. Kumar, Y. Jiang, D. Ma, *Angew. Chem. Int. Ed.* **2017**, *56*, 16136–16179.

[2] a) S. A. Lawrence, Amines: Synthesis Properties and Applications, Cambridge Univ. Press, **2004**; b) A. Ricci, Amino Group Chemistry: From Synthesis to the Life Sciences, Wiley-VCH, Weinheim, **2008**.

[3] a) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2011**, *2*, 27–50. (b) C. Valente, M. Pompeo, M. Sayah, M. G. Organ, *Org. Process Res. Dev.* **2014**, *18*, 180−190; c) C. Sambiagio, S. P. Marsden, A. J. Blacker, P. C. McGowan, *Chem. Soc. Rev*. **2014**, *43*, 3525–3550; d) I. P. Beletskaya, A. V. Cheprakov, *Organometallics*. **2012**, *31*, 7753–7808; e) F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 6954–6971.

[4] a) Y. Tamaru, Modern Organonickel Chemistry, John Wiley & Sons, **2006**; b) S. Z. Tasker, E. A. Standley, T. F. Jamison, *Nature* **2014**, *509*, 299–309; c) N. Hazari, P. R. Melvin, M. M. Beromi, *Nat. Rev. Chem.* **2017**, *1*, 0025; d) V. P. Ananikov, *ACS Catal.* **2015**, *5*, 1964–1971.

[5] a) M. Marin, R. J. Rama, M. C. Nicasio, *Chem. Rec.* **2016**, *16*, 1819–1832. b) C. M. Lavoie, M. Stradiotto, *ACS Catal*. **2018**, *8*, 7228–7250.

[6] For selected examples, see a) J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 6054–6058; b) N. H. Park, G. Teverovskiy, S. L. Buchwald, *Org. Lett.* **2014**, *16*, 220–223; c) R. Y. Liu, J. M. Dennis, S. L. Buchwald, *J. Am. Chem. Soc.* **2020**, *142*, 4500–4507; d) S. Ge, R. A. Green, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 1617–1627; e) A. R. Martin, D. J. Nelson, S. Meiries, A. M. Z. Slawin, S. P. Nolan, *Eur. J. Org. Chem.* **2014**, 3127–3131; f) N. F. F. Nathel, J. Kim, L. N. Hie, X. Y. Jiang, N. K. Garg, *ACS Catal.* **2014**, *4*, 3289–3293; g) S. G. Rull, J. F. Blandez, M. R. Fructos, T. R. Belderrain, M. C. Nicasio, *Adv. Synth. Catal.* **2015**, *357*, 907–911; h) R. T. McGuire, C. M. Simon, A. A. Yadav, M. J. Ferguson, M. Stradiotto, *Angew. Chem. Int. Ed*. **2020**, *59*, 8952-8956; i) J. S. K. Clark, M. J. Ferguson, R. McDonald, M. Stradiotto, *Angew. Chem. Int. Ed*. **2019**, *58*, 6391-6395.

[7] For examples on other electrophiles, see a) A. C. Malapit, M. Borrell, M. W. Milbauer, C. E. Brigham, M. S. Sanford. *J. Am. Chem. Soc.* **2020,** *142*, 5918-5923; b) E. M. Wiensch, J. Montgomery, *Angew. Chem., Int. Ed.* **2018**, *57*, 11045–11049; c) T. Harada, Y. Ueda, T. Iwai, M. Sawamura, *Chem. Commun.* **2018**, *54*, 1718–1721.

[8] a) E. B. Corcoran, M. T. Pirnot, S. Lin, S. D. Dreher, D. A. DiRocco, I. W. Davies, S. L. Buchwald, D. W. C. MacMillan, *Science* **2016**, *353*, 279–283; b) M. S. Oderinde, N. H. Jones, A. Juneau, M. Frenette, B. Aquila, S. Tentarelli, D. W. Robbins, J. W. Johannes, *Angew. Chem. Int. Ed.* **2016**, *55*, 13219–13223; c) M. Kudisch, C.-H. Lim, P. Thordarson, G. M. Miyake, *J. Am. Chem. Soc.* **2019**, *141*, 19479–19486; d) C.-H. Lim, M. Kudisch, B. Liu, G. M. Miyake, *J. Am. Chem. Soc.* **2018**, *140*, 7667–7673; e) G. Li, L. Yang, J.-J. Liu, W. Zhang, R. Cao, C. Wang, Z. Zhang, J. Xiao, D. Xue, *Angew. Chem. Int. Ed.* **2021**, *42*, DOI:10.1002/anie.202012877.

[9] a) Y. Kawamata, J. C. Vantourout, D. P. Hickey, P. Bai, L. Chen, Q. Hou, W. Qiao, K. Barman, M. A. Edwards, A. F. Garrido-Castro, J. N. deGruyter, H. Nakamura, K. Knouse, C. Qin, K. J. Clay, D. Bao, C. Li, J. T. Starr, C. Garcia-Irizarry, N. Sach, H. S. White, M. Neurock, S. D. Minteer, P. S. Baran, *J. Am. Chem. Soc.* **2019**, *141*, 6392–6402; b) C. Kawamata, Y. Li, H. Nakamura, J. C. Vantourout, Z. Liu, Q. Hou, D. Bao, J. T. Starr, J. Chen, M. Yan, P. S. Baran, *Angew. Chem., Int. Ed*. **2017**, *56*, 13088–13093; c) D. Liu, Z.-R. Liu, C. Ma, K.-J. Jiao, B. Sun, L. Wei, J. Lefranc, S. Herbert, T.-S. Mei, *Angew. Chem. Int. Ed.* **2021**, *42*, DOI: 10.1002/anie.202016310.

[10] a) Q. M. Kainz, C. D. Matier, A. Bartoszewicz, S. L. Zultanski, J. C. Peters, G. C. Fu, *Science* **2016**, *351*, 681–684; b) P. Ramírez-López, A. Ros, A. Romero-Arenas, J. Iglesias-Sigüenza, R. Fernández, J. M. Lassaletta, *J. Am. Chem. Soc.* **2016**, *138*, 12053–12056; c) K. Zhao, L. Duan, S. Xu, J. Jiang, Y. Fu, Z. Gu, *Chem* **2018**, *4*, 599–612; d) X. Zhang, K. Zhao, N. Li, J. Yu, L.-Z. Gong, Z. Gu, *Angew. Chem., Int. Ed.* **2020**, *59*, 19899–19904; e) F. Zhou, J. Guo, J. Liu, K. Ding, S. Yu, Q. Cai, *J. Am. Chem. Soc*. **2012**, *134*, 14326-14329; f) O. Kitagawa, M. Takahashi, M. Yoshikawa, T. Taguchi, *J. Am. Chem. Soc.* **2005**, *127*, 3676–3677; g) J. Frey, A. Malekafzali, I. Delso, S. Choppin, F. Colobert, J. Wencel-Delord, *Angew. Chem., Int. Ed.* **2020**, *59*, 8844-8848; h) Y. Chen, C. Zhu, Z. Guo, W. Liu, X. Yang, *Angew. Chem., Int. Ed.* **2021**, *60*, doi.org/10.1002/anie.202015008.

[11] a) C. Robert, *The Organometallic Chemistry of the Transition Metals*, **2005**; b) J. F. Hartwig, *Organotransition Metal Chemistry, from Bonding to Catalysis*. New York, 2010; c) M. R. Uehling, R. P. King, S. W. Krska, T. Cernak, S. L. Buchwald, *Science* **2019**, *363*, 405–408; d) G. M.Torres, Y. Liu, B. A. Arndtsen, *Science* **2020**, *368*, 318–323.

[12] a) G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *Angew. Chem., Int. Ed*. **2003**, *42*, 3690–3693; b) J. P. Wolfe, R. A. Singer, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc*. **1999**, *121*, 9550-9561; c) G. A. Grasa, M. S. Viciu, J. Huang, C. Zhang, M. L. Trudell, S. P. Nolan, *Organometallics* **2002**, *21*, 2866; d) B. C. Hamann, J.F. Hartwig, *J. Am. Chem. Soc.*, **1998**, *120*, 7369–7370.

[13] a) D. Janssen-Muller, C. Schlepphorst, F. Glorius, *Chem. Soc. Rev*. **2017**, *46*, 4845; b) F. Wang, L.-J. Liu, W. Wang, S. Li, M. Shi, *Coord. Chem. Rev*. **2012**, *256*, 804; c) J. Thongpaen, R. Manguin, O. Basle, *Angew. Chem. Int. Ed*. **2020**, *59*, 10242–10251.

[14] a) S. Würtz, F. Glorius, *Acc. Chem. Res*. **2008**, *41*, 1523–1533; b) C. Valente, S. Çalimsiz, K. H. Hoi, D. Mallik, M. Sayah, M. G. Organ, *Angew. Chem. Int. Ed.* **2012**, *51*, 3314–3332; c) F. Izquierdo, S. Manzinia, S. P. Nolan, *Chem. Commun.* **2014**, *50*, 14926–14937; d) M. P. V. B. Sofie; N. Fady, S. J. C. Catherine, *Inorganics* **2019**, *7*, 78; For selected examples on chiral NHC-Ni catalysis, see: e) C.-Y. Ho, W. Chan, L. He, *Angew. Chem. Int. Ed.* **2015**, *54*, 4512-4516; f) Y. Chen, L. Dang, C.-Y. Ho, *Nat. Commun*. **2020**, *11*, 2269; g) H. Wang, G. Lu, G. J. Sormunen, H. A. Malik, P. Liu, J. Montgomery, *J. Am. Chem. Soc.* **2017**, 139, 9317−9324; h) R. Kumar, Y. Hoshimoto, H. Yabuki, M. Ohashi, S. Ogoshi, *J. Am. Chem. Soc.* **2015**, *137*, 11838−11845.

[15] a) see ref.12a; b) G. Altenhoff, R. Goddard, C. W. Lehmann, F. Glorius, *J. Am. Chem. Soc.* **2004**, *126*, 15195–15201; c) S. Würtz, C. Lohre, R. Fröhlich, K. Bergander, F. Glorius, *J. Am. Chem. Soc.* **2009**, *131*, 8344–8345.

[16] a) Y. Cai, X.-T. Yang, S.-Q. Zhang, F. Li, Y.-Q. Li, L.-X. Ruan, X. Hong, S.-L. Shi, *Angew. Chem., Int. Ed.* **2018**, *57*, 1376–1380; b) Y. Cai, J.-W. Zhang, F. Li, J.-M. Liu, S.-L. Shi, *ACS Catal.* **2019**, *9*, 1–6; c) D. Shen, Y. Xu, S.-L. Shi, *J. Am. Chem. Soc.* **2019**, *141*, 14938–14945; d) W.-B. Zhang, X.-T. Yang, J.-B. Ma, Z.-M. Su, S.-L. Shi, *J. Am. Chem. Soc.* **2019**, *141*, 5628–5634; e) Y. Cai, X. Ye, S. Liu, S.-L. Shi, *Angew. Chem., Int. Ed.* **2019**, *58*, 13433–13437; f) D. Shen, W.-B. Zhang, Z. Li, S.-L. Shi, Y. Xu, *Adv. Synth. Catal*. **2020**, *362*, 1125-1130; g) Y. Cai, L.-X. Ruan, A. Rahman, S.-L. Shi, *Angew. Chem., Int. Ed.* **2021**, 60, 5262–5267; h) Z.-C. Wang, J. Gao, Y. Cai, X. Ye, S.-L. Shi, *CCS Chem*. **2021**, DOI:10.31635/ ccschem.021.202101001; For a concomitant development of ligand, see i) J. Diesel, A. M. Finogenova, N. Cramer, *J. Am. Chem. Soc.* **2018**, *140*, 4489–4493; j) J. Diesel, D. Grosheva, S. Kodama, N. Cramer, *Angew. Chem., Int. Ed*. **2019**, *58*, 11044–11048.

[17] M. Breuer, et al. *Angew. Chem. Int. Ed.* **2004**, *43*, 788–824.

[18] C. Chen, F.-S. Liu, M. Szostak, *Chem. Eur. J.* **2021**, *27*, DOI:10.1002/chem.202003923.

[19] a) N. H. Park, E. V. Vinogradova, D. S. Surry, S. L. Buchwald, *Angew. Chem., Int. Ed.* **2015**, *54*, 8259–8262; b) A. Khadra, S. Mayer, D. Mitchell, M. J. Rodriguez, M. G. Organ, *Organometallics* **2017**, *36*, 3573−3577.

[20] V. Sridharan, P. A. Suryavanshi, J. C. Menendez, *Chem. Rev.* **2011**, *111*, 7157–7259.

[21] a) S. G. Rull, I. Funes-Ardoiz, C. Maya, F. Maseras, M. R. Fructos, T. R. Belderrain, M. C. Nicasio, *ACS Catal.* **2018**, *8*, 3733–3742; b) see ref. 6d.

[22] a) A. Poater, B. Cosenza, A. Correa, S. Giudice, F. Ragone, V. Scarano, L. Cavallo, *Eur. J. Inorg. Chem.* **2009**, *13*, 1759-1766; b) L. Falivene, Z. Cao, A. Petta, L. Serra, A. Poater, R. Oliva, V. Scarano, L. Cavallo, *Nat. Chem.* **2019**, *11*, 827-879.

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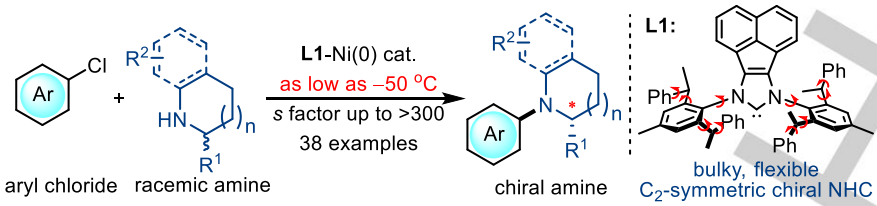

An unprecedented low-temperature, asymmetric Ni-catalyzed C−N cross-coupling of sterically hindered secondary amines with aryl chlorides *via* kinetic resolution is reported. A bulky yet flexible, chiral NHC ligand enables both low barrier oxidative addition and reductive elimination and high levels of enantiocontrol. Computational studies indicate that multiple σ-bond rotations of the C_2-symmetric chiral NHC adapt to the changing needs of catalytic processes.

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