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Nickel-Catalyzed *N*-Arylation of Optically Pure Amino Acid Esters with Activated (Hetero)aryl Electrophiles

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ABSTRACT

An efficient method for the C–N cross-coupling of (hetero)aryl (pseudo)halides with optically pure α-amino acid esters employing a commercially available nickel catalyst and weak inorganic base was developed. This is the first example of Ni-catalyzed *N*-arylation of amino acid esters without the use of electrochemistry, which was shown to effectively couple a variety of amino acid *tert*-butyl esters with (hetero)aryl chlorides, bromides, and tosylates in high yields and excellent enantioretention. Base-mediated racemization was revealed during control experiments, but increasing the steric bulk of the amino acid ester group limited the amount of racemization of the product.

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Key Words: Amination, Cross-coupling, Amino acid esters, Nickel.

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INTRODUCTION

Transition metal catalysis is widely employed for cross-coupling reactions in modern synthetic organic chemistry, enabling the development of complex molecules from readily available starting materials. The development of catalysts for this purpose is accomplished through the application of carefully designed ancillary ligands that coordinate to the metal center of interest to enhance the catalytic performance. The palladium-catalyzed C(sp^2)–N cross-coupling of NH substrates and (hetero)aryl pseudo(halides), known as the Buchwald-Hartwig amination, is an incredibly established methodology that is now widely used in the synthesis of biologically active molecules.[1, 2] Initially, palladium catalysts were predominant in the cross-coupling of amines and (hetero)aryl electrophiles, but the chemistry continues to advance forward to include non-precious metals in these syntheses.[3]

Chiral aromatic amines are essential building blocks for the synthesis of many bioactive molecules.[4, 5] Different stereoisomers can have remarkably diverse biological properties, which brings forth the need for developing enantioselective reactions to synthesize optically pure aromatic amines.[6] Among the variety of functionalized chiral amines, amino acids are commercially available and are essential building blocks for peptides, proteins, and many physiologically relevant substances.[7, 8] In particular, the synthesis of *N*-heteroaryl α-amino acids is of interest as they have been useful synthetic intermediates for diverse medicinal molecules.[9] The *N*-arylation of amino acids and esters have traditionally been accomplished through nucleophilic aromatic substitutions (S_NAr), and other indirect methods.[10, 11] More recently, transition metal-catalyzed *N*-arylations of amino acid esters with aryl (pseudo)halides have been developed to provide a direct approach to these molecules. However, these compounds can be quite challenging to obtain due to the lower pK_a of the α-proton of the chiral amino acid ester,

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leading to partial or complete racemization of this stereocenter; this can still be a problem even under weakly basic reaction conditions. Historically, the transition metal-catalyzed aminations of (hetero)aryl (pseudo)halides with optically pure amino acids involved copper-catalyzed Ullmann-type reactions that typically required aryl bromide and iodide electrophiles.[12-15] There are limited examples of palladium-catalyzed *N*-arylations involving α-amino acid esters that show enantioretention, as significant racemization was prevalent.[16, 17] Recent examples have been successful in obtaining optical purity, but the substrate scope has been limited to aryl triflates or heteroaryl chlorides.[18-20] Regarding nickel catalysis, there is only a single report from Baran and co-workers employing electrochemistry for the *N*-arylation of amino acid esters, but the electrophile scope consists of only two aryl bromides and racemization is a persistent problem.[21] There are no examples of base-metal catalyzed *N*-arylations of α-amino acid esters employing simple aryl chloride electrophiles, which are generally the most attractive substrates for cross-coupling reactions due to both cost and availability.

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We have previously developed methods for the nickel-catalyzed $C(sp^2)$–N cross-coupling of aliphatic amines and (hetero)aryl (pseudo)halides using the air-stable pre-catalyst (PAd-DalPhos)Ni(*o*-tolyl)Cl.[3] Due to the success of this now-commercialized pre-catalyst, and others, for the monoarylation of amines, and the limited examples of α-amino acid ester nucleophiles in nickel catalysis, the development of a general method for the nickel-catalyzed *N*-arylation of α-amino acid esters seemed desirable. Previously, our pre-catalyst systems largely employed metal alkoxide bases, the use of which is not ideal due to the propensity of the cross-coupled amino acid products to undergo racemization. We recently made use of weak inorganic and organic bases with Ni/DalPhos pre-catalysts for $C(sp^2)$–N cross-couplings of amides and fluoroalkyl amines, and sought to utilize these bases for amine monoarylation.[22-24] Herein, we report the development of a general, enantioretentive method for the nickel-catalyzed *N*-arylation of α-amino acid esters.

EXPERIMENTAL

General Experimental Considerations. All reactions were set up inside a nitrogen-filled, inert atmosphere glovebox and product isolation was carried out under standard benchtop conditions. Toluene and 1,4-dioxane used in the glovebox were deoxygenated by purging with nitrogen followed by storage over activated 4 Å molecular sieves for 48 h. All solvents used within the glovebox were stored over activated 4 Å molecular sieves. Flash column chromatography was performed on silica gel (SiliaFlash P60, Silicycle). All ^{1}H NMR (500 MHz), ^{13}C NMR (125.8 MHz), and ^{19}F NMR (470 MHz) spectra were recorded at 300 K. Chemical shifts are expressed in parts per million (ppm) referenced using the solvent signals $CDCl_3$ (^{1}H 7.26 ppm, residual $CHCl_3$; ^{13}C 77.16 ppm, $CDCl_3$) or to an external sample (0.5% $(CF_3)C_6H_5$ in $CDCl_3$ at -63.7 ppm) for ^{19}F. Splitting patterns are indicated as follows: brs, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; quintet; m, multiplet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dt, doublet of triplets; td, triplet of doublets. All coupling constants (*J*) are reported in Hertz (Hz). Mass spectra were obtained using ion trap (ESI) instruments operating in positive mode, GC data were obtained on an instrument equipped with a SGE BP-5, 30 m, 0.25 mm i.d. column, and HPLC data were obtained under conditions outlined specifically for each compound below.

General Procedure for the *N*-Arylation of Amino Acids with Aryl (pseudo)Halides. In a nitrogen-filled glovebox, (CyPAd-Dalphos)Ni(o-tol)Cl (10 mol%), aryl (pseudo)halide (1.0 equiv, 0.12 M), Cs_2CO_3 (4.1 equiv), and amino acid ester (1.1 equiv) were added to a screw capped vial

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containing a magnetic stir bar, followed by the addition of 1,4-dioxane. Unless stated otherwise, each product was synthesized from the corresponding aryl chloride. The vial was sealed with a cap containing a PTFE septum, removed from the glovebox and placed in a temperature-controlled aluminum heating block set to 110 °C for 18 h with magnetic stirring. The vial was then removed from the heating block and left to cool to ambient temperature. The crude reaction mixture was then filtered through a short Celite/SiO_2 plug (3:1 v/v) eluting with ethyl acetate, and the volatile materials were evaporated *in vacuo*. The crude product was purified by flash-column chromatography to afford the purified product.

(*S*)-*tert*-butyl 2-((4-cyanophenyl)amino)propanoate (3a). The title compound was synthesized according to the general procedure and purified by flash column chromatography on silica gel eluting with 15% ethyl acetate/hexanes to afford **3a** in an 90% isolated yield (106 mg, 0.43 mmol) as a pale yellow oil. The compound was also synthesized using the aryl bromide in an 83% calibrated GC yield and from the aryl tosylate in an 88% calibrated GC yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 (d, *J*= 8.8 Hz, 2H), 6.55 (d, *J*= 8.8 Hz, 2H), 4.03 (q, *J*= 6.9 Hz, 1H), 1.45 (s, 12H); $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$): δ 172.7, 150.0, 133.9, 120.3, 112.9, 99.8, 82.4, 51.9, 28.1, 18.6. *m/z* ESI+ found 269.1262 [M+Na]+ calculated for $C_{14}H_{18}N_2NaO_2$ 269.1260. The enantiomeric excess was determined by HPLC on a Chiralpak AD-H column with a 95:5 Hexane (1% CyNH2):iPrOH mobile phase at a 0.9 mL/min flow rate. t= 24.785 min. Enantiomeric ratio = >99:1.

(*S*)-*tert*-butyl 2-(pyridin-2-ylamino)propanoate (3b). The title compound was synthesized according to the general procedure and purified by flash column chromatography on silica gel

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eluting with 20% ethyl acetate/hexanes to afford **3b** in an 88% isolated yield (94 mg, 0.42 mmol) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.06 (dd, *J*= 5.0, 1.1 Hz, 1H), 7.37 (ddd, *J*= 8.5, 7.0, 1.7 Hz, 1H), 6.56 (ddd, *J*= 7.1, 5.1, 0.7 Hz, 1H), 6.40 (d, *J*= 8.4 Hz, 1H), 4.94 (d, *J*= 7.2 Hz, 1H), 4.42 (quintet, *J*= 7.3 Hz, 1H), 1.44 (s, 12H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 173.8, 157.7, 148.0, 137.3, 113.4, 108.3, 81.4, 50.8, 28.1, 18.8. *m/z* ESI+ found 223.1437 [M+H]+ calculated for $C_{12}H_{19}N_2O_2$ 223.1441. The enantiomeric excess was determined by HPLC on a Chiralpak AD-H column with a 95:5 Hexane (1% CyNH2):iPrOH mobile phase at a 0.9 mL/min flow rate. t_{major}= 26.420 min, t_{min}= 15.431 min. Enantiomeric ratio= 97:3.

(*S*)-*tert*-butyl 2-((4-(trifluoromethyl)phenyl)amino)propanoate (3c). The title compound was synthesized according to the general procedure and purified by flash column chromatography on silica gel eluting with 20% ethyl acetate/hexanes to afford **3c** in a 92% isolated yield (128 mg, 0.44 mmol) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (d, *J*= 8.4 Hz, 2H), 6.60 (d, *J*= 8.5 Hz, 2H), 4.04 (q, *J*= 6.9 Hz, 1H), 1.45 (s, 12H); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): δ 173.2, 149.4, 126.80–126.77 (m), 112.6, 82.1, 52.2, 28.1, 18.8. ^{19}F NMR (470 MHz, $CDCl_3$): δ -61.2. *m/z* ESI+ found 312.1180 [M+Na]+ calculated for $C_{14}H_{18}F_3NNaO_2$ 312.1182. The enantiomeric excess was determined by HPLC on a Chiralpak AD-H column with a 95:5 Hexane (1% CyNH2):iPrOH mobile phase at a 0.9 mL/min flow rate. t= 5.244 min. Enantiomeric ratio= >99:1.

(*S*)-*tert*-butyl 2-((4-cyanophenyl)amino)-3-methylbutanoate (3d). The title compound was synthesized according to the general procedure and purified by flash column chromatography on silica gel eluting with 15% ethyl acetate/hexanes to afford **3d** in a 94% isolated yield (124 mg, 0.45 mmol) as a yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, *J*= 8.8 Hz, 2H), 6.58 (d, *J*=

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8.8 Hz, 2H), 3.80 (d, *J*= 5.4, 1H), 2.16–2.10 (m, 1H), 1.45 (s, 9H), 1.02 (dd, *J*= 19.2, 6.9 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$): δ 171.6, 150.8, 133.8, 120.3, 113.0, 99.7, 82.4, 61.9, 31.5, 28.2, 18.9, 18.7. *m/z* ESI+ found 297.1571 [M+Na]+ calculated for $C_{16}H_{22}N_2NaO_2$ 297.1573. The enantiomeric excess was determined by HPLC on a Chiralpak AD-H column with a 95:5 Hexane (1% CyNH2):iPrOH mobile phase at a 0.9 mL/min flow rate. t_{major}= 25.058 min, t_{min}= 13.142 min. Enantiomeric ratio= 96:4.

(*S*)-*tert*-butyl 2-((2-cyanophenyl)amino)-3-methylbutanoate (3e). The title compound was synthesized according to the general procedure and purified by flash column chromatography on silica gel eluting with 20% ethyl acetate/hexanes to afford **3e** in a 95% isolated yield (125 mg, 0.46 mmol) as a pale yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (m, 1H), 7.35 (ddd, *J*= 8.6, 7.3, 1.6 Hz, 1H), 6.70 (td, *J*= 7.6, 0.8 Hz, 1H), 6.62 (d, *J*= 8.5, 1H), 3.79 (d, *J*= 5.8, 1H), 2.17 (ttd, *J*= 6.7, 6.5, 6.6 Hz, 1H), 1.44 (s, 9H), 1.06 (dd, *J*= 18.5, 6.9 Hz, 6H); $^{13}C\{^{1}H\}$ NMR (125.8 MHz, $CDCl_3$): δ 171.2, 149.8, 134.2, 133.0, 117.4, 111.5, 97.1, 82.2, 62.6, 31.5, 28.1, 19.0, 18.7. *m/z* ESI+ found 297.1569 [M+Na]+ calculated for $C_{16}H_{22}N_2NaO_2$ 297.1572. The enantiomeric excess was determined by HPLC on a Chiralpak AD-H column with a 95:5 Hexane (1% CyNH2):iPrOH mobile phase at a 0.9 mL/min flow rate. t= 5.398 min. Enantiomeric ratio= >99:1.

(*S*)-*tert*-butyl 3-methyl-2-((4-(trifluoromethyl)phenyl)amino)butanoate (3f). The title compound was synthesized according to the general procedure and purified by flash column chromatography on silica gel eluting with 10% ethyl acetate/hexanes to afford **3f** in an 92% isolated yield (140.1 mg, 0.44 mmol) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, *J*= 7.7 Hz, 2H), 6.63 (d, *J*= 7.6 Hz, 2H), 3.79 (m, 1H), 2.13 (m, 1H), 1.45 (s, 9H), 1.03 (dd, *J*=

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14.3, 6.5 Hz, 6H); $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$): δ 172.1, 150.2, 126.7, 119.6 (q, *J*= 32.6 Hz), 112.7, 82.1, 62.3, 31.6, 28.2, 19.0, 18.7. ^{19}F NMR (470 MHz, $CDCl_3$): δ -61.1. *m/z* ESI+ found 340.1495 $[M+Na]^+$ calculated for $C_{16}H_{22}F_3NNaO_2$ 340.1495. The enantiomeric excess was determined by HPLC on a Chiralpak AD-H column with a 95:5 Hexane (1% CyNH2):iPrOH mobile phase at a 0.9 mL/min flow rate. t= 6.105 min. Enantiomeric ratio= >99:1.

(2*S*,3*S*)-*tert*-butyl 2-((2-cyanophenyl)amino)-3-methylpentanoate (3g). The title compound was synthesized according to the general procedure and purified by flash column chromatography on silica gel eluting with 10% ethyl acetate/hexanes to afford **3g** in an 84% isolated yield (116 mg, 0.40 mmol) as a pale yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.40 (dd, *J*= 7.7, 1.3 Hz, 1H), 7.35 (ddd, *J*= 8.6, 7.3, 1.5 Hz, 1H), 6.69 (td, *J*= 7.5, 0.8 Hz, 1H), 6.62 (d, *J*= 8.5 Hz, 1H), 3.88 (d, *J*= 5.7 Hz, 1H), 1.94–1.86 (m, 1H), 1.67–1.61 (m, 1H), 1.44 (s, 9H), 1.37–1.30 (m, 1H), 1.01–0.96 (m, 6H); $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$): δ 171.1, 149.6, 134.2, 133.0, 117.7, 117.4, 111.4, 97.1, 82.2, 61.3, 37.9, 28.1, 25.8, 15.5, 11.6. *m/z* ESI+ found 311.1732 $[M+Na]^+$ calculated for $C_{17}H_{24}N_2NaO_2$ 311.1728. The enantiomeric excess was determined by HPLC on a Chiralpak AD-H column with a 95:5 Hexane (1% CyNH2):iPrOH mobile phase at a 0.9 mL/min flow rate. t= 5.055 min. Enantiomeric ratio= >99:1.

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(2*S*,3*S*)-*tert*-butyl 2-((4-cyanophenyl)amino)-3-methylpentanoate (3h). The title compound was synthesized according to the general procedure and purified by flash column chromatography on silica gel eluting with 15% ethyl acetate/hexanes to afford **3h** in a 80% isolated yield (111 mg, 0.38 mmol) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.42–7.39 (m, 2H), 6.58–6.56 (m, 2H), 3.80 (d, *J*= 5.4, 1H), 1.85 (ddt, *J*= 8.8, 6.8, 5.1 Hz, 1H), 1.63–1.56 (m, 1H), 1.45 (s, 9H), 1.35–

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1.29 (m, 1H), 0.99–0.95 (m, 6H); $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$): δ 171.4, 150.5, 133.8, 120.4, 112.9, 99.6, 82.5, 60.5, 38.0, 28.2, 26.0, 15.4, 11.8. *m/z* ESI+ found 311.1724 $[M+Na]^+$ calculated for $C_{17}H_{24}N_2NaO_2$ 311.1730. The enantiomeric excess was determined by HPLC on a Chiralpak AD-H column with a 95:5 Hexane (1% CyNH2):iPrOH mobile phase at a 0.9 mL/min flow rate. t_{major}= 18.548 min, t_{min}= 9.669 min. Enantiomeric ratio= 98:2.

(*S*)-*tert*-butyl 2-((2-cyanophenyl)amino)-4-methylpentanoate (3i). The title compound was synthesized according to the general procedure and purified by flash column chromatography on silica gel eluting with 15% ethyl acetate/hexanes to afford **3i** in a 79% isolated yield (104 mg, 0.38 mmol) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.40 (dd, *J*= 7.7, 1.2 Hz, 1H), 7.36 (ddd, *J*= 8.6, 7.3, 1.5 Hz, 1H), 6.71 (td, *J*= 7.7, 0.7 Hz, 1H), 6.63 (d, *J*= 8.5 Hz, 1H), 4.74 (br s, 1H), 4.00 (t, *J*= 7.1 Hz, 1H), 1.87–1.77 (m, 1H), 1.74–1.64 (m, 2H), 1.42 (s, 9H), 1.00 (d, *J*= 6.6 Hz, 3H), 0.95 (d, *J*= 6.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$): δ 172.4, 149.6, 134.3, 133.0, 117.6, 111.4, 97.0, 82.1, 55.7, 41.9, 28.1, 25.0, 22.8, 22.3. *m/z* ESI+ found 311.1730 $[M+Na]^+$ calculated for $C_{17}H_{24}N_2NaO_2$ 311.1725. The enantiomeric excess was determined by HPLC on a Chiralpak AD-H column with a 95:5 Hexane (1% CyNH2):iPrOH mobile phase at a 0.9 mL/min flow rate. t= 5.120 min. Enantiomeric ratio= >99:1.

(*S*)-*tert*-butyl 3-(*tert*-butoxy)-2-((4-cyanophenyl)amino)propanoate (3j). The title compound was synthesized according to the general procedure and purified by flash column chromatography on silica gel eluting with 15% ethyl acetate/hexanes to afford **3j** in a 90% isolated yield (106 mg, 0.43 mmol) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.43–7.40 (m, 2H), 6.59–6.65 (m, 2H), 4.08 (t, *J*= 3.6 Hz, 1H), 3.78 (dd, *J*= 8.7, 3.7 Hz, 1H), 3.64 (dd, *J*= 8.7, 3.7 Hz, 1H), 1.44 (s, 9H),

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1.16 (s, 9H); $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$): δ 170.2, 150.6, 133.8, 120.4, 113.1, 99.7, 82.3, 73.6, 62.2, 56.7, 28.1, 27.5. *m/z* ESI+ found 341.1833 $[M+Na]^+$ calculated for $C_{18}H_{26}N_2O_3Na$ 341.1836. The enantiomeric excess was determined by HPLC on a Chiralpak AD-H column with a 95:5 Hexane (1% CyNH2):iPrOH mobile phase at a 0.9 mL/min flow rate. t_{major}= 24.512 min, t_{min}= 14.026 min. Enantiomeric ratio= 97:3.

(*S*)-*tert*-butyl 3-(tert-butoxy)-2-(quinoxalin-6-ylamino)propanoate (3k). The title compound was synthesized according to the general procedure and purified by flash column chromatography on silica gel eluting with 15% ethyl acetate/hexanes to afford **3l** in a 79% isolated yield (103 mg, 0.38 mmol) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 8.62 (d, *J*= 2.0 Hz, 1H), 8.51 (d, *J*= 2.0 Hz, 1H), 7.85 (d, *J*= 2.0 Hz, 1H), 7.21 (dd, *J*= 9.1, 2.6 Hz, 1H), 6.91 (d, *J*= 2.6 Hz, 1H), 5.13 (m, 1H), 4.24 (br s, 1H), 3.85 (dd, *J*= 8.7, 3.5 Hz, 1H), 3.75 (dd, *J*= 8.7, 3.5 Hz, 1H), 1.47 (s, 9H), 1.17 (s, 9H); $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$): δ 170.3, 148.4, 145.3, 144.7, 140.7, 138.4, 130.3, 122.9, 104.3, 82.2, 73.5, 62.0, 57.0, 28.2, 27.5. *m/z* ESI+ found 346.2129 $[M+H]^+$ calculated for $C_{19}H_{28}N_3O_3$ 346.2125. The enantiomeric excess was determined by HPLC on a Chiralpak AD-H column with a 95:5 Hexane (1% CyNH2):iPrOH mobile phase at a 0.9 mL/min flow rate. t= 23.072 min. Enantiomeric ratio= >99:1.

(*S*)-*tert*-butyl 2-((4-cyanophenyl)amino)pentanoate (3l). The title compound was synthesized according to the general procedure and purified by flash column chromatography on silica gel eluting with 10% ethyl acetate/hexanes to afford **3l** in a 85% isolated yield (112 mg, 0.41 mmol) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, *J*= 8.8 Hz, 2H), 6.56 (d, *J*= 8.8 Hz, 2H), 3.97 (t, *J*= 6.2 Hz, 1H), 1.85–1.79 (m, 1H), 1.75–1.68 (m, 1H), 1.44–1.41 (m, 11H), 0.95 (t, *J*= 7.4

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Hz, 3H); $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$): δ 172.3, 150.4, 133.8, 120.3, 112.9, 99.7, 82.4, 56.2, 34.8, 28.1, 18.7, 13.9. *m/z* ESI+ found 297.1575 [M+Na]+ calculated for $C_{16}H_{22}N_2O_2Na$ 297.1579. The enantiomeric excess was determined by HPLC on a Chiralpak AD-H column with a 95:5 Hexane (1% CyNH2):iPrOH mobile phase at a 0.9 mL/min flow rate. t_{major}= 32.158 min, t_{min}= 13.970 min. Enantiomeric ratio= 95:5.

(*S*)-*tert*-butyl 2-((6-methoxypyridin-2-yl)amino)pentanoate (3m). The title compound was synthesized according to the general procedure and purified by flash column chromatography on silica gel eluting with 10% ethyl acetate/hexanes to afford **3m** in an 81% isolated yield (109 mg, 0.39 mmol) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 7.30 (t, *J*= 7.9 Hz, 1H), 6.02 (d, *J*= 7.9 Hz, 1H), 5.98 (d, *J*= 7.8 Hz, 1H), 4.74–4.70 (m, 1H), 4.39 (q, *J*= 6.9 Hz, 1H), 3.85 (s, 3H), 1.87–1.80 (m, 1H), 1.74–1.67 (m, 1H), 1.50–1.42 (m, 11H), 0.95 (t, *J*= 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (125.8 MHz, $CDCl_3$): δ 173.5, 163.6, 159.9, 140.0, 99.2, 97.9, 81.3, 55.2, 53.2, 35.1, 28.2, 19.0, 14.1. *m/z* ESI+ found 303.1680 [M+Na]+ calculated for $C_{15}H_{24}N_2O_3Na$ 303.1679. The enantiomeric excess was determined by HPLC on a Chiralpak AD-H column with a 95:5 Hexane (1% CyNH2):iPrOH mobile phase at a 0.9 mL/min flow rate. t= 7.767 min. Enantiomeric ratio= >99:1.

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RESULTS AND DISCUSSION

We began by investigating the cross-coupling of 4-chlorobenzonitrile (**1a**) and L-alanine *tert*-butyl ester hydrochloride (**2a**) using a variety of commercially available bisphosphine and *N*-heterocyclic carbene (NHC) ancillary ligands with Ni(cod)$_2$ (cod = 1,5-cyclooctadiene; Table 1). The initial screening involved toluene as the solvent with weak inorganic base potassium phosphate (K_3PO_4) at 110 °C (see Tables S1 and S2 in the Supplementary Material for full screening conditions). We initially explored several bisphosphine ligands (**L1**–**L8**) and NHC ligands (**L9**–**L10**) that have previously shown activity in Ni-catalyzed C(sp^2)–N cross-couplings. The ligands CyPAd-DalPhos (**L2**) and PhPAd-DalPhos (**L3**) were most successful under these conditions, with moderate conversions to product **2a**, while PAd-DalPhos (**L1**), ThioPAd-DalPhos (**L4**), and NHP-DalPhos (**L5**) were ineffective in this transformation (Table 1, entries 1–5). Outside of the DalPhos family of ligands, only dppf (**L7**) showed modest conversion to the desired product, with JosiPhos CyPF-Cy (**L6**), DPEPhos (**L8**), IPr (**L9**), and SIPr (**L10**) providing no conversion to product (Table 1, entries 6-10). The catalytic loading was kept at 10 mol % each for Ni(cod)$_2$ and ligand, as lowering the loading led to decreased catalytic performance. Changing the solvent from toluene to 1,4-dioxane led to a significant increase in conversion for CyPAd-DalPhos, but completely shutdown the catalysis for PhPAd-DalPhos (Table 1, entries 11–12). Earlier screening had revealed that strong bases lead to significant erosion of the stereocenters in the product, which is why weak bases were chosen for this cross-coupling. We have recently shown that the use of a dual-base system comprised of organic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and sodium triflate (NaOTf) or sodium trifluoroacetate (NaTFA) can be successful in facilitating C–N cross-coupling reactions.[23,24] This dual-base system had comparable results to K_3PO_4 (Table 1, entry 16). However, it was found that weak inorganic base cesium carbonate

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(Cs_2CO_3) provided the best conversion to product (Table 1, entry 17). With hopes of improving these conditions further, we attempted catalysis employing the air-stable pre-catalyst (CyPAd-DalPhos)Ni(*o*-tolyl)Cl (**C1**) as pre-catalysts of this type have generally shown greater catalytic performance than the analogous Ni(cod)$_2$/**L** mixtures for C(sp^2)–N cross-coupling. The pre-catalyst was successful in fully converting the electrophile to product (Table 1, entry 18). Other solvents were tested with **C1**, but 1,4-dioxane remained the optimal choice (Table 1 entries, 19–20). It was also found that the use of this pre-catalyst allowed the reaction to be performed at temperatures as low as 65 °C with no loss of performance (Table 1, entries 20–22). However, a reaction temperature of 110 °C was applied for the reaction scope to accommodate more challenging nucleophile and electrophile pairings.

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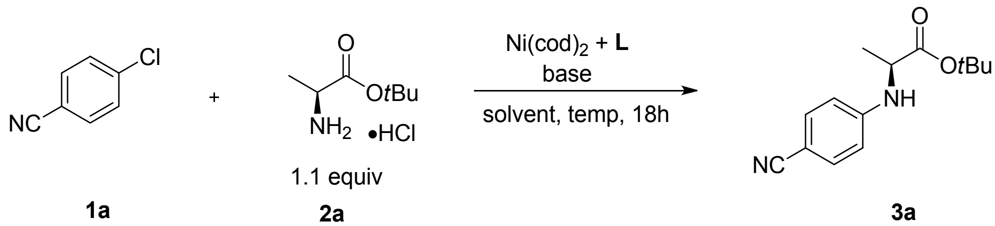
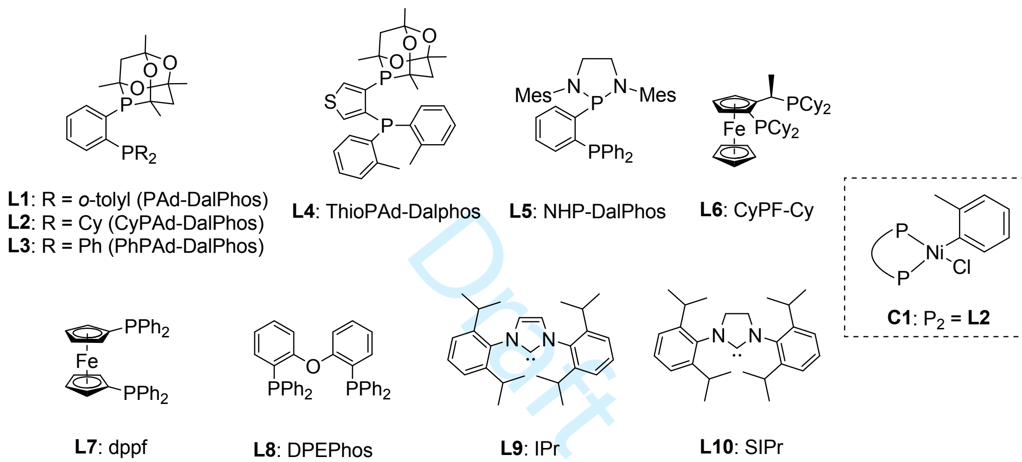
Table 1: Ligand screen and optimization for the Ni-catalyzed cross-coupling of 1a with L-alanine *tert*-butyl ester hydrochloride (**2a**)[a]





entry	ligand	temp (°C)	base	solvent	yield 3a (%)[b]	remaining 1a (%)[b]
1	**L1**	110	K_3PO_4	toluene	0	94
2	**L2**	110	K_3PO_4	toluene	52	0
3	**L3**	110	K_3PO_4	toluene	58	4
4	**L4**	110	K_3PO_4	toluene	0	92
5	**L5**	110	K_3PO_4	toluene	0	55
6	**L6**	110	K_3PO_4	toluene	0	96

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7	**L7**	110	K_3PO_4	toluene	20	0
8	**L8**	110	K_3PO_4	toluene	0	84
9	**L9**	110	K_3PO_4	toluene	0	64
10	**L10**	110	K_3PO_4	toluene	0	48
11	**L1**	110	K_3PO_4	1,4-dioxane	0	100
12	**L2**	110	K_3PO_4	1,4-dioxane	78	0
13	**L3**	110	K_3PO_4	1,4-dioxane	0	85
14	**L4**	110	K_3PO_4	1,4-dioxane	0	85
15	**L7**	110	K_3PO_4	1,4-dioxane	9	41
16[c]	**L2**	110	DBU/NaTFA	1,4-dioxane	72	24
17[d]	**L2**	110	Cs_2CO_3	1,4-dioxane	93	7
18[e]	**C1**	110	Cs_2CO_3	1,4-dioxane	**>95**	**<5**
19[e]	**C1**	110	Cs_2CO_3	toluene	90	0
20[e]	**C1**	110	Cs_2CO_3	CPME	95	0
21[e]	**C1**	80	Cs_2CO_3	1,4-dioxane	**>95**	**<5**
22[e]	**C1**	65	Cs_2CO_3	1,4-dioxane	**>95**	**<5**

[a]Reaction conditions: $Ni(cod)_2$ (10 mol%), **L1–L8** (10 mol%) or **L9–L10** (20 mol%), K_3PO_4 (4.1 equiv), **1a** (0.12 mmol, 1.0 equiv), **2a** (1.1 equiv), and solvent (1.0 mL, [**1a**] = 0.12 M). [b]Conversion to **3a** and remaining **1a** are estimated on the basis of calibrated GC data, with the remaining mass balance attributed to unidentified byproducts. [c]DBU (2.3 equiv), NaTFA (2.3 equiv). [d]Cs_2CO_3 (4.1 equiv). [e]**C1** pre-catalyst is used instead of $Ni(cod)_2$.

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Upon establishing the optimized conditions, the effect of steric bulk on the ester group of the amino acid hydrochloride was investigated (Table 2). It was found that the use of bulky *tert*-butyl esters was necessary for complete retention of stereochemistry after the cross-coupling reaction; the use of methyl and ethyl amino esters gave full conversion to product but led to significant decreases in enantiomeric excess (*ee*) (Table 2, entries 1–3). As the steric bulk decreased the resulting percentage *ee* also decreased, demonstrating a clear correlation between the two. The same steric effect on enantioretention was observed when using the L-valine amino ethyl ester, with complete erosion of the stereocenter being observed compared to the reaction employing the analogous tert-butyl ester (Table 2, entry 4–5). Attempts to use unprotected amino acids as coupling partners were unsuccessful. On the basis of these collective optimization results, the *tert*-butyl ester amino acids were used for examination of the substrate scope.

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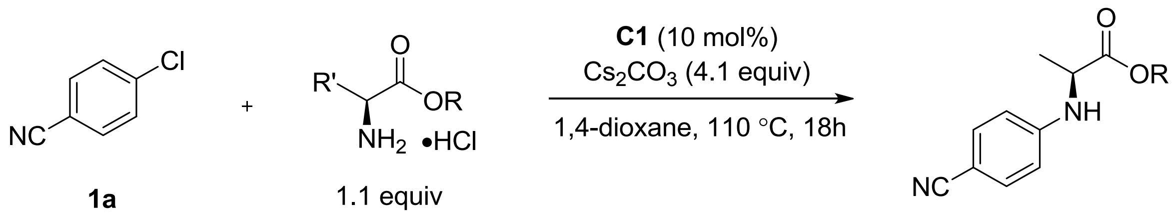
Table 2: The steric influence of the ester moiety of the amino acid on % enantioretention.



entry	R	R'	yield (%)[a]	*ee* (%)[b]
1	Me	Me	>95	34
2	Et	Me	>95	40
3	*t*Bu	Me	>95	>99
4	Et	*i*Pr	83	0
5	*t*Bu	*i*Pr	>95	92

[a]Product yields were determined by GC analysis. [b]Percentage *ee* of product was determined by chiral HPLC analysis.

We then explored the scope of reactivity using the established optimized conditions for the Ni-catalyzed C(sp^2)–N cross-coupling of selected amino acid *tert*-butyl esters and (hetero)aryl chlorides (Chart 1). We found that an assortment of functionalized (hetero)aryl chlorides, bromides and tosylates were efficiently cross-coupled to the *tert*-butyl esters of L-alanine (**3a**–**3c**), L-valine (**3d**–**3f**), L-isoleucine (**3g**–**3h**), L-leucine (**3i**), protected L-serine (**3j**–**3k**), and L-norvaline (**3l**–**3m**) in yields greater than 70%, with the products exhibiting excellent enantiopurity ranging from 90-99% *ee*. The reaction worked best with activated electrophiles containing electron-withdrawing

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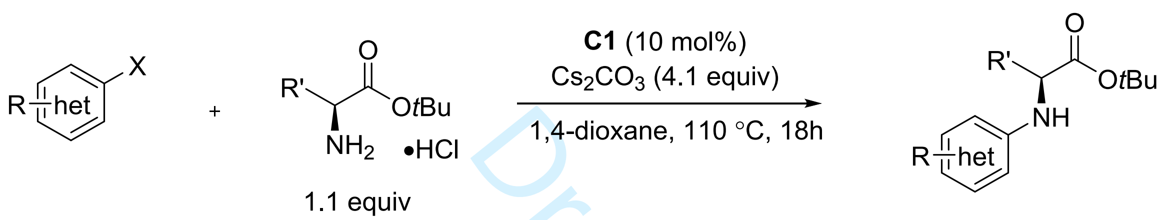
substituents such as nitrile (**3a, 3d, 3h, 3j, 3l**) and trifluoromethyl (**3c, 3f**) groups, including in *ortho*-positions (**3e**, **3g**, **3i**). Additionally, heterocyclic electrophiles containinig pyridine (**3b**, **3m**) and quinoxaline (**3k**) cores were also successfully employed. Electron-rich electrophiles were typically inadequate coupling partners. Additionally, the tert-butyl esters of L-proline and L-glutamic acid did not provide any product under these conditions.

Chart 1: Scope of the Ni-catalyzed C-N cross-coupling of amino acid *tert*-butyl ester hydrochlorides with (hetero)aryl (pseudo)halides.



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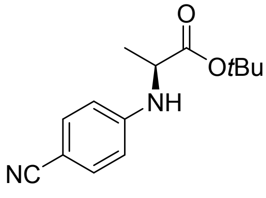
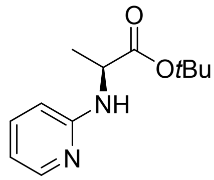
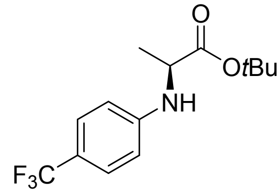


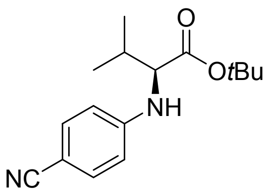
3a, 90% (>99% ee)
83%[b], 88%[c]



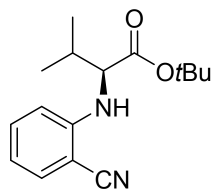
3b, 88% (94% ee)



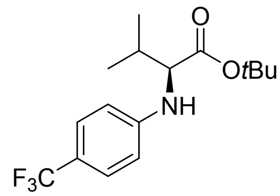
3c, 92% (99% ee)



3d, 94% (92% ee)



3e, 95% (>99% ee)



3f, 92% (>99% ee)

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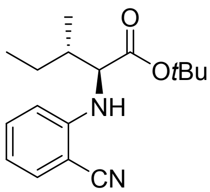
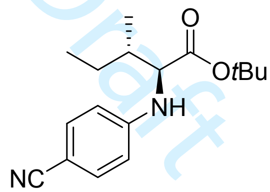
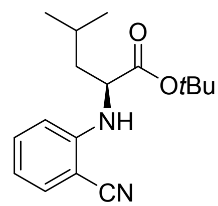


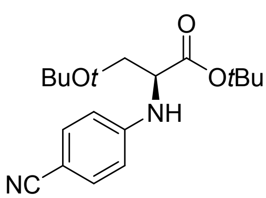
3g, 84% (>99% ee)



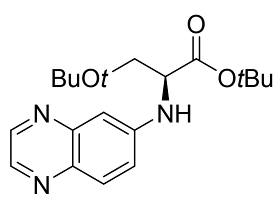
3h, 80% (96% ee)



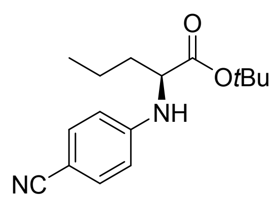
3i, 79% (>99% ee)



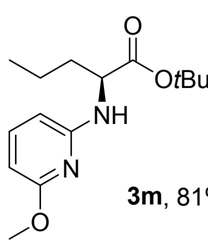
3j, 90% (94% ee)



3k, 79% (>99% ee)



3l, 85% (90% ee)



3m, 81% (>99% ee)

[a]The reaction time is unoptimized; yields of isolated products reported following purification by column chromatography using silica gel. X = Cl unless otherwise noted. [b]X = Br. [c]X = OTs. Yields from aryl bromide or sulfonates determined by calibrated GC analysis.

To gain a better understanding of the racemization process, several control experiments were conducted to investigate whether the racemization was occurring to the amino ester starting material or the cross-coupled product. Combining the enantiopure amino acid ester hydrochloride **2a** and **C1** without the presence of base or electrophile did not cause erosion of enantioselectivity (Table 3, entry 1). However, upon addition of base with and without **C1** present, the enantioretention dropped significantly, with *ee*'s at 18% and 15%, respectively (Table 3, entries 2–3). Next, the isolated enantiopure cross-coupled product **3a** was subjected to the same screen of reaction conditions as the amino acid starting material. The results were almost identical to those involving **2a**, demonstrating that a large excess of base present can lead to significant erosion of the stereocenter in the cross-coupled product, not just the starting material (Table 3, entries 4–6). It is plausible that the long (unoptimized) reaction time for these reactions is what leads to the lower *ee*'s for some of the cross-coupled products, and that these values could be improved with optimization of each specific electrophile and nucleophile pairing.

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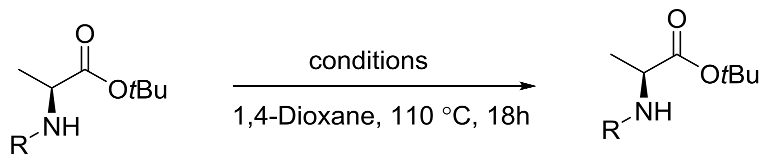
Table 3: Experiments to determine source of racemization



Entry	R	conditions	initial *ee* (%)[a]	final *ee* (%)[a]
1	H	10 mol% **C1**	>99	>99
2	H	4.1 equiv Cs_2CO_3	>99	18
3	H	10 mol% **C1** + 4.1 equiv Cs_2CO_3	>99	15
4[b]	Ar	10 mol% **C1**	>99	>99
5[b]	Ar	4.1 equiv Cs_2CO_3	>99	14
6[b]	Ar	10 mol% **C1** + 4.1 equiv Cs_2CO_3	>99	10

[a] The initial and final percentage ee was determined by chiral HPLC analysis. [b]Ar = 4-cyanophenyl.

CONCLUSION

In conclusion, we have established the first Ni-catalyzed C(sp^2)–N cross-coupling of enantiopure amino acid esters and (hetero)aryl (pseudo)halides without the need for electrochemistry. A series of enantiopure amino acid *tert*-butyl ester hydrochlorides were cross-coupled with a varied scope of (hetero)aryl halide and sulfonate electrophiles, affording a variety of *N*-heteroaryl amino esters with high yields and exceptional enantiomeric purity. Using *tert*-butyl

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amino acid esters was necessary for producing cross-coupled products with high enantioretention Additionally, control experiments indicated that base-mediated racemization can occur in the amino acid and cross-coupled product with or without pre-catalyst present.

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COMPETING INTERESTS STATEMENT

The authors declare the following competing financial interests: Dalhousie University has filed patents on the DalPhos ancillary ligands and derived nickel pre-catalysts used in this work, from which royalty payments may be derived.

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AUTHOR CONTRIBUTION STATEMENT

All authors contributed to the conceptualization of the project and writing and editing of the manuscript. T.L. and J.P.T. conducted all of the experimental work and data collection/analysis.

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DATA AVAILABILITY

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The primary research data are available by contacting the authors. Optimization of catalytic conditions, as well as NMR spectra and HPLC traces of the reaction products reported herein are provided in a supplementary materials file.

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