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Asymmetric Synthesis via Stereospecific C–N and C–O Bond Activation of Alkyl Amine and Alcohol Derivatives

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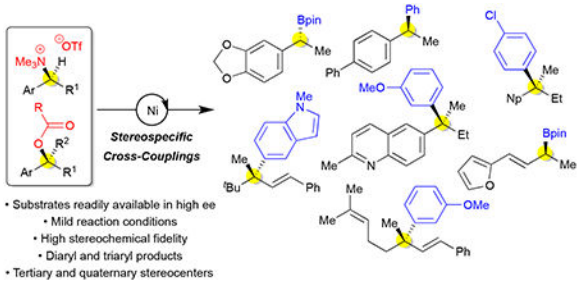
Abstract

This perspective showcases our development of benzylic and allylic amine and alcohol derivatives as electrophiles for stereospecific, nickel-catalyzed cross-coupling reactions, as well as the prior art that inspired our efforts. The success of our effort has relied on the use of benzyl ammonium triflates as electrophiles for cross-couplings via C–N bond activation and benzylic and allylic carboxylates for cross-couplings via C–O bond activation. Our work, along with others' exciting discoveries, has demonstrated the potential of stereospecific, nickel-catalyzed cross-couplings of alkyl electrophiles in asymmetric synthesis, and enables efficient generation of both tertiary and quaternary stereocenters.

Graphical Abstract



Stereospecific, nickel-catalyzed cross-couplings of alkyl ammonium salts and carboxylates enable preparation of highly enantioenriched products with tertiary and quaternary stereocenters.

1. Introduction

Transition metal-catalyzed cross-couplings have revolutionized organic chemistry, allowing creative and nonobvious disconnections in organic synthesis. Compared to cross-couplings of sp^2-hybridized carbons,[1] cross-couplings of sp^3-hybridized carbons are much less

Conflicts of interest

There are no conflicts to declare.

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developed due to challenging oxidative addition and reductive elimination steps, along with competitive side reactions.[2] However, cross-couplings of sp^3-hybridized carbons are gaining increased attention.[3]

In particular, the use of alkyl reagents in transition metal-catalyzed cross-coupling reactions provides opportunities for the incorporation of stereochemical information. As complementary approaches, enantioselective and stereospecific cross-couplings offer distinct advantages (Scheme 1a).[4] Enantioselective cross-couplings rely on catalyst-controlled asymmetric induction and allow for the first installation of stereochemistry in a molecule. Stereospecific reactions are substrate-controlled with respect to product stereochemistry, and conserve stereochemical information while building complexity. Because a stereocenter has been set previously, stereospecific cross-couplings do not require steric or electronic differentiation to afford high enantiospecificity (es).[5] This makes stereospecific cross-couplings particularly useful for late-stage synthesis and for generating stereocenters where enantioselective catalysis fails.

When forming $C(sp^3)$–$C(sp^2)$ bonds, either the electrophile or nucleophile can be enantioenriched. A number of methods have been developed for the use of secondary and tertiary alkylmetal reagents in stereospecific reactions (Scheme 1b), which have been recently reviewed.[6] This perspective will focus instead on our use of enantioenriched electrophiles in stereospecific transition metal-catalyzed cross-coupling reactions, as well as precedent that inspired our work and related concurrent examples (Scheme 1c).

Although the S_N2 reaction is of historical and pedagogical importance, the stereospecific reaction of a secondary electrophile to generate a tertiary carbon stereocenter is an atypical disconnection. Elimination (E2) competes with stereospecific substitution. This challenge is even more pronounced for the preparation of all-carbon quaternary stereocenters from tertiary electrophiles.[7] By offering an alternative mechanism, transition metal catalysis offers an opportunity to expand the utility of stereospecific substitutions to secondary and tertiary enantioenriched electrophiles, while also enabling the use of mild and functional group-tolerant nucleophilic partners. Palladium-catalyzed cross-couplings of alkyl halides are typically stereospecific and proceed with inversion at the stereogenic center.[8] However, as the steric hindrance of the electrophile increases, the energy barrier for oxidative addition increases, making palladium-catalyzed cross-couplings of secondary and tertiary halides more challenging.[9] On the other hand, first-row transition metal complexes are highly reactive toward oxidative addition and slow to undergo β-hydride elimination,[4c,9] which makes them ideal catalysts for cross-coupling reactions involving alkyl electrophiles. However, oxidative addition of nickel complexes with alkyl halides typically proceeds through radical intermediates, resulting in stereoablative reactions.[10]

Instead, non-traditional electrophiles—namely, amine and alcohol derivatives—provide a complementary alternative to alkyl halides and an entry into stereospecific reactions to afford tertiary and quaternary stereocenters. Amines and alcohols are generally air- and moisture-stable and have low toxicity. Additionally, although few methods exist for the preparation of enantiomerically enriched alkyl halides, amines and alcohols are readily available in high enantiopurity.[3a] Furthermore, amine and alcohol derivatives can engage in

polar, two-electron oxidative addition with low-valent nickel complexes, thereby enabling stereospecific transformations.[11] With this review, we aim to showcase the work that we and others have conducted to expand the synthetic utility of enantioenriched amine- and alcohol-based electrophiles in transition metal-catalyzed cross-coupling reactions to prepare tertiary and quaternary stereocenters.

2. C(sp^3)–N Bond Activation of Amine Derivatives

2.1 Secondary Allylic and Benzylic Amines

The carbon–nitrogen (C–N) bond is ubiquitous, present in many organic and biological molecules.[12] Although C–N bonds are typically considered inert due to high bond dissociation energies and poor leaving group ability,[13] significant attention has been given to the activation and use of C(sp^2)–N bonds in transition metal-catalyzed cross-coupling reactions.[14] In contrast, the use of alkyl amines as electrophiles in cross-coupling reactions has been much less examined, and much of this focus has been on allylic amine substrates. In a seminal report in 1995, Trost and coworkers reported a nickel-catalyzed cross-coupling of tertiary allylic amines with boronic acids wherein the boronic acid served as both the nucleophile and a Lewis acid activating group for the amine.[15] Tian and coworkers utilized this strategy for the activation of allylic amines in palladium-catalyzed cross-couplings with boronic acids[16] and substitutions with other nucleophiles.[17]

Subsequently, Tian and coworkers proposed that the presence of a sulfonyl group would activate allylic amines toward C(sp^3)–N bond cleavage.[18] Reaction of enantioenriched allylic sulfonamide **1** with catalytic copper(I) iodide and phenylmagnesium bromide afforded **2** as a single regioisomer in 84% yield (Scheme 2a). This transformation proceeded with complete inversion of configuration at the allylic stereocenter. In applying this strategy to benzylic amines, a second tosyl group was necessary to activate the more stubborn benzylic C–N bond. Arylation of enantioenriched benzylic sulfonimide **3** with 4-methoxyphenylmagnesium bromide also proceeded with inversion of configuration to afford diarylethane **4** (Scheme 2b), albeit in modest stereochemical fidelity. This pivotal work demonstrated that a benzylic C–N bond could indeed be converted to a C–C bond stereospecifically, but that considerable activation of the nitrogen was necessary.

2.2 Secondary and Tertiary Aziridines

At the time we began our work, aziridines were the only other electrophiles that had been demonstrated in cross-couplings via C–N bond activation. Like allylic and benzylic amines, aziridines are versatile synthetic intermediates, especially for the preparation of valuable β-substituted amines. Like epoxides, aziridines experience significant ring strain (26–27 kcal/mol),[19] which renders them susceptible to nucleophilic ring-opening. Transition metal catalysis offers an alternative to classic aziridine alkylation and arylation, which require strong nucleophiles and often afford poor regioselectivity.[20] However, the development of transition metal-catalyzed cross-coupling reactions of aziridines faces challenging oxidative addition and competitive β-hydride elimination.[21] In seminal reports, Hillhouse[22] and Wolfe[23] demonstrated that aliphatic *N*-sulfonyl aziridines undergo oxidative addition with stoichiometric nickel or palladium species to form isolable azametallocyclobutanes, wherein

the metal has inserted into the less hindered C–N bond. Alper and coworkers also demonstrated that carbonyl insertion could outcompete β-hydride elimination in rhodium-catalyzed reactions of styrenyl aziridines to form β-lactams with high regioselectivity for insertion into the benzylic C–N bond.[24]

Building on this precedent, Doyle and Huang reported the first catalytic activation of an aziridine C(sp^3)–N bond in a cross-coupling reaction.[25] Under nickel catalysis, styrene-derived *N*-tosyl aziridines underwent a Negishi cross-coupling with alkylzinc reagents. Use of dimethylfumarate **6** (Scheme 3a) as ligand was essential; this electron-deficient olefin is proposed to accelerate the challenging reductive elimination.[26] The reaction went with complete regioselectivity for cleavage of the benzylic C–N bond. With respect to stereospecificity, when enantiopure aziridine **5** was subjected to the cross-coupling conditions, amine **7** was generated in only 11% ee. The enantiomeric excess of recovered **5** was unchanged. The authors thus proposed that oxidative addition is irreversible with a subsequent stereoablative step.

Expanding on these studies, Doyle and Huang then reported a nickel-catalyzed Negishi cross-coupling of 1,1-disubstituted aziridines, affording β-substituted phenethylamines.[27] The electron-deficient olefin ligand **Fro-DO** was crucial in achieving C–C bond formation over β-hydride elimination. To test the stereospecificity of the cross-coupling reaction, the authors subjected enantioenriched aziridine **8** to the reaction conditions with *n*-butylzinc bromide (Scheme 3b). However, product **9** was obtained in only 20% ee. Although this was the first example of a transition metal-catalyzed cross-coupling of a benzylic electrophile forming an all-carbon quaternary stereocenter with any stereospecificity, the low stereochemical fidelity indicated that a stereoablative or epimerization step was competitive with the stereospecific pathway. Recovered **8** was enantiopure, which is consistent with the transformation proceeding through an irreversible oxidative addition, at or after which a stereoablative step occurs. The authors proposed that the most likely mechanism for oxidative addition is single-electron transfer (SET) from a nickel(I) species to generate a stabilized benzylic radical intermediate. They also proposed that by using a chiral ligand, this cross-coupling could be stereoconvergent. Indeed, when racemic aziridine **10** was subjected to the reaction conditions with chiral electron-deficient olefin ligand **11**, β-substituted phenethylamine **12** was formed in 73% yield and 27% ee (Scheme 3c). Notably, this result is the first example of a stereoselective cross-coupling with a tertiary, non-allylic electrophile. Based on this result, Doyle and coworkers developed an enantioselective nickel-catalyzed reductive cross-coupling of styrenyl aziridines and aryl iodides, which proceeds with good yields and enantioselectivities.[28]

In a complementary example, Minakata and coworkers demonstrated a stereospecific, palladium-catalyzed Suzuki–Miyaura cross-coupling of styrenyl aziridines and aryl boronic acids.[29] *N*-heterocyclic carbene (NHC) ligands efficiently promoted the cross-coupling while suppressing β-hydride elimination. Reaction of enantioenriched aziridine **5** with *p*-tolylboronic acid afforded β-substituted amine **15** in 74% yield and complete stereochemical fidelity (Scheme 4). The cross-coupling proceeded with inversion of configuration, consistent with oxidative addition occurring via an S_N2- or S_N2'-type mechanism to give intermediates **13** or **14**.

Three transition metal-catalyzed cross-coupling reactions of unactivated aliphatic *N*-sulfonyl aziridines have also been reported. Doyle[30] and Jamison[31] reported nickel-catalyzed Negishi cross-couplings employing aryl- and alkylzinc reagents, respectively. Michael also reported a palladium-catalyzed Suzuki–Miyaura cross-coupling of alkyl aziridines and arylboronic acids.[32] Unlike the cross-coupling reactions of benzylic aziridines, these cross-couplings of unactivated alkyl aziridines displayed complete regioselectivity for oxidative addition into the least substituted C(sp^3)–N bond to afford linear products.

2.3 Secondary Benzylic Ammonium Salts

The work by Tian, Doyle, Minakata, and others impressively demonstrates the potential of using benzylic amine derivatives and azirdines as substrates for stereospecific cross-couplings to yield highly enantioenriched diarylalkanes. This prior art also taught us that both the nitrogen activating group and the catalyst components would be crucial in achieving high stereochemical fidelity in such cross-couplings. We needed to identify a nitrogen leaving group and conditions that would not lead to radical intermediates, epimerization, or β-hydride elimination. We proposed that the C(sp^3)–N bond of benzyl amines, when activated as an ammonium salt, would undergo nickel-catalyzed cross-coupling reactions in a stereospecific fashion. Cross-coupling reactions of aryl ammonium salts were known,[33] and the trimethylammonium group was unlikely to undergo SET to form alkyl radical intermediates due to the lack of an available **π*** orbital. However, although allylic and benzylic ammonium salts had been utilized as electrophiles in reactions with organometallic nucleophiles,[34] their use in transition metal-catalyzed cross-coupling reactions was limited to a single example. Csákÿ and coworkers demonstrated the rhodium-catalyzed cross-coupling of gramine-derived ammonium iodide **16** with phenylboronic acid, affording 3-benzylindole **17** in 85% yield (Scheme 5).[35] Notably, this gramine-derived substrate benefits from weakening of the C–N bond by the indole, and no other benzylic ammonium salts were included.

Our goal was to develop a general method for the stereospecific cross-coupling of benzylic electrophiles and functional group-tolerant coupling partners.[36] Although great progress had been made with Grignard[18,37–39] and organozinc coupling partners,[8c,40–41] no enantioselective cross-couplings of benzylic electrophiles were known with arylboronic reagents at the time we began our work, and there was only a single stereospecific example of a benzylic α-cyanohydrin mesylate.[8b] Highly enantioenriched benzylic amines are ideal electrophile precursors, because they are readily prepared, are stable to long-term storage, and offer a functional group handle orthogonal to halides and ethers.[12,42] Enantioenriched ammonium triflates **18** were readily prepared in quantitative yield via methylation of the corresponding chiral tertiary amines and did not require chromatographic purification.

The combination of $Ni(cod)_2$ and a monodentate phosphine, $P(o\text{-Tol})_3$, proved optimal for catalyzing the cross-coupling, affording enantioenriched diarylmethanes in good yields, high stereochemical fidelity, and inversion of configuration at the benzylic stereocenter (Scheme 6). The weakly coordinating triflate counterion gave the best reactivity. We hypothesize that this may be due to more facile coordination of the boronate to a more electrophilic Ni(II) intermediate. Either K_3PO_4 or CsF could serve as the base; however, if base-sensitive

functional groups were present, the use of CsF proved advantageous. The mild conditions tolerated a wide range of functional groups, including ether **20**, alkene **21**, ester **22**, and nitrile **23**, highlighting the advantage of an arylboronic acid over a Grignard partner. In addition to arylboronic acids, a vinylboronic acid underwent the cross-coupling to give **24** in 96% yield and >99% es. To expand the ammonium triflate scope beyond those with napthyl substitution—a common limitation in stereospecific cross-couplings[37–40,43–44]—higher catalyst loadings and a change of ligand to ^{t}Bu-XantPhos were required. Using these modified conditions, diarylethanes **25** and **26** were obtained with excellent stereochemical fidelity albeit lower yields. Additionally, these conditions allowed selective C–N bond activation in the presence of ethers, highlighting the orthogonal functionality of ammonium salts.

In 2014, we reported improved conditions for the stereospecific cross-coupling of secondary benzylic ammonium salts.[45] By conducting the cross-coupling of ammonium triflates **27** and arylboronic acids in the presence of $Ni(cod)_2$ without exogenous ligand, diarylalkanes were obtained in higher yields than under our first-generation conditions (Scheme 7). As before, the reaction proceeds with inversion at the benzylic stereocenter with high levels of stereochemical fidelity. Under our original conditions, heteroaromatic boronic acids gave only modest yields and enantiospecificities. Under the “phosphine-less” reaction conditions, heteroaromatic groups were well tolerated, including benzofuran **28**. These conditions also tolerated bulky groups at R, including isopropyl (**29**). In addition to aryl boronic acids, vinyl boronic acids underwent the cross-coupling to afford products **30** and **31** in good yields and excellent stereochemical fidelity. Finally, although the stereochemical fidelity was slightly diminished, non-naphthyl-substituted ammonium triflates underwent the reaction with moderate to good yields. Electron-poor substrates were most efficient (**32**), but the cross-coupling also afforded *p*-methoxyphenyl-substituted **33** in 53% yield.

Expanding the utility of benzylic ammonium salts in cross-coupling reactions, we also developed a stereospecific, nickel-catalyzed Miyaura borylation.[46] As the first example of a cross-coupling utilizing a benzylic electrophile to afford highly enantioenriched organoboranes, this provides a complementary method to previous methods for the asymmetric synthesis of benzylic boronate esters.[47] Reaction of ammonium triflates **34** with B_2pin_2, $Ni(cod)_2$, and PPh_3 afforded enantioenriched benzylic pinacol boronates in good yields and stereochemical fidelity (Scheme 8a). Heteroaryl substitution was well tolerated, affording benzofuran **35** in 64% yield. Increased substitution adjacent to the benzylic stereogenic center was also tolerated, with **36** forming in 50% yield. Notably, products with such branched substituents are not accessible under asymmetric hydroboration conditions.[48] Other diboranes also successfully underwent the cross-coupling reaction to afford boronate esters (**37**). With the more electron-donating PPh_2Cy and increased reaction temperature, benzylic ammonium triflates without naphthyl substitution engaged in the cross-coupling (Scheme 8b). Enantioenriched boronate products **39**, **40**, and **41** were obtained in good yields and stereospecificities.

In analogy to stereospecific cross-couplings of benzylic ethers, we hypothesize that the stereospecific cross-couplings of benzylic ammonium salts **42** proceed via oxidative addition of an electron-rich Ni(0) complex into the C–N bond, generating either η^1- or η^3-bound

nickel(II) intermediate **43** or **44** (Scheme 9a).[49] Transmetalation with the activated boronate to form intermediate **45** (or its η^3 analogue) and subsequent reductive elimination then delivers cross-coupled product **46**. Consistent with oxidative addition into the C–N bond, benzylnickel(II) triflate **48** was produced in 51% isolated yield upon reaction of ammonium triflate with stoichiometric $Ni(cod)_2$ and PPh_2Cy. The structure of **48** was confirmed by X-ray crystallography (Scheme 9b), and **48** proved reactive as a substrate and catalytically competent in the Suzuki–Miyaura arylation. Because retention of configuration during transmetalation and reductive elimination is precedented for alkyl metal species,[50] we propose that inversion of configuration occurs during oxidative addition of the nickel catalyst into the benzylic C–N bond. Additionally, because the cross-couplings afford higher yields for substrates with naphthyl substituents instead of phenyl substituents, we propose that oxidative addition likely occurs via an S_N2'-type mechanism (**TS-1**). Partially breaking the aromaticity of the naphthyl group is far less endothermic than fully breaking the aromaticity of a phenyl substituent in this step. An analogous mechanism had been previously proposed by Jarvo for her stereospecific cross-couplings of benzylic ethers.[43] To test this hypothesis, we compared the borylation of ammonium triflates **49** and **52** (Scheme 9c). For ammonium triflate **49**, if the methoxy group sterically blocks addition at C1, S_N2'-type attack of nickel at C3 would result in complete loss of aromaticity. Indeed, no desired product **50** was observed. However, S_N2'-type attack on ammonium triflate **52** maintains some aromaticity in intermediate **53**, resulting in product **54** in 49% yield.

Excitingly, our efforts seem to have reinvigorated interest in utilizing ammonium salts as electrophiles in transition metal-catalyzed cross-coupling reactions, including the development of nickel-catalyzed carboxylation[51] and reduction[52] of benzylic ammonium triflates. Additionally, non-metal-catalyzed stereospecific reactions of benzylic ammonium triflates have been reported subsequent to our work.[53] Further, Tortosa and coworkers have demonstrated that copper catalysts can also be used, specifically in their stereospecific arylation of propargylic ammonium salts.[54] Reaction of enantioenriched propargylic ammonium triflate **55** with aryl Grignard reagent affords **56** in 98% yield (Scheme 10). The reaction proceeds with α-regioselectivity and inversion of configuration in excellent stereochemical fidelity. A subsequent report from this group has also utilized enantioenriched propargylic ammonium triflates to generate allenes in high ee's.[55] Additionally, the use of benzylic ammonium salts in cross-coupling reactions has led to the development of alternative activating groups for amines, including pyridinium salts, reported by us[56] and others.[57] Overall, we are excited to have identified a novel mode of $C(sp^3)$–N bond activation, which allows for the stereospecific formation of new C–C bonds.

3. C(sp³)–O Bond Activation of Benzylic Alcohol Derivatives

3.1 Secondary Benzylic Ethers

Alcohols are readily available substrates, making them ideal candidates to participate as electrophiles in cross-coupling reactions. Indeed, nickel-catalyzed $C(sp^2)$–O bond activation of phenols, enols, and their derivatives is well developed.[58] However, productive activation of $C(sp^3)$–O bonds is more challenging; they undergo slow oxidative addition due to their high bond dissociation energies.[59] Overcoming this barrier, Shi and coworkers reported the

first nickel-catalyzed C(sp^3)–O bond activation of benzylic ethers.[60] Reaction of ether **57** with methylmagnesium bromide under nickel catalysis afforded product **58** quantitatively (Scheme 11). Complete selectivity for the benzylic ether over an aryl ether was observed.

In 2011, Jarvo and coworkers reported the first stereospecific, nickel-catalyzed cross-coupling of secondary benzylic ethers.[39] Reaction of enantioenriched ether **59** with methylmagnesium iodide afforded **60** in 72% yield (Scheme 12a). Optimization of the ligand was key to promoting the desired reactivity by accelerating oxidative addition and minimizing β-hydride elimination. This cross-coupling proceeded with excellent stereochemical fidelity for inversion at the benzylic stereocenter. The authors demonstrated the utility of this method by synthesizing a diarylethane with potent tubulin polymerization inhibition activity. They subsequently utilized enantioenriched secondary methyl ethers as electrophiles in additional stereospecific, nickel-catalyzed cross-couplings, including a Kumada cross-coupling with alkyl Grignard reagents[61] and an intramolecular Heck reaction.[62]

By changing the alcohol activating group from a methyl ether to a 2-methoxyethyl ether, Jarvo and coworkers expanded the stereospecific, nickel-catalyzed methylation scope to secondary dibenzylic ethers without naphthyl substituents.[37] Under nickel catalysis, cross-coupling of enantioenriched dibenzylic ether **61** and methylmagnesium iodide afforded diarylethane **63** in 65% yield and 98% es (Scheme 12b). The authors proposed that the traceless directing group accelerates oxidative addition by forming five-membered chelate **62** with magnesium salts,[10h,44b,63] thereby allowing the use of less reactive electrophiles. In subsequent publications, Jarvo and coworkers used this traceless directing group for stereospecific, nickel-catalyzed cross-coupling reactions of secondary benzylic ethers with aryl Grignard reagents to afford enantioenriched triarylmethanes.[38,64] Additionally, they utilized a similar directing group for the stereospecific, nickel-catalyzed Negishi cross-coupling of secondary benzylic esters with dimethylzinc.[40]

Benzylic tetrahydropyrans, tetrahydrofurans, and lactones also undergo ring-opening under similar nickel-catalyzed methylation conditions.[65] When multiple stereogenic centers are present, the ring opening occurs with inversion at the benzylic stereogenic center without affecting or being affected by the other stereogenic centers. Reaction of *cis*-**64** afforded *syn*-**65** in 93% yield and excellent diastereoselectivity (Scheme 12c). When the *trans* diastereomer was used, *anti* product was obtained in the same yield and diastereoselectivity. Jarvo has also demonstrated this C(sp^3)–O bond activation and ring-opening strategy in a stereospecific, nickel-catalyzed cross-electrophile reductive coupling to efficiently synthesize cyclopropanes from tetrahydropyrans.[66] Overall, the work by Jarvo and coworkers demonstrated that nickel-catalyzed cross-couplings of enantioenriched benzylic ethers with Grignard and organozinc reagents occur with excellent levels of stereochemical fidelity. Their seminal reports certainly showed the power of stereospecific cross-couplings of readily available enantioenriched electrophiles, and inspired much of our effort with benzylic ammonium triflates, as well as benzylic pivalates as discussed below.

3.2 Secondary Benzylic Carboxylates and Carbamates

In the stereospecific cross-couplings discussed above, Grignard reagents were used as the nucleophilic coupling partners. Although Grignard reagents are less expensive than their boronic acid counterparts, we imagined that the convenience and functional group tolerance offered by using an organoboron reagent would often be an attractive alternative. Based on our previous success with the activation of the C(sp^2)–O bond of aryl pivalates,[67] we focused our attention on developing a stereospecific, nickel-catalyzed Suzuki–Miyaura cross-coupling of benzylic pivalates.[68] Predicting that boronate coordination to an electrophilic Ni(II) intermediate may be a key step in transmetallation,[69] we hypothesized that the nickel(II) pivalate may be able to undergo transmetalation with an aryl boronate due to the weaker coordination of the pivalate versus the alkoxides generated with benzylic ether substrates. The weaker C–O bond may also lead to a higher concentration of the oxidative addition intermediate, further facilitating a more difficult transformation. Enantioenriched secondary pivalates were prepared via Corey–Bakshi–Shibata (CBS) reduction of the corresponding ketones, followed by acylation.[70] In the presence of $Ni(cod)_2$ and electron-rich PCy_2Ph, cross-coupling of enantioenriched pivalate **66** and phenylboronic acid afforded diarylethane (*R*)-**67** in 93% yield and 54% es with retention of configuration (Scheme 13a). In contrast, conditions without exogenous ligand afforded (*S*)-**67** in improved yield and stereochemical fidelity with inversion of configuration. Stereoretention had not been previously reported in any stereospecific cross-coupling of a benzylic electrophile, and we were intrigued by this result.

In analogy to our benzylic ammonium triflates (see Scheme 9 above), we hypothesized that the stereochemical outcome is dictated by the oxidative addition step. To confirm that the overall stereoretention was indeed due to the oxidative addition step, we wanted to isolate the oxidative addition from the subsequent transmetallation and reductive elimination. Inspired by a similar experiment by Fu,[50b] we subjected deuterated pivalate **68** to stoichiometric $Ni(cod)_2$ and PCy_3, and allowed β-hydride elimination to take place. Alkene **69** was the major product with alkene **70** as a minor byproduct (Scheme 13b). Formation of alkene **69** is consistent with β-hydride elimination (via synperiplanar C–Ni and C–D bonds) of the intermediate resulting from stereoretentive oxidative addition. This suggested that oxidative addition in the presence of phosphine ligand proceeds via a distinct mechanism from the precedented S_N2'-type oxidative addition of nickel complexes into ammonium salts and ether electrophiles. Without phosphine ligand, oxidative addition likely follows the S_N2'-type mechanism, consistent with the observed inversion of configuration at the benzylic stereocenter.

Under the “phosphine-less” conditions, reaction of enantioenriched **71** with arylboroxine had good functional group tolerance (Scheme 13c). The use of boroxine resulted in better yields and higher levels of chirality transfer, indicating that water had a detrimental effect on the reaction. Notably, aryl chloride is tolerated (**73**), providing a functional group handle for further cross-coupling reactions. Steric hindrance was also well tolerated, as evidenced by the *i*-Pr group in **72**. Electron-poor (**74**) and -rich (**75**) heteroaryl-substituted pivalates underwent the cross-coupling, although the yield was diminished for **75**. Additionally,

biphenyl-substituted pivalate underwent the reaction to afford **76** in good stereochemical fidelity, albeit diminished yield.

Concurrent with our report of this work, Jarvo and coworkers reported a stereospecific, nickel-catalyzed Suzuki–Miyaura cross-coupling of dibenzylic carbamates **77a** (Scheme 14).[43] Excitingly, they also observed that the ligand determined whether the cross-coupling proceeds with retention or inversion of configuration. Furthermore, they were able to optimize conditions to achieve excellent stereochemical fidelity in both pathways. The ability to access both product enantiomers in high ee from a single enantiomer of starting material overcomes the common limitation of stereospecific reactions. This work, along with stereochemical flips observed in allylic substrates, set the stage for advancing the field's understanding of what reaction parameters can be used for stereodivergency in stereospecific cross-coupling reactions.

Towards this goal of mechanistic understanding, subsequent computations by Jarvo, Houk, and Hong studied the transformation of pivalate **77b** to form **78**. Their calculations suggest that with phosphine ligand PCy_3, there is a preference for oxidative addition via cyclic transition state **TS-2**, resulting in retention of stereochemistry.[71] When using *N*-heterocyclic carbene (NHC) ligand SIMes, there is a preference for oxidative addition by S_N2' back-side attack through an open transition state (**TS-3**), leading to inversion of configuration. They propose that the major factor contributing to this change in mechanism is the difference in energy caused by bending the C1–Ni–ligand angle to accommodate the formation of the Ni–O bond in **TS-2**. For PCy_3, the nickel–ligand interaction involves mainly σ-donation, so there is less of an energy penalty for C1–Ni–ligand angle distortion than when using SIMes, which has a more rigid nickel–ligand bond due to additional d–p back-donation.

Functional group tolerance was good for both reaction conditions, including reaction of heteroaryl boronic esters **79** and **80**. Although naphthyl substitution was not required, this report is limited to dibenzylic carbamates. This requirement results from coordination of the nickel to the aryl group prior to oxidative addition, which is consistent with both computed mechanistic pathways and is similar to the previously proposed S_N2'-type mechanism. Jarvo and coworkers later used this method to synthesize enantioenriched diarylalkanes and trialkylmethanes.[72]

The use of enantioenriched alcohol derivatives has continued to gain increasing attention in transition metal catalysis. Benzylic pivalates have been used in subsequent reports of nickel-catalyzed reactions, including a Suzuki–Miyaura cross-coupling to form triarylmethanes[73] a stereospecific intramolecular cross-electrophile coupling,[74] and a stereospecific Miyaura borylation.[75] C(sp^3)–O activating groups now include 2-pyridyl etherates[76] and vinyl dioxanones.[77] In a related reaction, Tunge and Mendis reported a stereospecific, palladium-catalyzed decarboxylative alkynylation of diarylcarbonates.[78] Additionally, Tang and coworkers demonstrated a transition metal-free stereospecific addition of vinyl boronic acids to enantioenriched benzylic mesylates.[79] Palladium-catalyzed dynamic kinetic resolution of dibenzylic carboxylates has also been recently reported.[80] By activating widely available enantioenriched alcohols as carboxylates and carbamates, cross-couplings with

organoboranes have been enabled, greatly increasing the functional group tolerance and convenience of these stereospecific reactions.

3.3 Tertiary Benzylic Carboxylates

Based on the proposed S_N2' oxidative addition and the high degree of steric hindrance tolerated in the stereospecific cross-coupling reactions of secondary benzylic carboxylates, we envisioned that a stereospecific, nickel-catalyzed cross-coupling of tertiary benzylic electrophiles may be possible. If the nickel catalyst was adding in an S_N2' fashion, increased steric hindrance at the benzylic position should be tolerated. This reaction would allow access to benzylic, all-carbon quaternary stereocenters in high enantiopurity. By using a stereospecific cross-coupling to accomplish this challenging transformation, there would be no need to differentiate similar alkyl groups with a chiral catalyst. Thus, when coupled with enantioselective ketone alkylation, we believed that this method would offer a powerful asymmetric synthesis of benzylic quaternary stereocenters from readily available, achiral ketone precursors. Notably, the only examples of metal-catalyzed cross-couplings of alkyl electrophiles to give quaternary centers in high enantioenrichment utilized allylic substrates;[81] no tertiary benzylic electrophiles had yet been demonstrated.

Capitalizing on this idea, we developed a stereospecific, nickel-catalyzed arylation of tertiary benzylic acetates with boronate esters.[82] Enantioenriched tertiary alcohols were readily prepared via Walsh's enantioselective addition of organozinc reagents to acetophenones.[83] Although pivalates could not be easily prepared likely due to steric congestion of the tertiary alcohol, acetates **82** were readily accessible and proved to be excellent substrates (Scheme 15).

The success of this reaction relied upon significant optimization of the catalyst system. The reaction conditions optimized for the cross-coupling of secondary benzylic pivalates afforded high yield of cross-coupled product but with low stereochemical fidelity. Addition of a monodentate phosphine ligand improved stereochemical fidelity, but also led to elimination byproducts. Hypothesizing that these were due to competitive β-hydride elimination, we investigated bidentate ligands, including those with hemilabile arms. By switching to a Buchwald ligand, CyJohnPhos, elimination products were reduced and the enantiospecificity was much improved, affording products with retention of stereochemistry.

A wide range of functional groups were well tolerated, including chloride **83**. An example of heteroaryl substitution was also demonstrated, affording **84** in 79% yield. As with the cross-coupling of secondary alcohol and amine derivatives, either an aryl substituent with an extended π-system or diaryl substitution (**85**) was required on the electrophile. Despite this limitation, this reaction was the first example of a transition metal-catalyzed cross-coupling of a benzylic tertiary electrophile to give products in high enantiomeric excess, and overcame traditional limitations in utilizing tertiary electrophiles in substitution reactions. It highlights the advantage of combining a stereospecific cross-coupling with known catalytic asymmetric reactions, and offers a highly efficient strategy for asymmetric synthesis of diaryl and triaryl alkanes with quaternary stereocenters.

4. C(sp³)–O Bond Activation of Allylic Alcohol Derivatives

4.1 Secondary Allylic Alcohol Derivatives

Stereospecific arylation of readily accessible 1,3-disubstituted secondary allylic electrophiles enables facile construction of enantioenriched products equipped with vinyl-substituted benzylic carbon stereocenters. Kobayashi was the first to report a stereospecific, nickel-catalyzed Suzuki–Miyaura cross-coupling of an allylic alcohol derivative.[84] Cyclic allylic acetate **86** underwent cross-coupling with phenylzinc borate reagent to afford product **87** with inversion of configuration (Scheme 16a). Sawamura and coworkers then developed stereospecific, palladium- and copper-catalyzed Suzuki–Miyaura cross-coupling reactions of allylic esters and phosphates (Scheme 16b).[85] These γ-selective reactions afforded products with retention of stereochemistry (**89**). Zhang,[86] Tian,[87] and Bäckvall[88] developed stereospecific cross-coupling reactions of allylic electrophiles that proceed with α-selectivity (**90**). However, no stereospecific, nickel-catalyzed cross-couplings of acyclic allylic electrophiles and arylboron reagents to deliver highly enantioenriched products had been reported.

Based on our studies of stereospecific, nickel-catalyzed cross-couplings of benzylic carboxylates and arylboronates, we envisioned that nickel-based catalysts may also serve as efficient, nonprecious metal catalysts for highly stereospecific and regioselective cross-couplings of 1,3-disubstituted allylic pivalates and arylboronates. In 2014, we reported the first stereospecific, nickel-catalyzed cross-coupling of an acyclic allylic electrophile to deliver a highly enantioenriched product.[89] Pivalates were readily prepared in high enantiomeric excess via CBS reduction and pivalation.[70] Reaction of pivalates **91** and arylboroxines with $Ni(cod)_2$ and $BnPPh_2$ afforded products with excellent yields, regioselectivities, and enantiospecificities (Scheme 17a). This method is mild and tolerates a wide scope of functional groups including heteroaryl substitution. Halides were well tolerated on the allylic pivalate (**93**) and arylboroxine (**94**), highlighting the orthogonality of the reaction to this group. Additionally, the cross-coupling had a high tolerance for steric hindrance at the benzylic position (**95**). We proposed that the reaction proceeds through a π-allylnickel intermediate with selectivity for forming the conjugated alkene in the product. Consistent with the intermediacy of a π-allylnickel complex, the reaction of alkene regioisomer **96** resulted in product **97** (Scheme 17b).

We also recognized that allylic boronates are useful intermediates in organic synthesis.[90] In 2005, Ito, Kawakami, and Sawamura reported a stereospecific, copper-catalyzed borylation of allylic carbonates to deliver highly enantioenriched γ-alkyl allylic boronates.[91] However, no stereospecific, transition metal-catalyzed borylation for the preparation of γ-aryl α-chiral allylic boronates had been reported. We envisioned that a stereospecific, nickel-catalyzed Miyaura borylation of γ-aryl allylic pivalates would deliver highly enantioenriched γ-aryl α-stereogenic boronates.[92] The optimal conditions for our stereospecific allylic arylation gave high yields and stereochemical fidelity for the Miyaura borylation, affording product (*S*)-**101** with inversion of stereochemistry (Scheme 18). However, when toluene was used as the solvent, product (*R*)-**101** formed with retention of configuration. Further optimization of ligand and other conditions led to high stereochemical fidelity and regioselectivity under

these stereoretentive conditions. Notably, this was the first example of solvent as the predominant factor in a stereochemical flip.[93]

Heteroaryl groups could be incorporated (**102**). Tether length of pendant olefins affected the stereochemical fidelity of the cross-coupling (**103**, **104**), potentially indicating a change in mechanism or epimerization pathway. In addition to aryl allylic boronates, γ-alkyl allylic boronate **105** was formed in high yield, regioselectivity, and enantiospecificity. Diborane coupling partners other than B_2pin_2 could be used; for example, boronate **106** was produced in 90% yield and 91% es.

Based on a series of mechanistic studies, we proposed that when the cross-coupling is run in nonpolar solvents, the pivalate leaving group directs the nickel. Oxidative addition occurs via closed transition state **TS-4**. Nickel adds to the *re* face of the alkene, thereby allowing R^1 and R^2 to be pseudoequatorial, which leads to retention of stereochemistry. More strongly coordinating carboxylates lead to higher stereochemical fidelity, consistent with carboxylate coordination to the nickel catalyst.

When conducted in more polar solvents, oxidative addition via an open transition state to give a charge-separated intermediate is competitive. Acetonitrile also appears to act as a ligand, coordinating nickel and prohibiting coordination of the pivalate. Favored transition state **TS-5** minimizes $A^{1,3}$-strain, affording inversion of configuration. Under the conditions optimized for stereoretention, *p*-substituted benzonitriles were added. There was excellent correlation between the electron-donating ability of the added nitrile and the stereospecificity, with more electron-poor benzonitriles leading to higher stereochemical fidelity under the retention conditions. This mechanistic insight offers exciting new options for stereodivergent synthesis and adds solvent as an additional parameter to accomplish stereochemical flips.

4.2 Tertiary Allylic Alcohol Derivatives

With our success in setting benzylic quaternary centers and allylic substitution, we targeted quaternary center formation via allylic arylation. In particular, we were excited to form products with the additional vinyl handle for further elaboration. The use of allylic halides and phosphate esters in enantioselective cross-coupling reactions to afford molecules containing all-carbon quaternary stereocenters with terminal alkenes is well developed (Scheme 19a).[81f,94] However, the preparation of enantioenriched products with all-carbon quaternary stereocenters and *internal* alkenes using enantioenriched allylic electrophiles was limited to reactions using stoichiometric copper (Scheme 19b).[81e,95] In an umpolung approach, Morken and coworkers developed a stereospecific, palladium-catalyzed cross-coupling of allylic boronate esters with aryl halides.[96]

As we considered an efficient and convenient approach to the synthesis of quaternary stereocenters substituted with internal alkenes, we were inspired to develop a stereospecific, nickel-catalyzed Suzuki–Miyaura cross-coupling of allylic pivalates and arylboronates (Scheme 20).[97] The secondary pivalates **111** were readily prepared in highly enantioenriched form using a CBS reduction.[98] Although electron-rich phosphine dppf gave high stereochemical fidelity, it afforded low yield, which we hypothesized was due to

decomposition of starting material from redox activity with the ferrocene. Changing the ligand to BISBI, which has a wide bite angle and a semi-rigid backbone,[99] afforded products in high yield and stereochemical fidelity. The use of aryl boronic acid in place of arylboroxine resulted in lower yields with significant hydrolysis of pivalate. Heteroaryl-substituted boroxines were well tolerated, affording products **112** and **113** in good yields. Steric hindrance at the stereogenic center was also well tolerated, affording **114** in 84% yield. As expected in MeCN solvent, the reaction proceeds with inversion of configuration. Additionally, the geometry of the starting alkene affects the stereochemistry. The allylic pivalate synthesized from nerol gives the opposite absolute configuration of product **115** as the allylic pivalate synthesized from geraniol (**116**).

We propose that oxidative addition proceeds through open transition state **TS-6**, where the nickel adds to the opposite face of the allylic system as the pivalate leaving group. This conformation minimizes any developing $A^{1,3}$ interactions. Acetonitrile may favor this open transition state by coordinating with the nickel catalyst and blocking coordination with the pivalate. Transmetalation and reductive elimination then deliver the product where the alkene is conjugated with the adjacent aryl group. This reaction offers an entry into the preparation of all-carbon quaternary stereocenters adjacent to internal alkenes in high regioselectivity and enantiospecificity.

5. Conclusions and Outlook

Inspired by the prior art from a range of groups, we have developed a series of stereospecific cross-couplings of benzylic and allylic amine and alcohol derivatives. The success of this effort has relied on the design of benzylic ammonium triflates as substrates for cross-couplings via C–N bond activation, and the development of benzylic and allylic carboxylates for cross-couplings via C–O bond activation. Our efforts, along with others' exciting discoveries, have demonstrated that stereospecific, transition metal-catalyzed cross-coupling reactions using enantioenriched electrophiles are useful in asymmetric synthesis, particularly when combined with highly efficient asymmetric reactions to generate the enantioenriched intermediates. We have also begun to uncover detailed understanding of how to manipulate catalyst systems and other reaction conditions to enable stereodivergency in these stereospecific reactions. Despite the clear potential of these reactions in asymmetric synthesis, challenges remain. The scope of benzylic ammonium salts and carboxylates remains limited by the need for polycyclic aryl substituents (e.g., naphthyl) or dibenzylic substrates, and few heteroaryl groups have been demonstrated. Continued efforts to understand mechanism are also needed to allow prediction of stereodivergent reaction conditions broadly across the full range of stereospecific cross-couplings. We are excited to continue to contribute to the development of this field, and ultimately hope that these stereospecific cross-couplings will advance into indispensible reactions for asymmetric synthesis.

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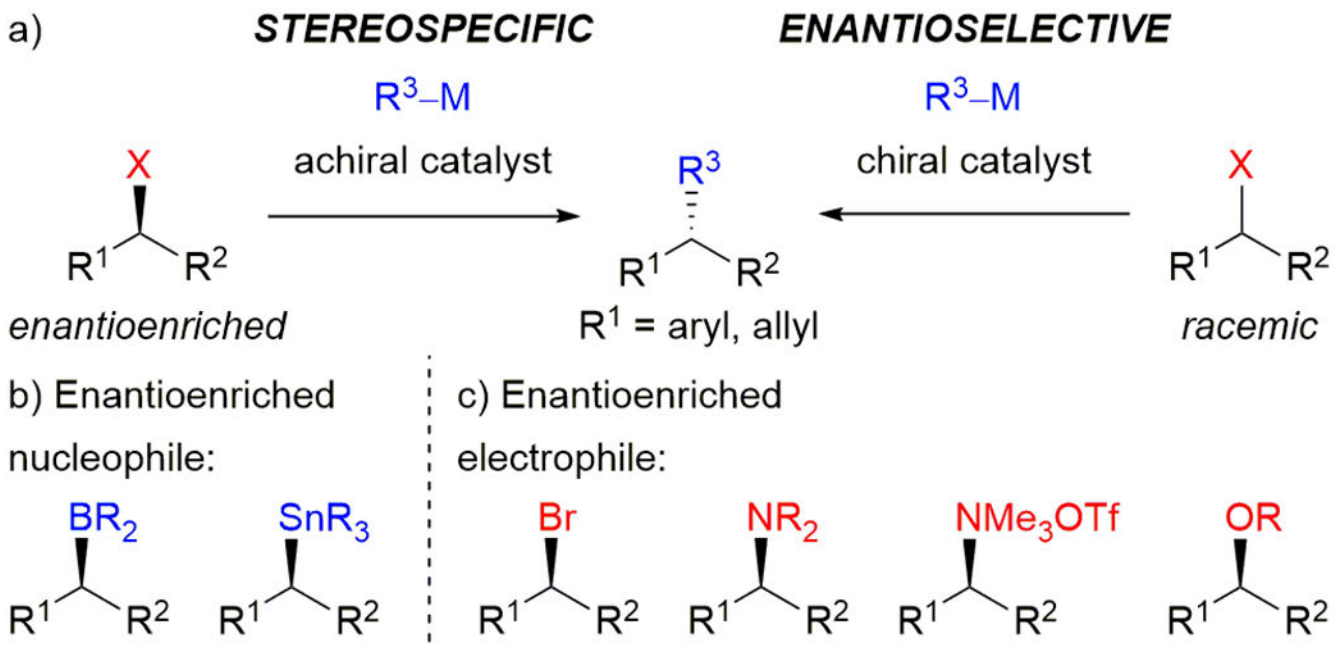
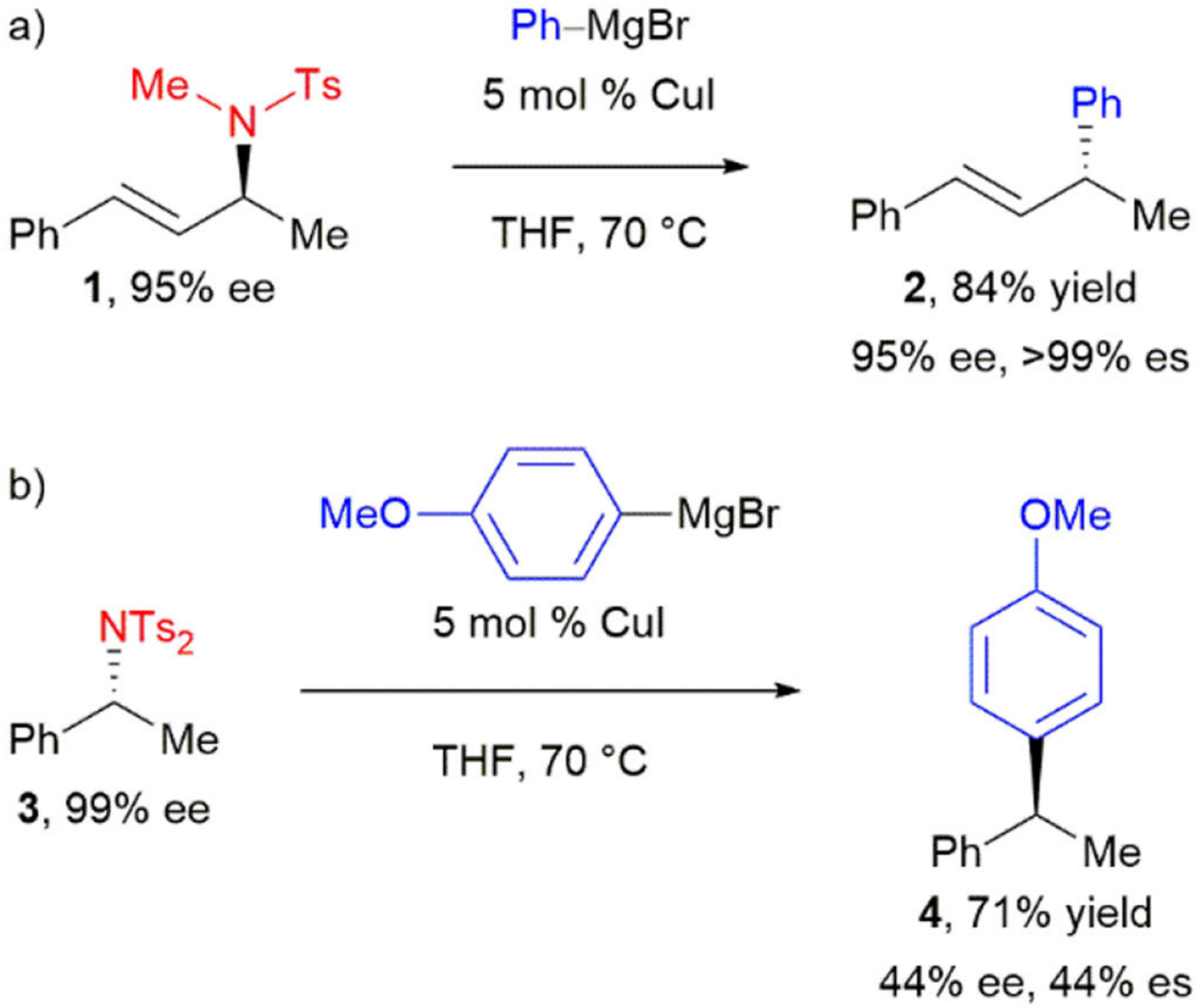
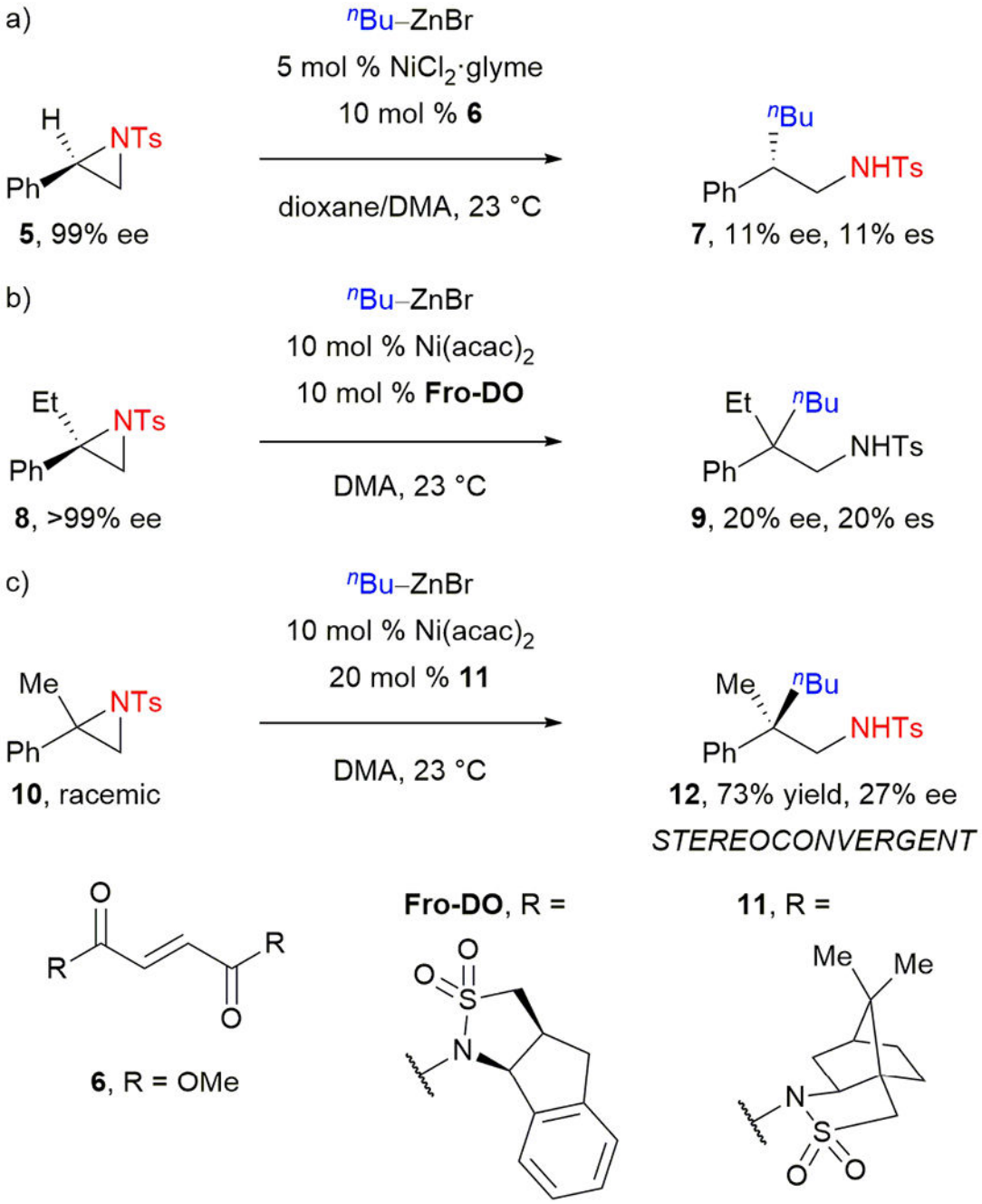


Scheme 1.

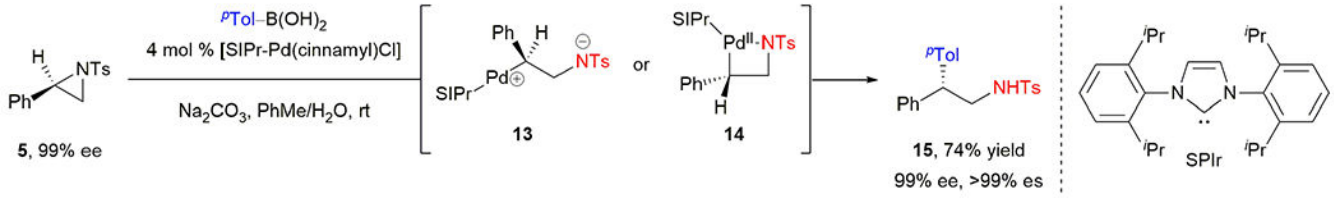
Alkyl reagents in transition metal-catalyzed cross-coupling reactions: (a) comparison of stereospecific and enantioselective reactions illustrated with alkyl electrophiles; (b) use of enantioenriched nucleophiles for stereospecific cross-couplings; and (c) use of enantioenriched electrophiles for stereospecific cross-couplings



Scheme 2.
Tian's stereospecific, copper-catalyzed arylation of enantioenriched amines with aryl Grignard reagents

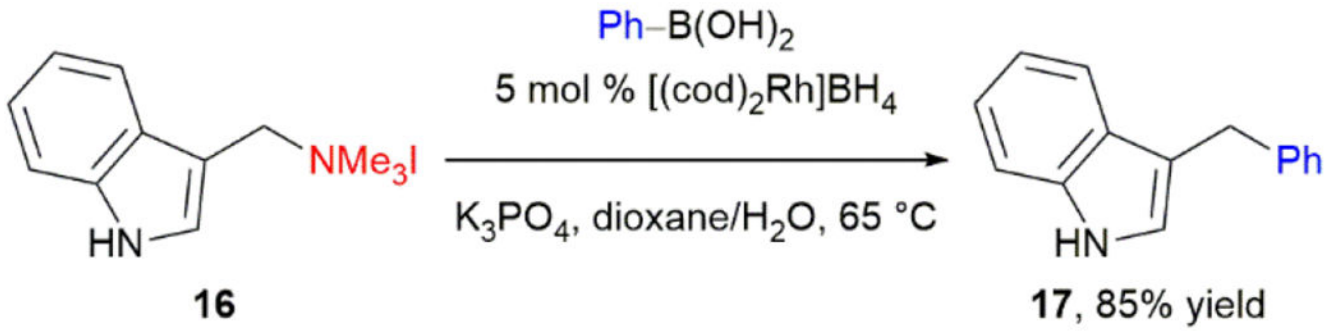


Scheme 3.
Doyle's nickel-catalyzed Negishi cross-coupling reactions of aziridines.

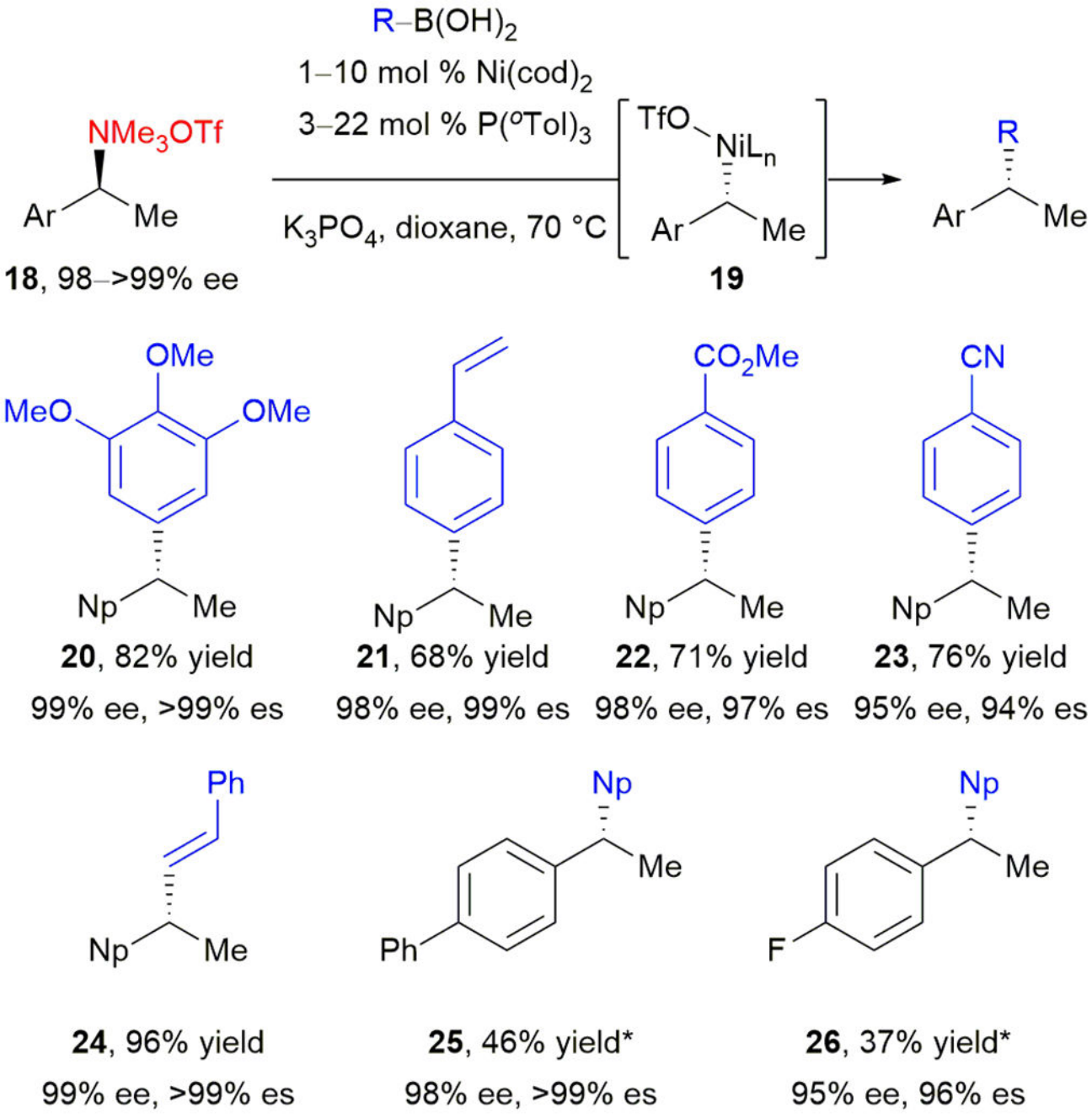


Scheme 4.

Minakata's stereospecific, palladium-catalyzed Suzuki–Miyaura cross-coupling of enantioenriched aziridines.

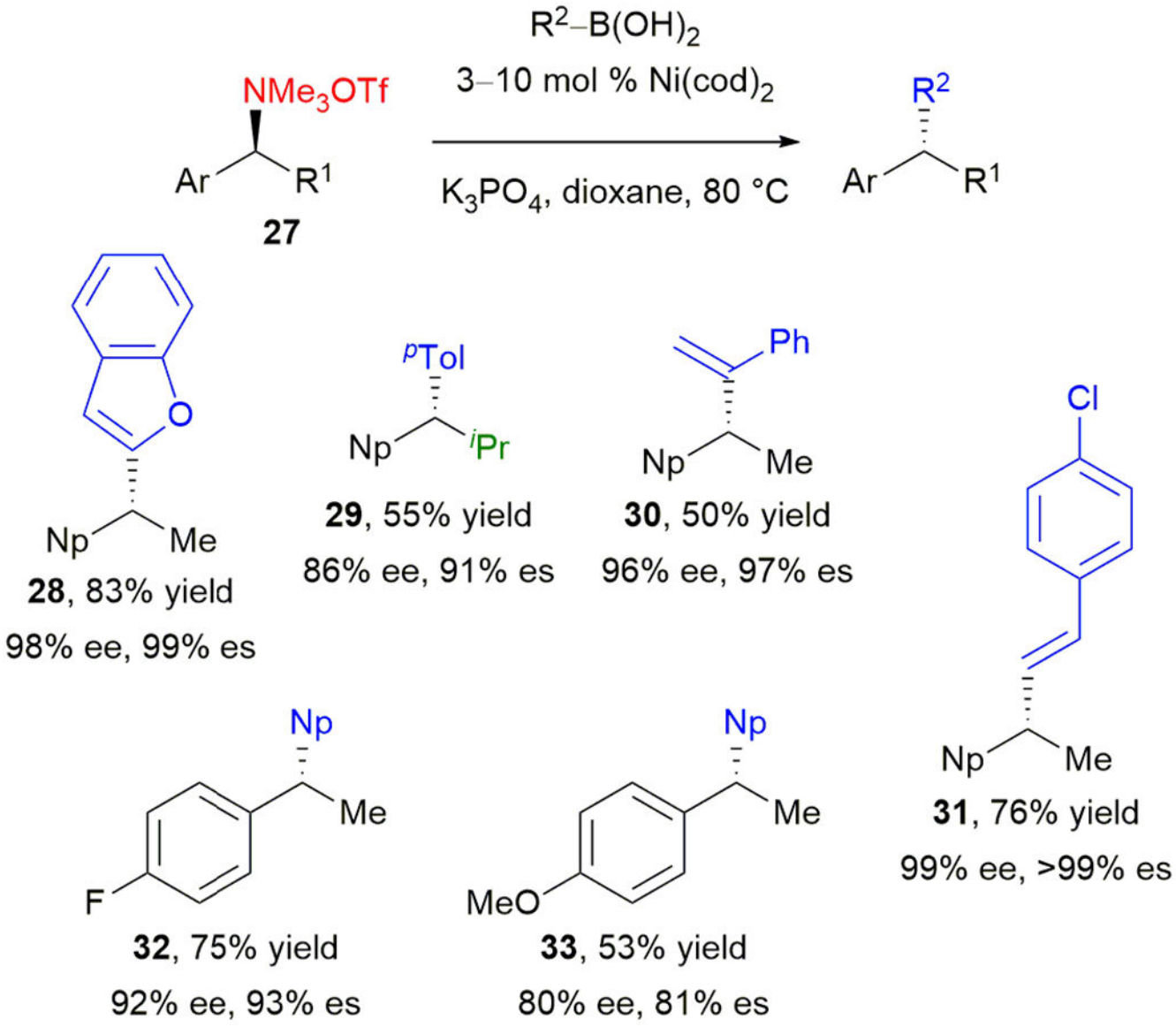


Scheme 5.
Csákÿ's rhodium-catalyzed Suzuki–Miyaura cross-coupling of a benzylic ammonium iodide.



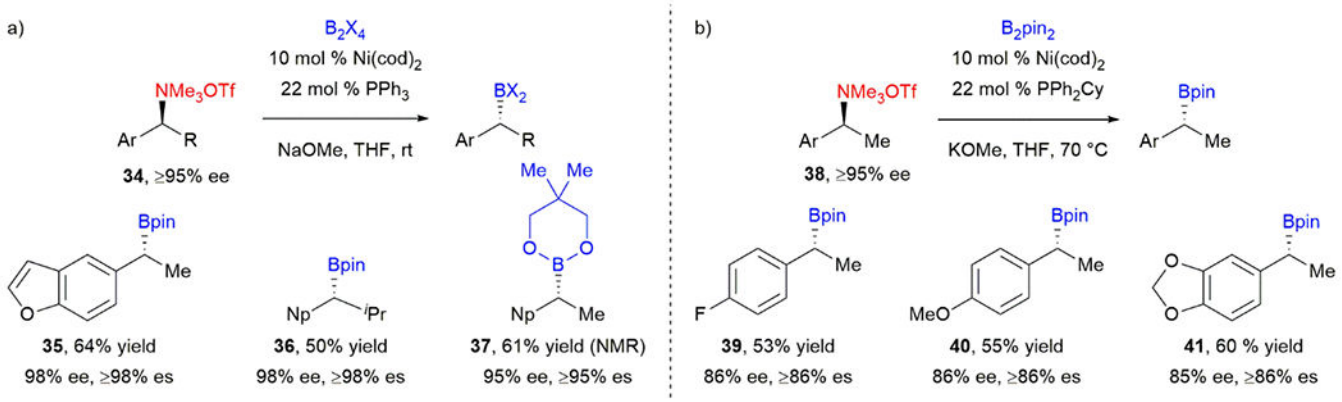
Scheme 6.

Our stereospecific, nickel-catalyzed arylation of benzylic ammonium triflates with boronic acids to form enantioenriched diarylethanes. *^{t}Bu-XantPhos used as ligand in place of P(^{o}Tol)$_3$.



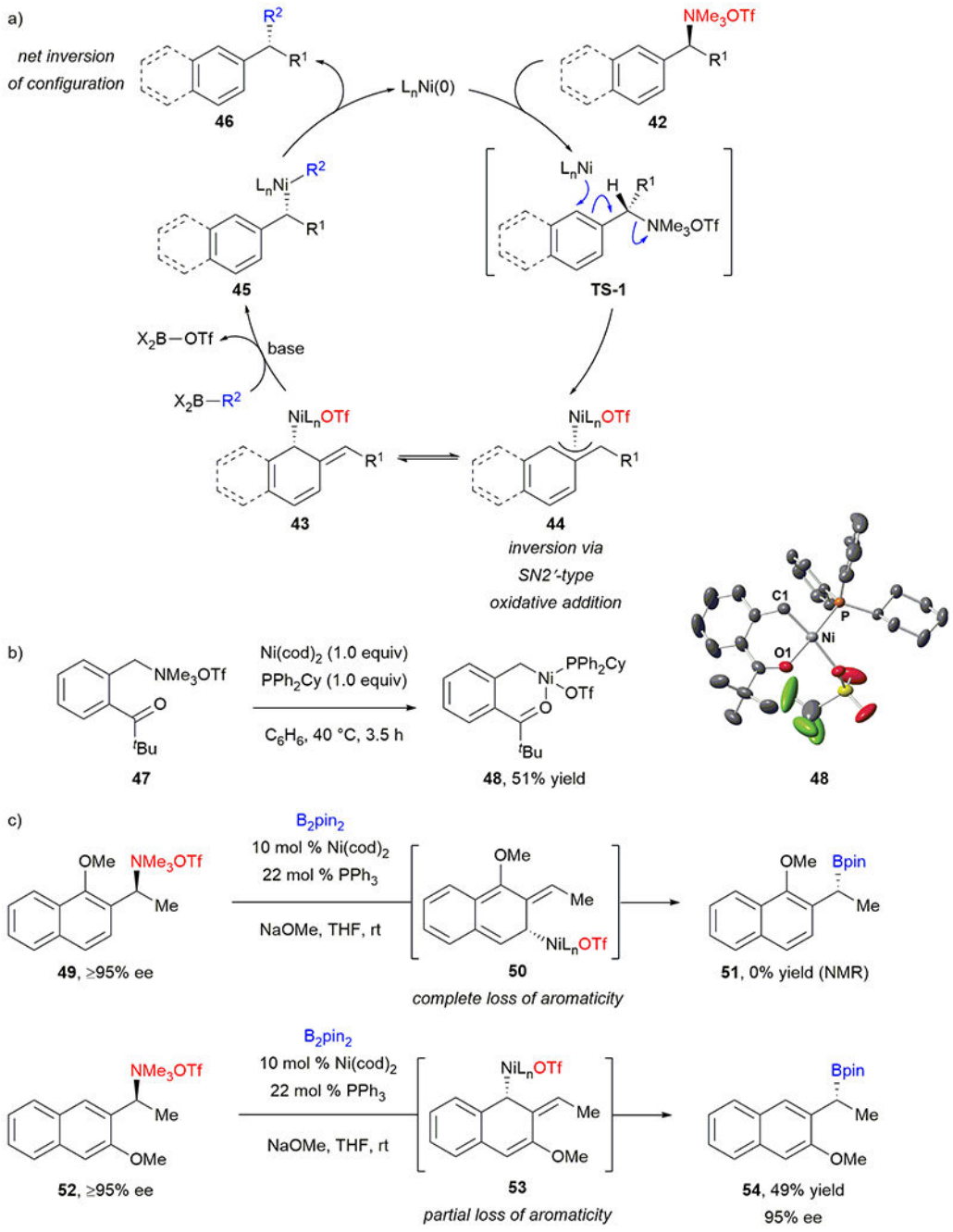
Scheme 7.

Our phosphine-less stereospecific, nickel-catalyzed cross-coupling of benzylic ammonium triflates.



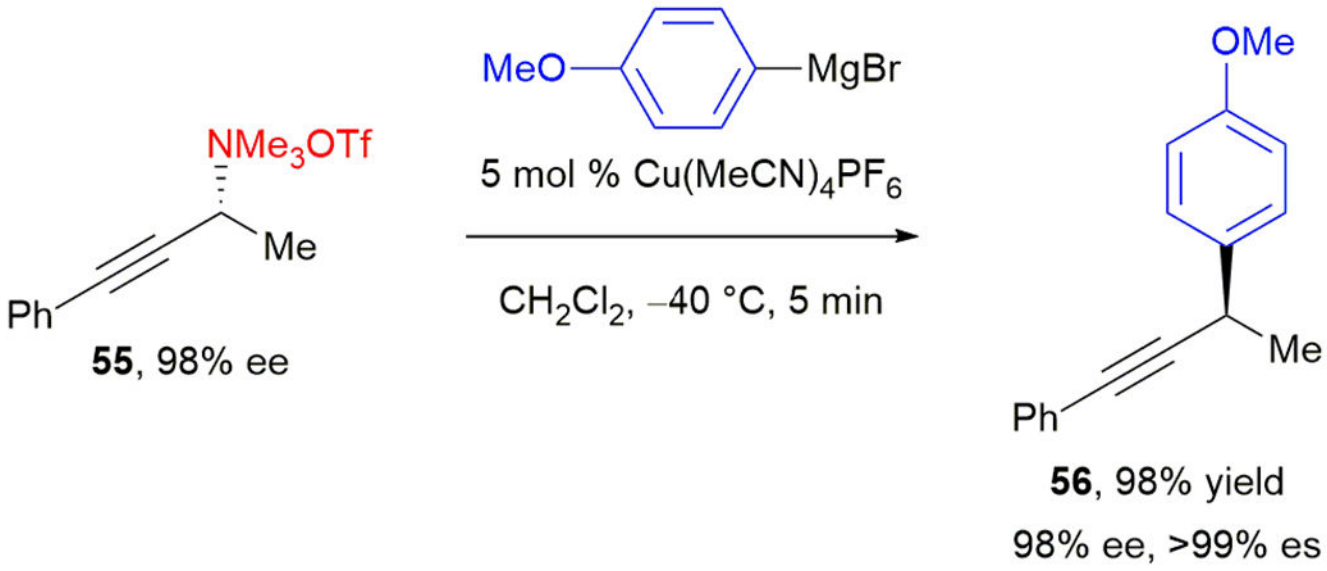
Scheme 8.

Our stereospecific, nickel-catalyzed Miyaura borylation of benzylic ammonium triflates to afford enantioenriched benzylic boronates using (a) naphthyl-substituted ammonium triflates, and (b) non-naphthyl-substituted ammonium triflates.



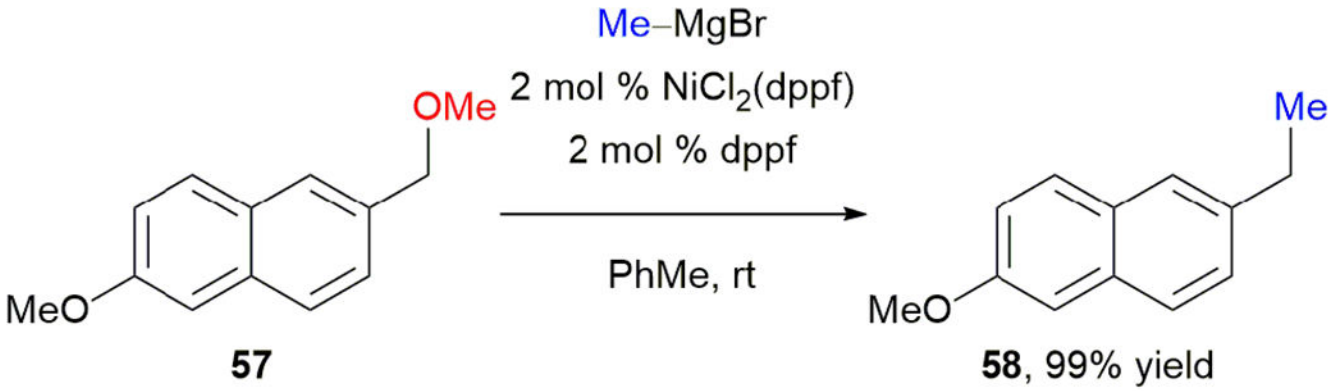
Scheme 9.

Stereospecific, nickel-catalyzed cross-coupling mechanism: (a) proposed catalytic cycle; (b) synthesis and crystal structure of oxidative addition complex **48**; (c) experiments demonstrating oxidative addition via an S_N2' mechanism.

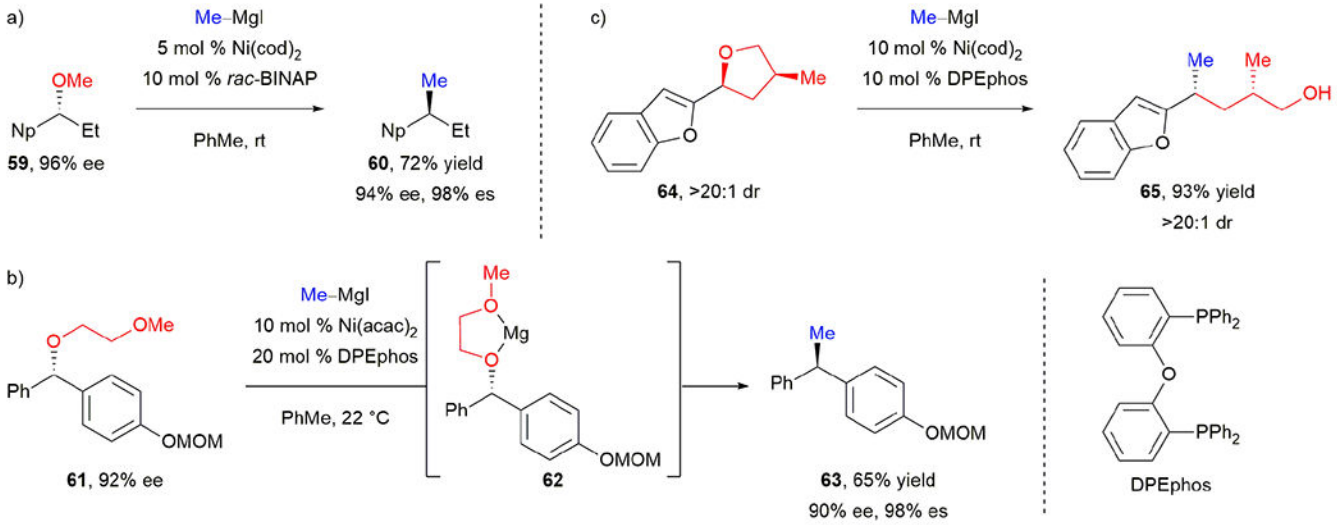


Scheme 10.

Tortosa's stereospecific, copper-catalyzed Negishi cross-coupling of enantioenriched propargylic ammonium triflates.

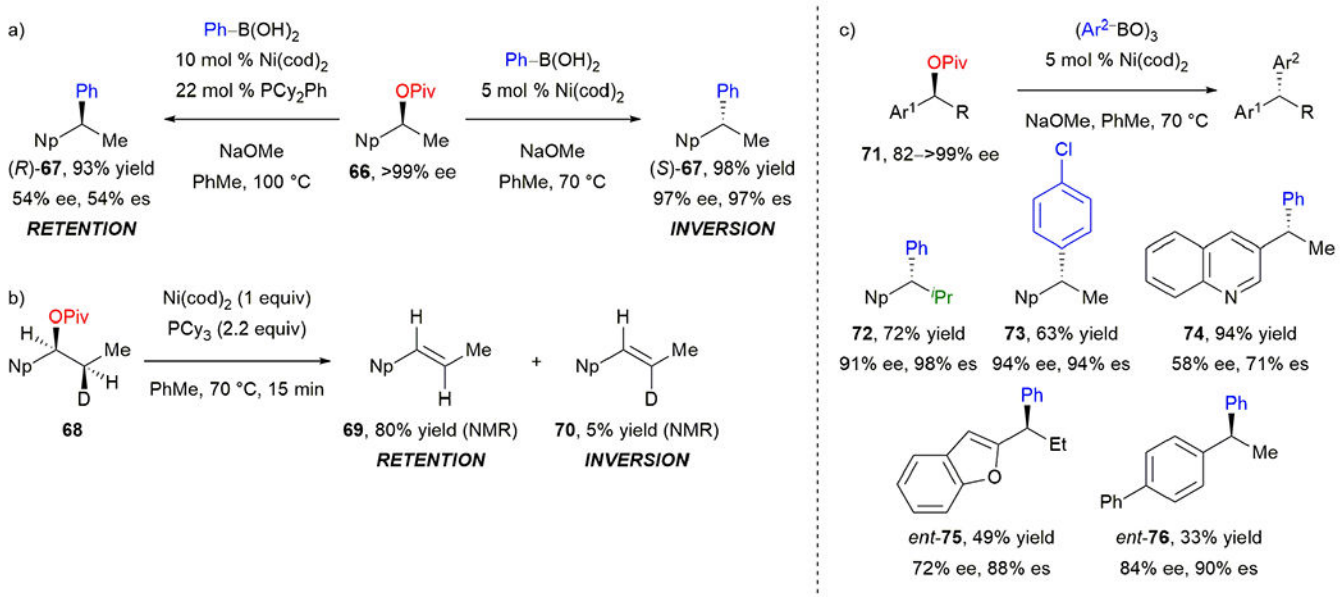


Scheme 11.
Shi's nickel-catalyzed Negishi cross-coupling of benzylic methyl ethers.



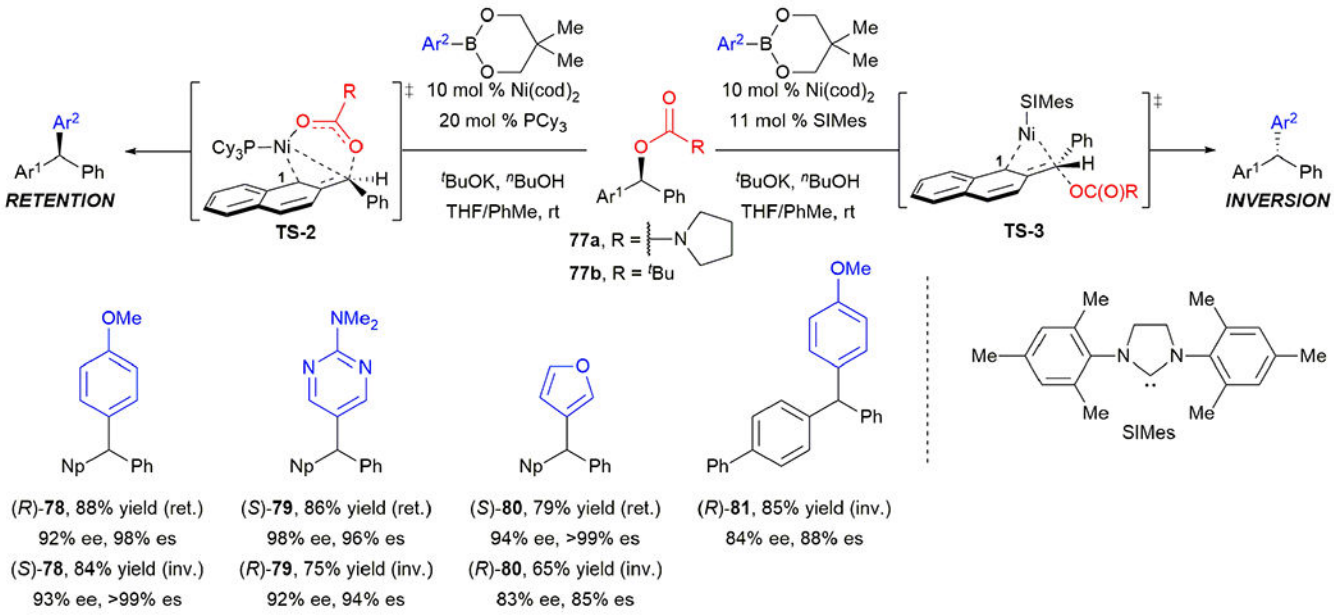
Scheme 12.

Jarvo's stereospecific, nickel-catalyzed Negishi cross-couplings of (a) secondary benzylic methyl ethers, (b) secondary benzylic ethers using a traceless directing group, and (c) tetrahydrofurans.



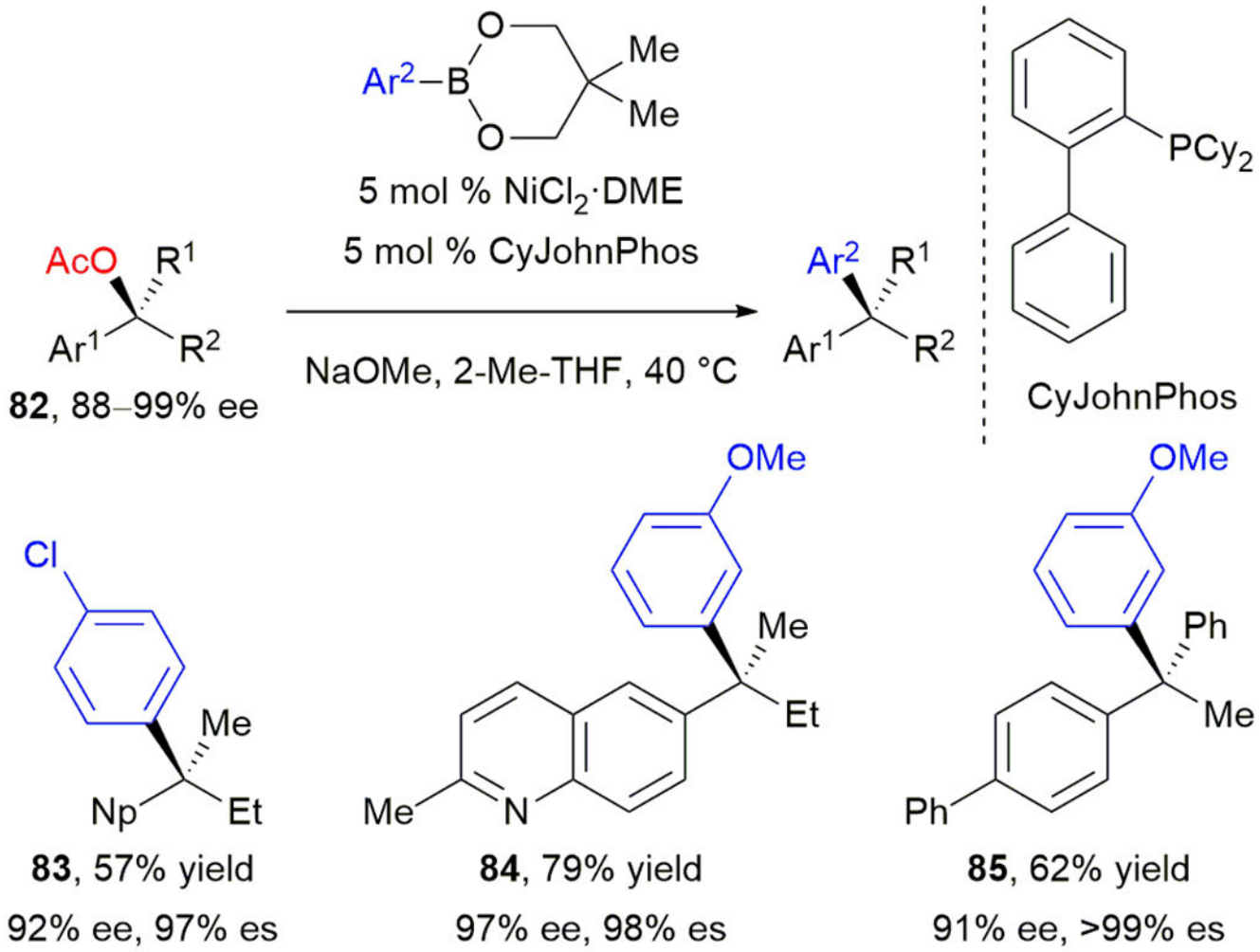
Scheme 13.

Our stereospecific, nickel-catalyzed Suzuki–Miyaura cross-coupling of secondary benzylic pivalates: (a) retention or inversion of stereochemistry depends on ligand; (b) mechanistic experiment; and (c) abbreviated scope.



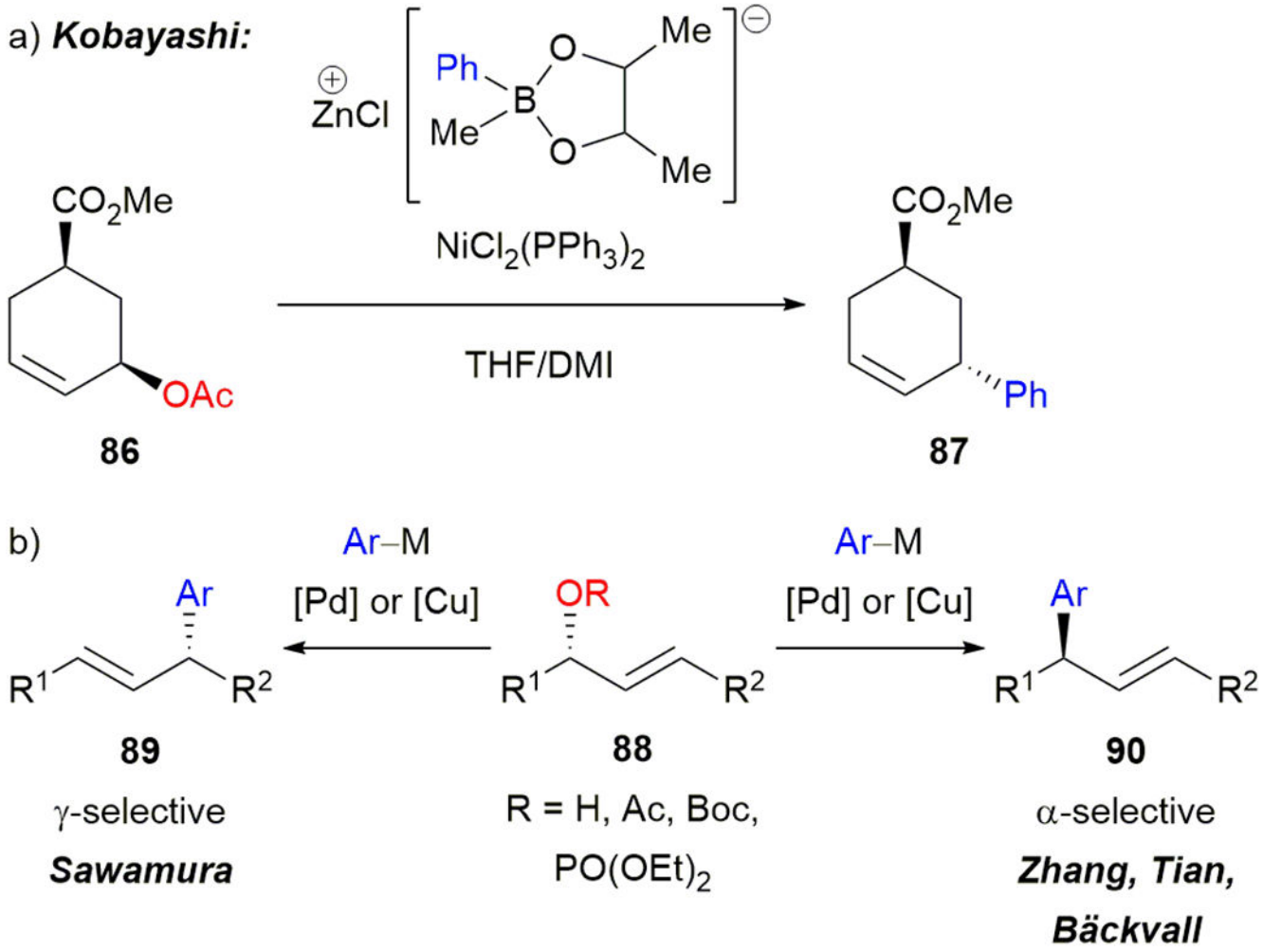
Scheme 14.

Jarvo's stereospecific, nickel-catalyzed Suzuki–Miyaura cross-coupling of secondary benzylic carbamates.



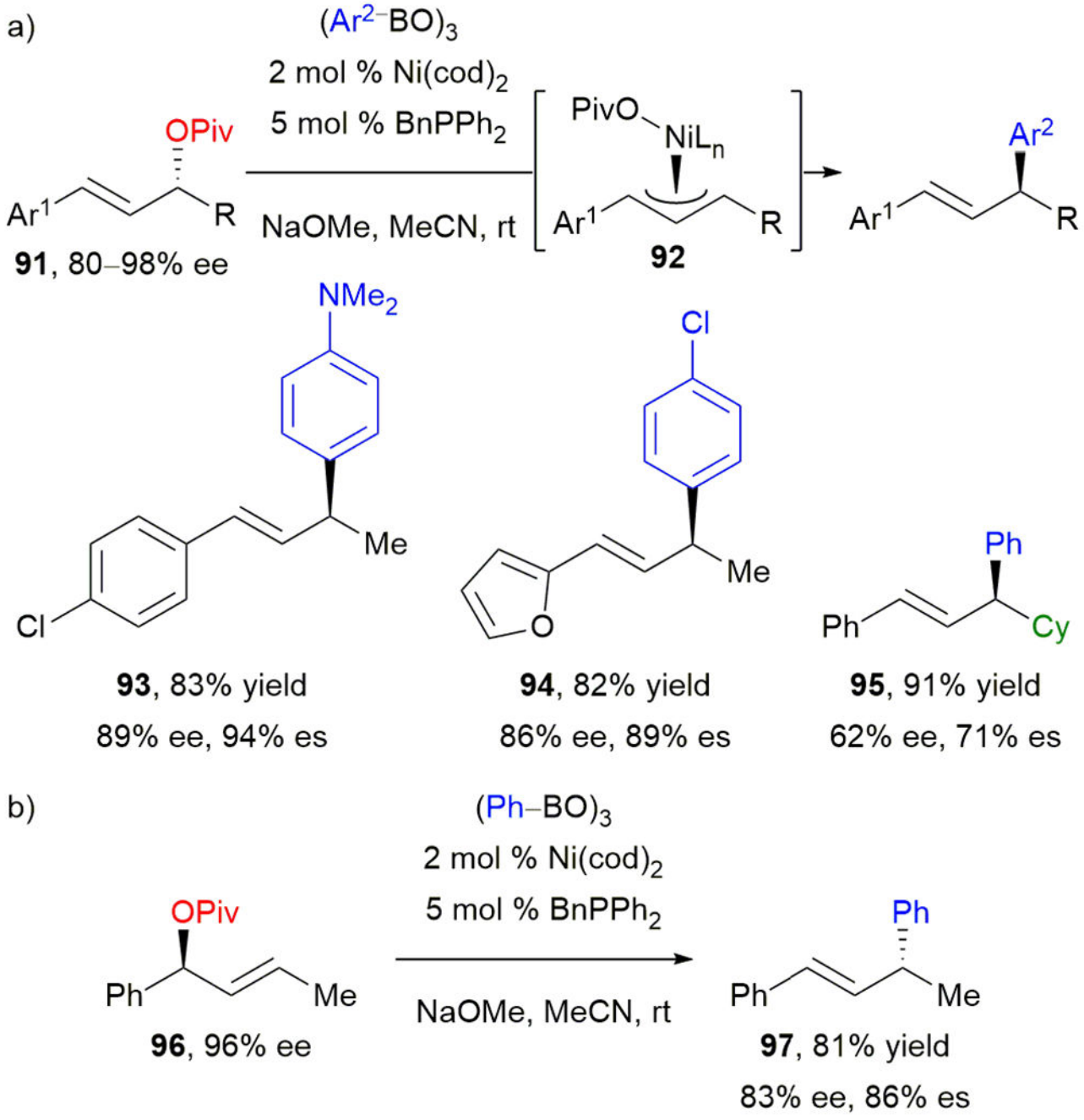
Scheme 15.

Our stereospecific, nickel-catalyzed Suzuki–Miyaura cross-coupling of tertiary benzylic acetates.



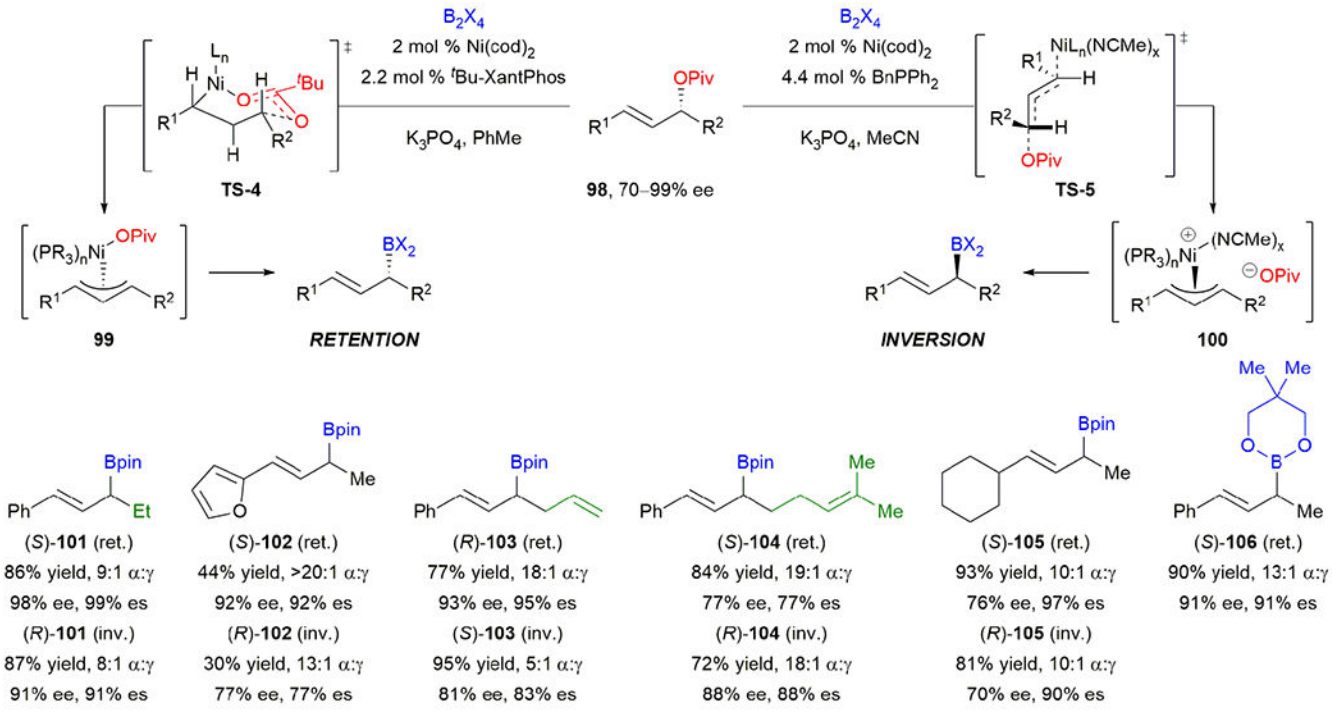
Scheme 16.

(a) Kobayashi's nickel-catalyzed arylation of cyclic allylic acetates. (b) Examples of stereospecific, transition metal-catalyzed arylations of 1,3-disubstituted allylic electrophiles.



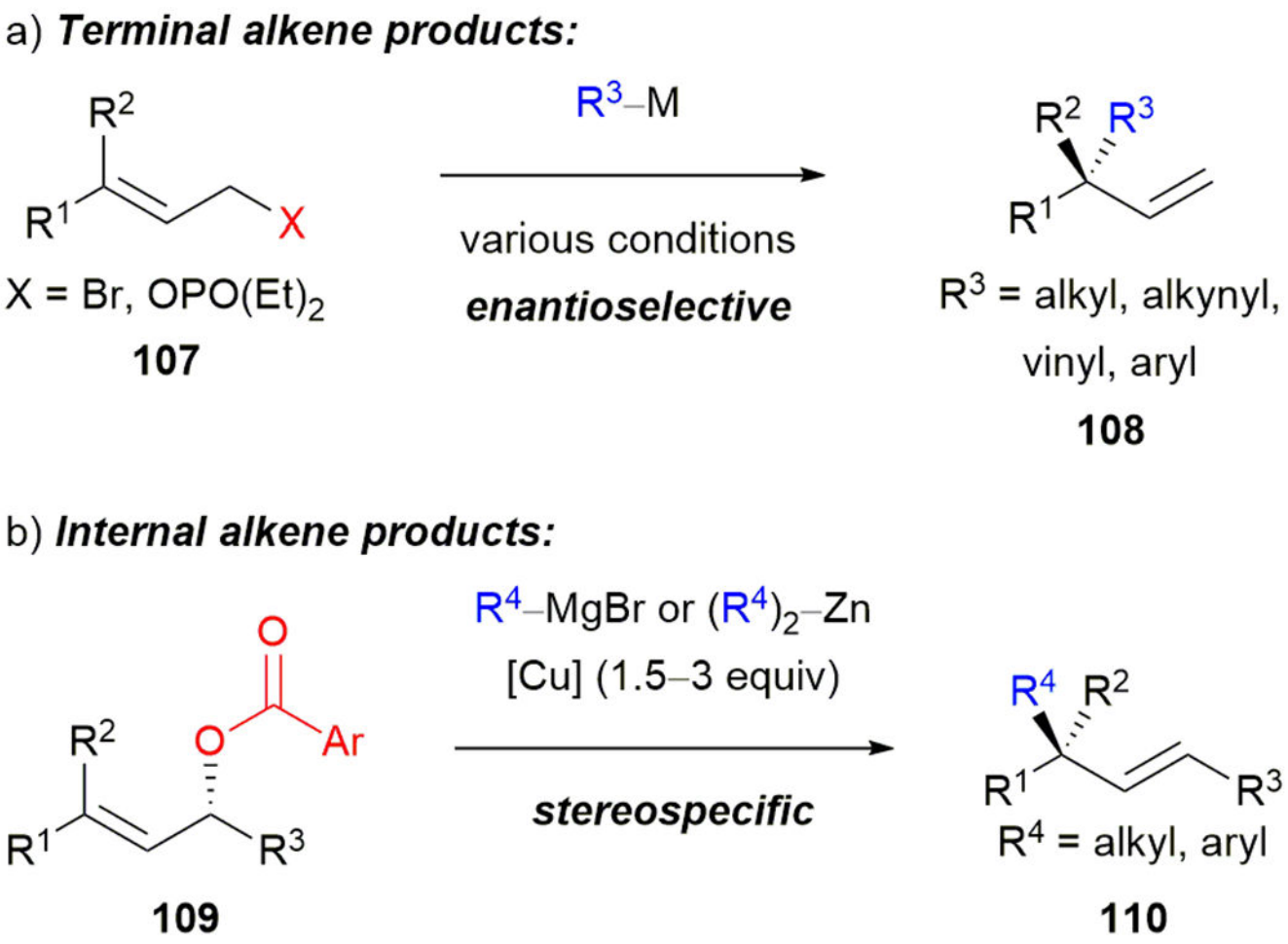
Scheme 17.

Our stereospecific, nickel-catalyzed Suzuki–MIyaura cross-coupling of allylic pivalates: (a) abbreviated scope, and (b) evidence for π-allylnickel intermediate.



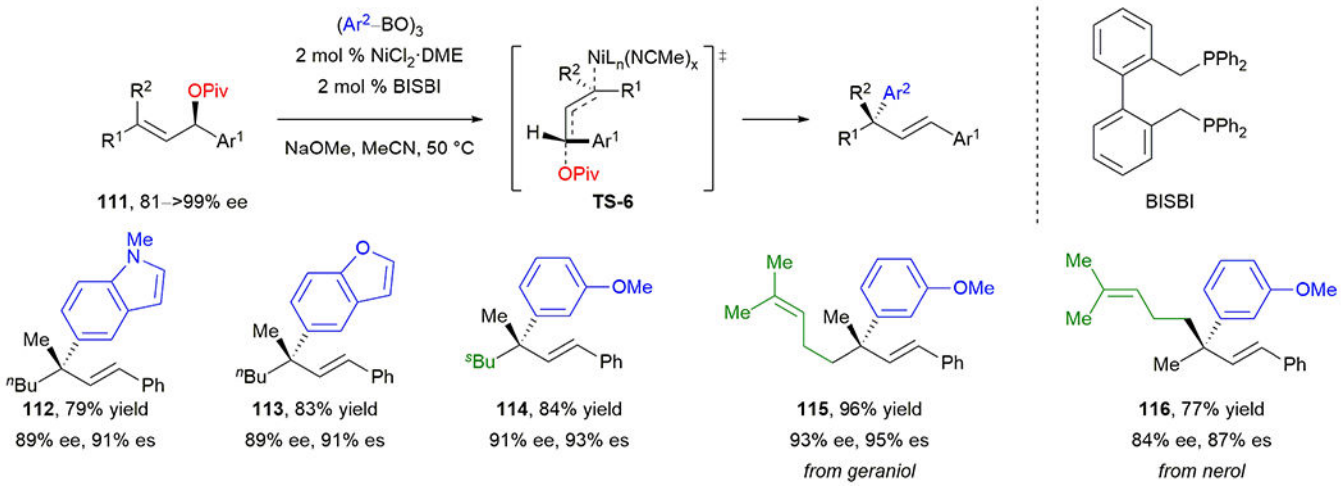
Scheme 18.

Our stereospecific, nickel-catalyzed Miyaura borylation of allylic pivalates.



Scheme 19.

(a) Enantioselective, transition metal-catalyzed allylic substitution reactions to form products with terminal alkenes. (b) Stereospecific allylic substitution reactions to prepare products with internal alkenes.



Scheme 20.

Our stereospecific, nickel-catalyzed Suzuki–Miyaura cross-coupling of allylic pivalates to form all-carbon quaternary stereocenters.