RESEARCH ARTICLE

Chiral Arylated Amines via C-N Coupling of Chiral Amines with Aryl Bromides Promoted by Light

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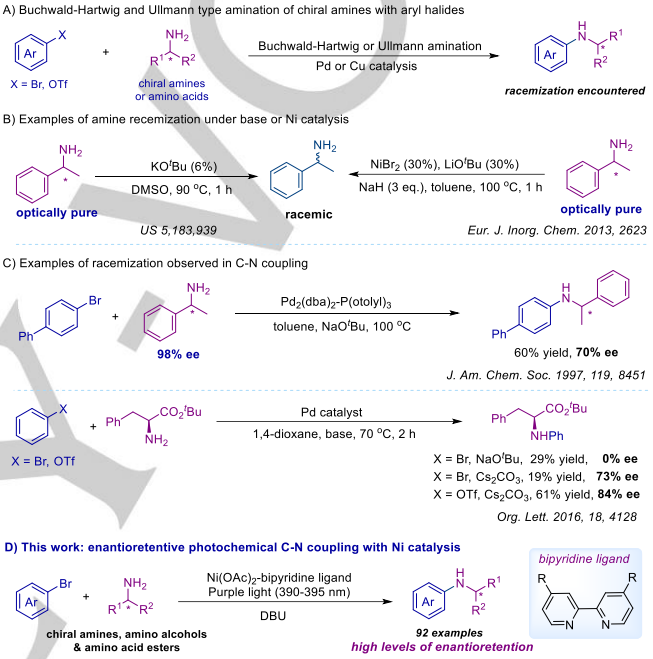
Abstract: The Buchwald-Hartwig C-N coupling reaction has found widespread applications in organic synthesis. Over the past two decades or so, many improved catalysts have been introduced, allowing various amines and aryl electrophiles to be readily used nowadays. However, there lacks a protocol that could be used to couple a wide range of chiral amines and aryl halides, without erosion of the enantiomeric excess (ee). Reported in this article is a method based on molecular Ni catalysis driven by light, which enables stereoretentive C-N coupling of optically active amines, amino alcohols, and amino acid esters with aryl bromides, with no need for any external photosensitizer. The method is effective for a wide variety of coupling partners, including those bearing functional groups sensitive to bases and nucleophiles, thus providing a viable alternative to accessing synthetically important chiral *N*-aryl amines, amino alcohols, and amino acids esters. Its viability is demonstrated by 92 examples with up to 99% ee.

Introduction

The palladium-catalyzed Buchwald-Hartwig amination[1] is ranked as one of the 20 most frequently used reactions in medicinal chemistry.[2] Together with the copper-catalyzed Ullmann type coupling,[3] it is also considered one of the most commonly used C-N bond formation reactions in modern organic chemistry (Scheme 1, A). Due to its much higher natural abundance and lower cost than palladium,[4] nickel has also been explored for catalyzing the C-N coupling of aryl halides with amines in the past two decades or so.[5-6] The efficiency and substrate scope of the nickel catalysis have been greatly improved with the advent of novel strategies in recent years.[7-9] Thanks to the Pd, Cu and Ni catalysis, diverse ranges of aryl amines can now be readily accessed via the C-N coupling reactions.

However, throughout the history of C-N coupling chemistry, there have been only sporadic reports on either Pd, Cu or Ni catalyzed coupling of chiral amines and amino acid esters to access chiral N-aryl amines and amino acids(esters), compounds of significant importance to the pharmaceutical industry.[10, 11] This discrepancy may not be surprising, however, as chiral amino compounds can be racemized by Pd,[10a] Ni[12] or a strong base such as alkali-metal alkoxides,[13] which are commonly employed in C-N coupling (Scheme 1, B, C). This is particularly acute for amino acids(esters), due to the presence of an acidic proton at their stereogenic centers.[10e, 10g] In the few successful examples using Pd catalysts bearing bulky ligands, the aryl electrophiles are limited to electron-deficient aryl bromides or more active aryl



Scheme 1. Metal catalyzed C-N coupling of aryl halides for the synthesis of chiral N-aryl amines and amino acid esters.

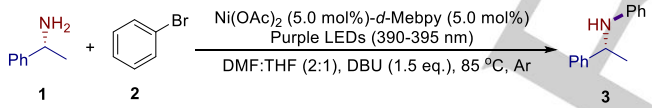
triflates[10d] and, in the case of heteroaryl halides, to chloropyridines.[10c,e-g] The Cu-catalyzed coupling of amino acids(esters) has been shown to be setereoretentive, albeit being limited to active aryl halides while requiring a relatively long reaction time.[11] In the burgeoning area of Ni-catalyzed C-N coupling, the only examples known thus far are seen in a recent report, in which electrochemical C-N coupling by Ni catalysis afforded chiral N-aryl amino acids esters with high yields but low levels of enantioretention.[9b] Clearly, a more general protocol that displays a wider substrate scope and retain the stereochemistry of the amino substrates remains highly desirable for further developing the widely used Buchwald-Hartwig C-N coupling reaction. Herein, we report a photochemically driven, Ni-catalyzed C-N coupling that enables a wide range of (hetero)aryl bromides to couple, stereoretentively, with chiral amines, amino alcohols, and amino acid esters (Scheme 1, D).

Results and Discussion

To develop a stereoretentive protocol for Ni-catalyzed C-N coupling, amine racemization must be avoided. We surmised that this could be achieved by stabilizing the metal with a bidentate ligand and by replacing the strong alkali-metal alkoxide base with a milder base. Indeed, while palladium complexes catalyze the racemization via a dehydrogenation/hydrogenation process triggered by hydrogen elimination, the racemization can be effectively suppressed by coordinating Pd with bidentate phosphine ligands.[10a] Bidentate pyridine ligands can be used to stabilize nickel species from decomposing into Ni nanoparticles,[14] which are known to catalyze amine racemization.[12] In our study into light-driven, Ni-catalyzed C-X (X = O, N) coupling, we have found that nickel complexes bearing bipyridine ligands are efficient catalysts, allowing for the coupling in the presence of a mild organic base, with no need for an additional photosensitizer.[15] Building on this basis, we set out to examine the possibility of Ni-catalyzed C-N coupling of chiral amines with aryl halides, aiming to establish a protocol that displays a wider substrate scope and a high level of enantioretention.

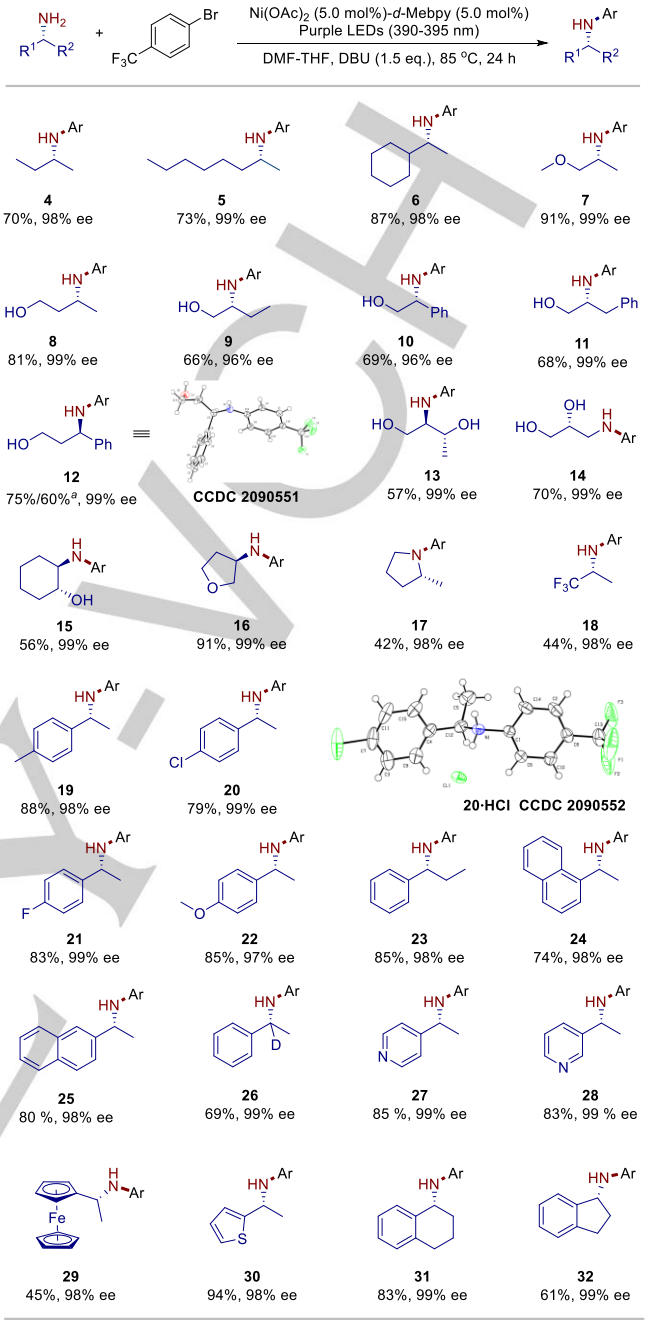
In our initial study, the coupling reaction of optically pure (*R*)-1-phenylethan-1-amine (**1**) with bromobenzene (**2**) was selected as a model system for reaction development. Delightedly, we found that using a Ni(II) complex in combination with a bipyridine ligand, the cross-coupling reaction readily took place under the irradiation of long-wave UV light (390-395 nm) in the absence of any external photosensitizer (Table 1). Among all the surveyed Ni catalysts (Table S1-S2, SI), the in-situ generated $Ni(OAc)_2$-d-Mebpy complex (d-Mebpy: 4,4'-dimethybipyridine) exhibited the best catalytic activity, affording the C-N coupling product (**3**) with 86% isolated yield (Table 1, entry 1).[16] Importantly, the

Table 1. Search for optimal reaction conditions for the target C-N coupling.[a]



Entry	Variation from standard conditions	Yield (%)
1	Standard conditions	86[b] (99%)[c]
2	Standard conditions, no ligand	10[d]
3	Standard conditions, UV (360-365 nm)	0[d]
4	Standard conditions, blue LEDs (460-465 nm)	10[d]
5	Standard conditions, white LEDs	0[d]
6	Standard conditions, green LEDs (530-535 nm)	0[d]
7	Standard conditions, no base	17[d]
8	Standard conditions, no nickel catalyst	0[d]
9	Standard conditions, no light, heating to 120 °C	0[d]

[a] Standard conditions: **1** (0.4 mmol), **2** (0.2 mmol), $Ni(OAc)_2$ (5.0 mol %), d-Mebpy (5.0 mol %), DBU (0.3 mmol), DMF:THF (2 mL), purple LEDs (390-395 nm), 85 °C, Ar, 24 h. [b] isolated yield. [c] The ee value was determined by HPLC with chiral stationary phases, and the absolute configuration of **3** was determined to be *R* by comparison of the HPLC retention time with literature. for details see SI. [d] Yields determined by ^1H NMR, using 1,3-benzodioxole as internal standard.

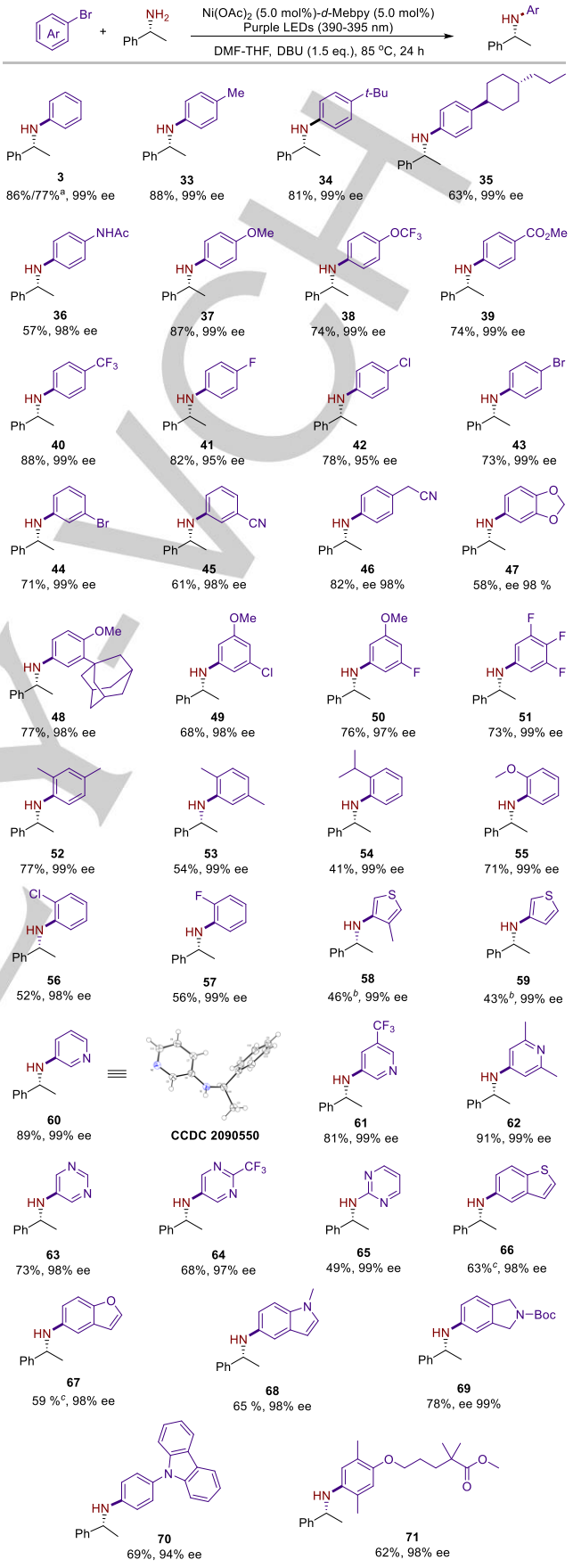


Scheme 2. Scope of chiral amines. Isolated yields are shown; configuration of the products and those below were determined by X-ray diffraction anyalysis or by analogy. [a] Gram scale reaction.

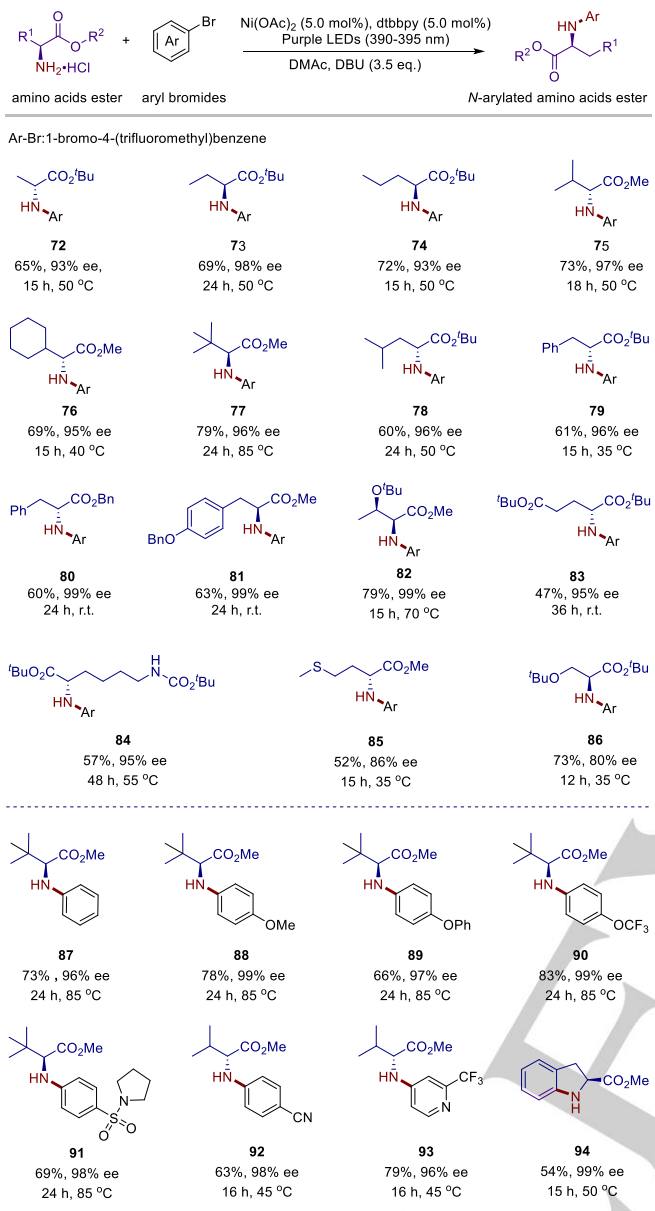
enantiomeric excess of **3** was 99%, showing complete retention of the amine stereochemistry in the C-N coupling. The bipyridine ligand is critical to the success of the reaction, with the product yield reduced considerably in its absence (entry 2). Further optimization indicates that light played a crucial role as well, as only the long-wave UV light afforded a high yield (Table 1, entries 3-6).[16] The choice of base also impacted on the reaction (entry 7), and pleasingly among the bases examined, the mild DBU promoted the reaction significantly better than other bases (Table S3-S4). Subsequent studies revealed a mixture of THF and DMF to be the optimum solvent for the coupling reaction (Table S5). Finally, control experiments showed that the reaction did not proceed in the absence of nickel catalyst or light (entries 8-9, Table S8).

With the optimized conditions in hand, we first explored the scope of chiral amines of this light-promoted C-N coupling reaction. As shown in Scheme 2, a wide range of diverse chiral amines could be coupled with 4-bromobenzotrifluoride, affording the desired products with high yields (**4-25**). Notably, the enantiomeric excess of products was excellent, >98% in most cases, showing a high level of enantioretention. Thus, when chiral aliphatic amines, such as 2-aminobutylamine, 2-octylamine and 1-cyclohexylethylamine, were used, the chiral aryl amines were obtained with high yields and ee's (**4-6**). We next extended the protocol to chiral amino alcohols, bearing in mind their importance in medicinal chemistry. It is significant to note that the desired products were obtained with good yields and high ee's (**7-15**), with no protection of the hydroxyl group required. In contrast, protection was required in a Pd-catalyzed C-N coupling of amino alcohols,[10a] demonstrating the advantage of the light-promoted C-N coupling reaction via nickel catalysis. The chiral aliphatic amines containing furan (**16**) and trifluoromethyl (**18**) and a tertiary chiral amine, arylated *α*-methylpyrrolidine (**17**),[17] could also be accessed.[18] It is noted that these chiral aliphatic amines, particularly those having sterically less differentiating substitutes at the stereogenic carbon, e.g. **4**, **7** and **18**, would be difficult to obtain by common asymmetric hydrogenation reactions. Equally, for chiral aryl amines with different substituents (**19**-**22**), phenyl propamine (**23**) and naphthyl amines (**24**-**25**), the desired chiral arylated amines were obtained with high ee's. Using the deuterated phenethylamine (**26**), the chiral amine product was obtained with 99% ee and full deuterium retention (94 D%). In contrast, H/D exchange may occur in the presence of a strong base or with metal catalysts capable of hydrogen elimination in traditional C-N coupling. Notable is also the formation of medicinally important aryl amines containing pyridine (**27**-**28**), thiophene (**30**), and tetralone (**31**) and indanone derivates (**32**), all with excellent ee's.

The scope of aryl halides was next examined. As summarized in Scheme 3, aryl bromides with a variety of functional groups reacted efficiently with optically pure (*R*)-1-phenylethan-1-amine (**1**), delivering the desired chiral aryl amines with high yields and excellent enantiomeric excess. Thus, the coupling of electron-neutral and rich aryl bromides afforded the desired chiral aryl amines in high yields with full retention of the amine stereochemistry (**3**, **33-37**). Such substates have been challenging with the traditional C-N coupling protocols.[10] Similar observations were made for aryl bromides bearing various electron-withdrawing substituents (**38-45**). It is noted that substrates with an ester group (**39**) or a cyano group (**45,46**) may not be compatible with the conventional, strongly-basic conditions. Indeed, transesterification in copper catalysis[19] and formation of impurities in palladium catalysis due to the cyano group[20] have been reported. In contrast, aryl bromides containing an ester or a cyano group are suitable with this protocol, demonstrating the advantage of using organic amines as base. Note for aryl bromides bearing a chloro or an additional bromo substituent, the corresponding mono-substituted chiral aryl amines were obtained with high yields (**42**-**44**), demonstrating not only a high degree of enantioretention but also chemoselectivity. Multisubstituted aryl bromides also worked successfully with this protocol (**47**-**51**), as showcased by the trifluoro-substituted aniline derivative **51**. In particular, aryl bromides with substitutes at the *ortho* position are viable substrates, causing no erosion of the amine stereochemistry in the coupling (**52**-**58**), albeit affording a



Scheme 3. Scope of aryl halides. Isolated yields are shown. [a] Gram scale reaction. [b] Catalyst (15 mol %, 36 h). [c] Catalyst (10 mol %).



Scheme 4. Scope of amino acid esters. Isolated yields are shown.

moderate yield in the case of the sterically more demanding isopropyl substituent (**54**).

Few examples have been reported of heteroaryl halides coupling with chiral amines,[9b, 10b,e-g, 20] which could easily lead to drug-like chiral amine molecules. As can be seen in Scheme 3, heteroaryl bromides are compatible with this Ni catalysis, affording the desired chiral aryl amines featuring a range of diverse heterocycles, thiophene (**58**, **59**), pyridine (**60-62**), pyrimidine (**63-65**), benzothiophene (**66**), benzofuran (**67**), indole (**68**), isoindole (**69**) and carbazole (**70**). These compounds would be difficult to access via asymmetric hydrogenation or reductive amination due to possible interference of the heteroatoms with metal coordination and their electron withdrawing effect. Furthermore, this methodology can be applied to the late-stage modification of drug molecules. An example is seen in the brominated Gemfibrozil methyl ester, amination of which afforded the chiral *N*-arylation product with 62% yields and 98% ee (**71**). These examples further demonstrate the power of the light-driven Ni catalysis in stereoretentive C-N coupling reactions.

Bearing in mind the significant importance of *N*-arylated amino acids esters in the synthesis of bio-medically active molecules,[21] we next explored the more challenging *N*-arylation of amino acid esters. However, when applied to valine methyl ester, the desired product was obtained with a good yield (74%) but a low ee (53%) under our standard condition (Table 1). We quickly found that temperature is critical to maintaining the stereochemistry for the C-N coupling with amino acids esters prone to racemization. Together with the mild DBU base, a lower temperature thus makes possible highly enantioretentive arylation of this class of substrates with aryl bromides, a reaction that is difficult with conventional methods where harsh conditions are usually employed. As summarized in Scheme 4, a wide range of amino acid esters, such as methyl, *tert*-butyl, or benzyl esters, are suitable for this *N*-arylation reaction. For amino acid esters of alanine (**72**), valine (**75**), cyclohexylglycine (**76**), leucine (**78**), phenylalanine (**79-80**), tyrosine (**81**), threonine (**82**), glutamic acid (**83**), lysine (**84**), the C-N coupling products were obtained with excellent levels of enantioretention. For methionine methyl ester (**85**) and serine tert-butyl ester (**86**), the *N*-arylated amino acid ester were obtained with reduced enantioretention, probably due to the proton being slightly more acidic. The previously reported Ni catalysis is less likely to work on these amino acid esters (See Section 2.2, Supporting Information).

We next evaluated the scope of aryl bromides. As can be seen in Scheme **4**, various aryl bromides can be brought into the C-N coupling, regardless of being electron-neutral (**87**), rich (**88-89**) or deficient (**90-92**) or being a heteroaryl (**93**), with little erosion of enantiomeric excess observed. Moreover, the protocol is suitable for intramolecular C-N coupling, as shown by the formation of indoline (**94**) with good yield and excellent enantiomeric excess. Note for amino acid esters bearing the *tert*-butyl group, a lower temperature is not necessary (see **77**, **87-91**). This is likely to stem from the steric encumbrance of the group which hinders the deprotonation of the *α*-proton.

The mechanism of this light-promoted Ni-catalyzed C-N coupling has not been thoroughly investigated. However, on the basis of our recent studies of C-O and C-N coupling reactions enabled by a similar Ni catalytic system[15] and closely related studies by other groups,[22-25] the coupling reaction in question is

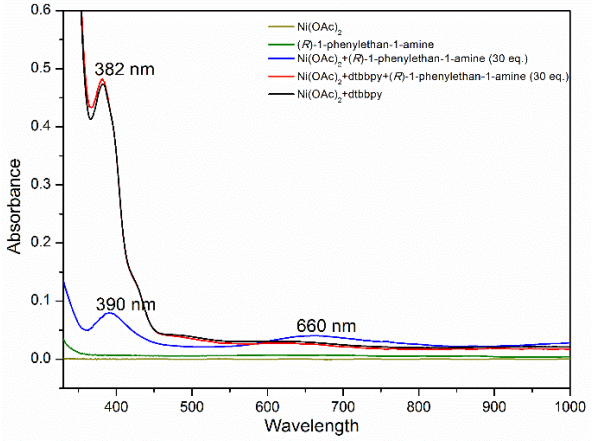
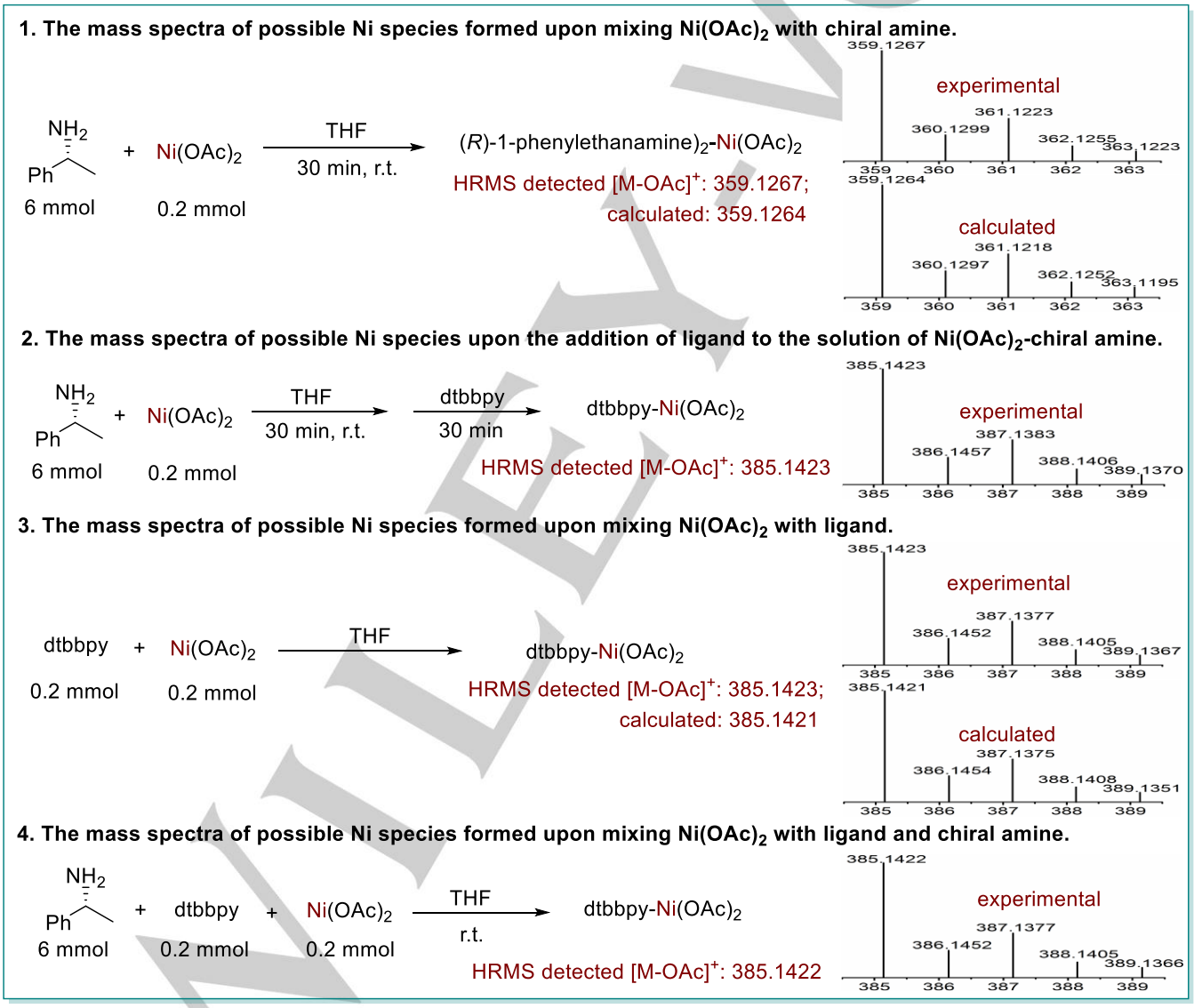


Figure 1. UV-Vis absorption spectra of dtbbpy, (*R*)-1-phenylethan-1-amine and Ni(II) species in THF (5.0×10^{-4} M, 1 mm pathlength quartz cuvette). For details, see Supporting Information (Section 4.1).

likely to proceed via a Ni(I)/Ni(III) cycle. The few probing experiments we have conducted appear to support this view.

First, the measurements of UV-Vis absorption support the formation of Ni(II)-dtbbpy species duing the catalysis, with or without the amine substrate. As showed in Figure 1, the species generated by in-situ mixing $Ni(OAc)_2$ and the chiral amine (*R*)-1-phenylethanamine in THF shows absorption bands similar to those of an octahedral Ni(II)-amine complex reported by the groups of Miyake[8c] and MacMillan[8e]. In contrast, the in situ-made $Ni(OAc)_2$-dtbbpy complex shows features distinctively different in the region of 350-800 nm, and more significantly, the presence of a large amount of (*R*)-1-phenylethanamine has little effect on its absorption, suggesting that Ni(II) is ligated by the bidentate dtbbpy ligand in the reaction mixture and the resulting Ni(II)-dtbbpy complex, which does not appear to interact with the chiral amine, is likely to be the light-absorbing species. This conjecture also explains why, without the ligand, the C-N coupling cannot take place under the irradiation of purple light.

We also measured the mass spectra of possible Ni species formed upon mixing the starting Ni(II) complex with an amine and ligand. As shown in Scheme 5, when $Ni(OAc)_2$ was mixed with an excess amount of the chiral amine for 30 min in THF, the HRMS revealed a *m/z* peak at 359.1267, which is consistent with the formation of $Ni(OAc)_2$[(*R*)-1-phenylethanamine] or {Ni(OAc)[(*R*)-1-phenylethanamine]}$^+$. However, after the addition of the dtbbpy ligand (1 equivalnet to Ni), the peak of the chiral amine-nickel complex disappeared and a new peak at *m/z* 385.1423 was detected, which was also detected by mixing $Ni(OAc)_2$ and dtbbpy in the absence of the amine and is consistent with the formation

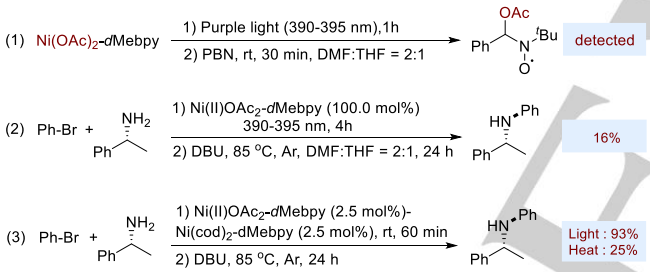


Scheme 5. Mass spectrometry study of possible Ni species.

of $Ni(OAc)_2$(dtbbpy) or [Ni(OAc)(dtbbpy)]$^+$. Similarly, when $Ni(OAc)_2$ was mixed with both the bipyridine and excess chiral amine, the peak at *m/z* 385.1422, but not that at 359.1267, was detected. These results lend further support to the notion that theactive catalytic species in the reaction is likely to be a Ni(II)-bipyridine complex.

Furthermore, when the in situ-made $Ni(OAc)_2$-dMebpy complex was irradiated by purple light for 1 h, the formation of OAc radical was observed by electron paramagnetic resonance (EPR) spectroscopy (Figure S15) with *N-tert*-butyl-*α*-phenylnitrone

(PBN) as a radical trap (Scheme 6, 1). The spin adduct of the OAc radical is characterized by hyperfine coupling constants that agree with the literature data.[26] The formation of the OAc radical indicates homolysis of the Ni-O bond and hence the formation of Ni(I) species under the irradiation of light. We next probed the possibility of oxidative addition at the Ni(I) species with an aryl halide and the following C-N coupling reaction. In the absence of substrates, the $Ni(OAc)_2$-dMebpy complex was irradiated under the purple light for 4 h, which was expected to generate a Ni(I) complex. Then in the dark, the substrates were introduced and reacted for 24 h, affording the corresponding arylamine with 16% yield (Scheme 6, 2). Still further, when the Ni(I) complex, generated in situ from the comproportionation of $Ni(II)(OAc)_2$-dMebpy and Ni(0)(dMebpy)(cod) complexes, was used as catalyst, the desired product was obtained in 93% yield under the irradiation of light and 25% yield under thermal conditions (Scheme 6, 3). In addition, as shown in Table 1, Ni(II) species are inactive without light irradiation. These observations support the view that this C-N coupling proceeds via a dMebpy-ligated Ni(I)/N(III) cycle, involving oxidative addition of ArBr at a Ni(I)-dMebpy species and reductive elimination of an aryl and amide group at Ni(III)-dMebpy to form the C-N bond, with light required to generate the Ni(I) species from off-cycle Ni(II)-dMebpy species and sustain the catalytic turnover.[8e] However, the possibility of a Ni(II)-amine species being the active catalyst and/or amine participation in the Ni(II)-dMebpy catalysed C-N coupling, as put forward by Miyake and coworkers, cannot be ruled out.[8c]



Scheme 6. Reactions aimed to probe the C-N coupling mechanism. Yields determined by ^{1}H NMR. For details, see SI.

Conclusion

In summary, we have developed a highly enantioretentive photochemical C-N coupling of commercially available chiral amines, amino alcohols, and amino acid esters with various aryl bromides. The reaction is catalyzed by an easily-available Ni(II)-dMebpy complex, with no need for an external photosensitizer. It exhibits a very wide substrate scope, good functional group compatibility and excellent levels of enantioretention, providing a practical, viable alternative pathway for the synthesis of chiral *N*-aryl amines, amino alcohols, and amino acid esters, some of the most important building blocks in pharmaceutical and agrochemical synthesis. The stabilizing bidentate ligand and mild organic base alongside the mild reaction conditions enabled by light are likely to be the key for the observed enantioretention.

Acknowledgements

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Keywords: C-N coupling • chiral *N*-aryl amines • chiral *N*-aryl amino acids • chiral *N*-aryl amino alcohols • nickel catalysis

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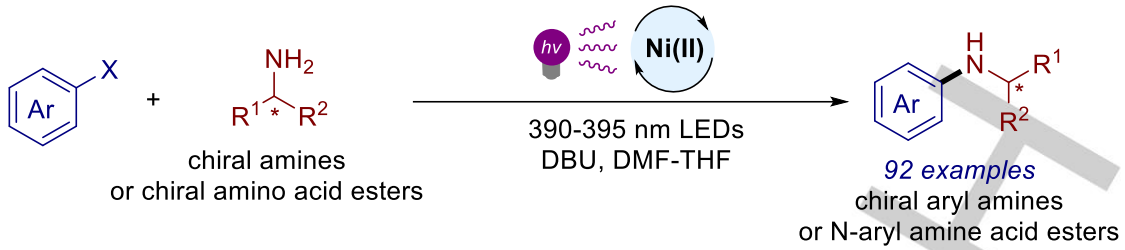

- ***Stereoretentive C-N coupling***
- ***No external photocatalysts added***
- ***Alkyl amine as base***
- ***Broad substrate scope***

A stereoretentive C-N coupling of optically active amines and amino acid esters with aryl bromides is achieved by nickel catalysis under light irradiation, without the use of any external photosensitizers.