Stereospecific Cross Couplings To Set Benzylic, All-Carbon Quaternary Stereocenters in High Enantiopurity

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S *Supporting Information*

ABSTRACT: Asymmetric preparation of all-carbon quaternary stereocenters is an important goal. Despite advances in formation of highly enantioenriched products with quaternary stereocenters proximal to a functional group, methods to install quaternary stereocenters isolated from functional groups are limited. Transition metal catalysis offers a potential solution, but prior cross couplings are limited to allylic substrates or deliver little to no enantiomeric enrichment. We report a stereospecific, nickel-catalyzed Suzuki–Miyaura arylation of tertiary benzylic acetates to deliver products with diaryl and triaryl quaternary stereocenters in high yields and ee's. This reaction employs an inexpensive, air-stable Ni(II) salt and commercially available phosphine ligand to transform tertiary alcohol derivatives, which are easily available in exceptional ee, into valuable products with stereoretention.

Scheme 1. Benzylic Stereocenters via Cross Couplings

A. Prior Art: Quaternary Benzylic Stereocenters

B. Prior Art: Tertiary Benzylic Stereocenters

C. This Work: Quaternary Benzylic Stereocenters

air-stable Ni(II) precatalyst, commercially available ligand, stereoretentive

Benzylic, all-carbon quaternary stereocenters are present in a variety of bioactive molecules, including natural products and those developed in pharmaceutical and medicinal chemistry.[1] Given their biomedical application, asymmetric synthesis of molecules with quaternary stereocenters is crucial, and great advances have been made to prepare several classes of quaternary stereocenters.[2] Tremendous progress has been made in intramolecular reactions to deliver quaternary stereocenters.[3] For intermolecular reactions, successful approaches focus largely on reactions at sp^2-carbons, such as enolate allylations[1b,4] or arylations,[1c] conjugate additions,[1d,5] redox-relay Heck reactions,[6] and hydrovinylations of styrenes.[7]

In contrast to these notable advances to deliver important carbonyl and vinyl products, synthesis of highly enantioenriched products with benzylic quaternary stereocenters isolated from functional groups remains a challenge. Stereospecific substitution (S$_N$2) of tertiary electrophiles is outcompeted by elimination (E2).[8] A transition metal-catalyzed cross coupling has the potential to overcome this limitation. However, the steric bulk of a tertiary alkyl group results in hindered oxidative addition (alkyl electrophiles) or transmetalation (alkyl nucleophiles). The presence of β-hydrogens leads to β-hydride elimination and isomerization. Thus, cross couplings to deliver quaternary stereocenters in high enantiomeric excess (ee) are limited to allylic electrophiles.[9] Cross couplings of nonallylic tertiary alkyl substrates typically result in achiral or racemic products (Scheme 1A).[10] In the single example of a cross coupling to form an enantioenriched quaternary stereocenter, Doyle showed a promising 27% ee in a Negishi cross coupling
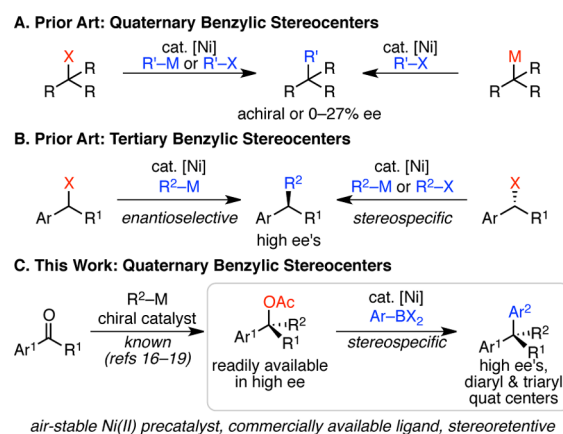
of an azirdine.[11] Given these limitations, one of the best current methods to prepare quaternary stereocenters isolated from functional groups is Aggarwal's enantiospecific, metal-free coupling of tertiary boronic esters with aryl lithium reagents.[12]

Unlike the limitations with tertiary electrophiles, extensive progress has been made in metal-catalyzed cross couplings of secondary electrophiles.[10a] In addition to enantioselective cross couplings pioneered by Fu,[13] Jarvo, we, and others have demonstrated stereospecific cross couplings of secondary benzylic electrophiles (Scheme 1B).[14] Given the high steric hindrance tolerated, including branched alkyl groups,[14i] we envisioned that a stereospecific cross coupling of tertiary electrophiles may be possible. When coupled with enantioselective ketone alkylation, this method would offer a powerful asymmetric synthesis of benzylic quaternary stereocenters from readily available, achiral ketone precursors (Scheme 1C). This strategy avoids differentiation of similar alkyl groups (R^1 and R^2) with a chiral catalyst, a highly challenging task at a saturated carbon of an acyclic substrate. We now report the successful development of a stereospecific, nickel-catalyzed Suzuki–Miyaura arylation of tertiary benzylic acetates to deliver diaryl and triaryl quaternary stereocenters in high yields and ee's. This reaction employs an inexpensive, air-stable Ni(II) salt and commercially available phosphine ligand to transform tertiary alcohol derivatives, which are easily available in exceptional ee's, into valuable products with stereoretention. This reaction demonstrates that transition metal catalysis can be used with nonallylic tertiary electrophiles in stereospecific substitutions.

Table 1. Optimization of Benzylic Arylation[a]
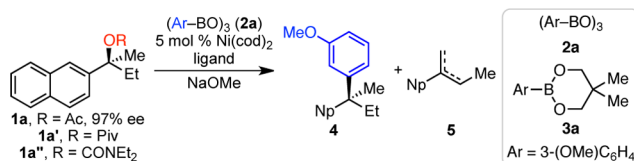
entry	ligand (mol %)	temp (° C)	solvent	yield (%)[b]		es (%)[d]
				4 (ee, %)[c]	5	
1	none	80	PhMe	93 (20)	2	21
2	PhPCy$_2$ (11)	80	PhMe	74 (87)	22	90
3	PhPCy$_2$ (11)	60	PhMe	72 (90)	25	93
4	PhPCy$_2$ (11)	60	THF	63 (93)	24	96
5	CyJohnPhos (11)	40	THF	57 (96)	9	99
6	CyJohnPhos (5)	40	THF	81 (96)	6	99
7	CyJohnPhos (5)	40	1,4-dioxane	97 (97)	5	>99
8	CyJohnPhos (5)	40	2-Me-THF	92 (96)	8	99
9[e]	CyJohnPhos (5)	40	2-Me-THF	90 (95)	6	98
10[e,f]	CyJohnPhos (5)	40	2-Me-THF	99 (97)	≤3	>99
11[e,f]	SIMes·HBF$_4$ (5)	40	2-Me-THF	0	0	

[a]Conditions: **1a** (0.10 mmol), **2a** (1.0 equiv), Ni(cod)$_2$ (5 mol %), ligand, NaOMe (2.0 equiv), solvent (0.4 M), unless otherwise noted. [b]Determined by ^{1}H NMR using an internal standard. Total yields over 100% reflect the error of ^{1}H NMR yields, particularly for minor products. [c]Determined by HPLC using a chiral stationary phase. [d]es = enantiospecificity = (ee$_{product}$)/(ee$_{starting\ material}$). [e]NiCl$_2$·DME in place of Ni(cod)$_2$. [f]Boronate ester **3a** (2.0 equiv) in place of boroxine **2a**.

We selected carboxylates of 2-(naphthalen-2-yl)butan-2-ol (**1**) for initial investigation. Tertiary alcohols are easily prepared in 89−99% ee via Walsh's enantioselective additions of alkyl,[15] vinyl,[16] and arylzinc reagents,[17] as well as allyl stannanes,[18] to acetophenones.[19] Acylation then delivers acetate **1a**, which is stable for >4 months when stored at −35 °C under N$_2$. Notably, pivalate **1a′** or carbamate **1a″** did not form under standard acylation conditions, indicating how sterically congested the tertiary alcohol is.

Using 3-(methoxy)phenyl boroxine as the model nucleophile, under conditions similar to those for the cross coupling of secondary benzylic pivalates with aryl boroxines, high yield of desired product **4** was observed (Table 1, entry 1).[14a] However, the stereochemical fidelity was poor (21% es). Because the use of monodentate phosphines had proven helpful in other stereospecific cross couplings, we investigated the use of PhPCy$_2$. High levels of stereochemical fidelity were achieved, particularly at lower reaction temperature and with THF as solvent (entries 2−4). However, alkenes **5** formed competitively. Although these alkenes may form via E2 elimination, they are more likely due to β-hydride elimination. Their formation depends on catalyst, and acetate **1a** largely decomposes by hydrolysis (not E2) in the presence of only NaOMe. We thus examined Buchwald ligands, hoping that the hemilabile arene would block the open coordination site necessary for β-hydride elimination.[20] Indeed, the use of 2-(dicylohexylphosphino)biphenyl, CyJohnPhos, resulted in less alkenes and even higher levels of stereochemical fidelity (entry 5). By using a 1:1 ratio of Ni(cod)$_2$:CyJohnPhos, high yield of **4** (81%) was observed (entry 6). To maximize the method's attractiveness, we prioritized the use of 2-methyl THF as a "greener" solvent (entries 6−8) and an air-stable nickel(II) precatalyst (NiCl$_2$·DME, entry 9). Under these conditions, the use of boronate ester **3a** in place of boroxine **2a** resulted in a near perfect yield and stereochemical fidelity (entry 10). Use of the analogous aryl boronic acid and pinacol ester resulted in 86% yield with 98% es, and 80% yield with 98% es, respectively.

However, cross coupling with the aryl potassium trifluoroborate resulted predominantly in hydrolysis of acetate **1a**; no desired product **4** was observed.[21] Although N-heterocyclic carbene ligands have been used in cross couplings of secondary benzylic carbamates,[14h] the use of 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazolium tetrafluoroborate (SIMes·HBF$_4$) as the ligand precursor resulted in no desired product **4** or alkene **5**; 90% recovered acetate was observed (entry 11). Given the potential for hydrolysis of acetate **1a** in the presence of NaOMe, we also investigated the use of 2-(naphthalen-2-yl)butan-2-ol itself as substrate. However, neither **4** nor **5** were observed, and 75% of the alcohol was recovered.

Under the optimized conditions, a range of aryl boronate esters underwent cross coupling (Scheme 2). Electron-rich (**7**, **8**, **14**, **15**) and electron-poor (**4**, **9−13**) aryl groups can be incorporated. A range of functional groups is well tolerated, including ether (**4**, **8**), aniline (**7**), aryl chloride and fluoride (**9**, **13**), amide (**10**), ester (**11**), trifluoromethyl (**12**), and dioxolane (**14**) groups. Aryl groups with increased steric hindrance can also be used successfully (**15**). In every case, near perfect levels of stereochemical fidelity were observed. Unfortunately, the use of heteroaryl boronic esters (pyridyl, furyl, indolyl) was not successful, and the use of vinyl boronate esters resulted in low yields. The absolute configuration of **10** was determined to be R via X-ray crystallography using Cu Kα radiation.[22] The expected S configuration of acetate **1a**, as well as the alcohol precursor to **18**, was also confirmed via X-ray crystallography. The conversion of (S)-**1a** to (R)-**10** demonstrates that this reaction proceeds with overall retention of absolute configuration.[23] Absolute configurations of other products were assigned by analogy.

A variety of tertiary acetates also successfully underwent arylation (Scheme 3). For the aryl substituent (Ar^1), electron-rich naphthyl groups (**16**) and increased steric hindrance (**17**) are well tolerated. Heteroaryl groups can also be used (**18**). Various alkyl substituents (R^1) can be incorporated, including alkyl chains capped with silyl ether (**19**), aryl (**20**, **22**), and

Scheme 2. Scope of Aryl Boronate Esters[a]
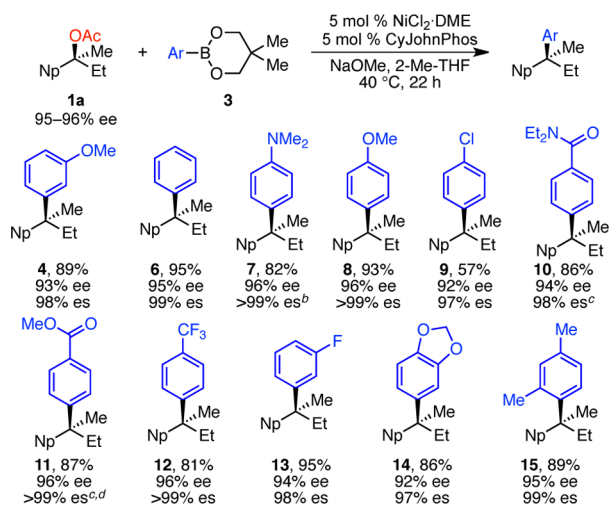
[a]Conditions: **1a** (0.40 mmol), **3** (2.0 equiv), NiCl₂·DME (5 mol %), CyJohnPhos (5 mol %), NaOMe (2.0 equiv), 2-Me-THF (0.4 M), 40 °C, 22 h, unless noted. Average isolated yields (±9%) and ee's (±1%, determined by HPLC or SFC using a chiral stationary phase) of duplicate reactions, unless otherwise noted. [b]Single experiment. [c]60 °C, 12 h. [d]3.0 equiv of **3**.

Scheme 3. Scope of Tertiary Acetates[a]
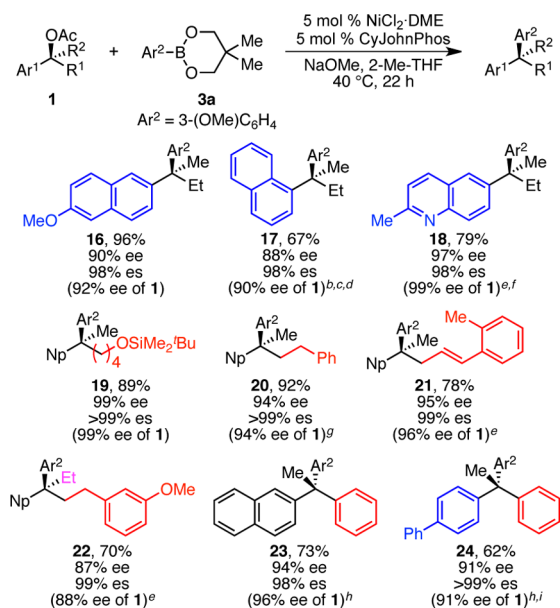
[a]Conditions: see Scheme 2. Average isolated yields (±7%) and ee's (±1%). [b]Single experiment. [c]78%, 83% ee, 99% es (84% ee of **1**). [d]0.3 mmol of **1**. [e]**2a** (0.83 equiv) in place of **3a**. [f]60 °C. [g]48 h. [h]Opposite enantiomer of **1** used. [i]10 mol % NiCl₂·DME, 10 mol % CyJohnPhos, 60 °C, 48 h.

vinyl (**21**) groups. Notably, this reaction is not limited to formation of methyl-substituted quaternary stereocenters; ethyl-substituted product **22** was formed in 70% yield and 99% es. However, an aryl substituent with an extended π-system is required; the arylation of 2-([1,1′-biphenyl]-4-yl)butan-2-yl acetate resulted in no product.

We also pursued the cross coupling of diaryl acetates to deliver triaryl quaternary stereocenters. These acetates are easily prepared via enantioselective addition of a diarylzinc to

an acetophenone. Triarylethane **23** formed in 73% yield, 94% ee, and 98% es (Scheme 3). As previously reported in related reactions of secondary diaryl carbamates,[14f–h] a naphthyl substituent is not required for diaryl acetates. By using 10 mol % Ni/CyJohnPhos catalyst and increased temperature and time, arylation resulted in 62% yield of triarene **24** with near perfect stereochemical fidelity. These conditions are not general for other non-naphthyl substrates, but this promising result suggests that broad scope of tertiary diaryl acetates may be possible with a future catalyst. Notably, the only other method that directly delivers triaryl quaternary stereocenters in high ee is Aggarwal's metal-free coupling.[12]

With respect to mechanism, a directed S_N2' oxidative addition, which has been proposed for stereoretentive cross couplings of secondary benzylic and allylic electrophiles,[9d,14h] is consistent with our observed stereoretention, as well as the requirement for a naphthyl substituent. In a directed oxidative addition, the acetate binds the nickel catalyst, directing it to add in an S_N2' fashion (**A**, Scheme 4). This mechanism also

Scheme 4. Putative Catalytic Cycle
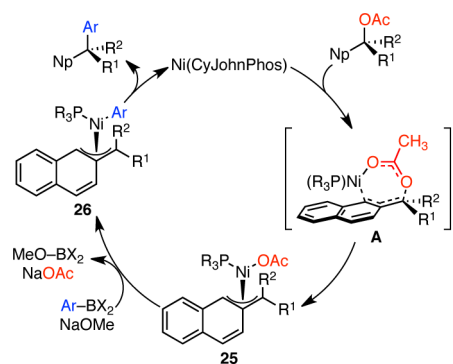
suggests why the steric hindrance of a tertiary acetate is tolerated; this increased bulk is remote to the carbon attacked. Transmetalation and reductive elimination are well precedented to proceed with stereoretention, ultimately resulting in net retention of configuration.[24] Studies are underway to investigate this intriguing mechanism further.

In summary, we developed a high-yielding Suzuki–Miyaura arylation of tertiary benzylic acetates to deliver products with diaryl and triaryl quaternary stereocenters in excellent stereochemical fidelity. By combining this stereospecific cross coupling with known enantioselective additions to acetophenones, this offers a highly efficient strategy for asymmetric synthesis of diaryl and triaryl quaternary stereocenters. This reaction overcomes traditional limitations in utilizing tertiary electrophiles in substitution reactions, and demonstrates that a transition metal-catalyzed cross coupling for the synthesis of enantioenriched quaternary stereocenters can go beyond allylic electrophiles. Efforts to expand the scope and to investigate the mechanism are ongoing.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information
The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08075.

     Experimental details and data (PDF)
     Crystal structure for **10** (CIF)
     Crystal structure for **1a** (CIF)
     Crystal structure for **S-1d** (CIF)

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Notes
The authors declare no competing financial interest.

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