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Stereospecific, Nickel-Catalyzed Suzuki–Miyaura Cross-Coupling of Allylic Pivalates to Deliver Quaternary Stereocenters

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Abstract

Recognizing the importance of all-carbon, quaternary stereocenters in complex molecule synthesis, a stereospecific, nickel-catalyzed cross-coupling of allylic pivalates with arylboroxines to deliver products equipped with quaternary stereocenters and internal alkenes was developed. The enantioenriched allylic pivalate starting materials are readily prepared, and a variety of functional groups can be incorporated on both the allylic pivalate and the arylboroxine. Additional advantages include the use of a commercially available and air-stable Ni(II) salt and BISBI ligand, mild reaction conditions, and high yields and ee's. The observed stereoinversion of this reaction is consistent with an open transition state in the oxidative addition step.

Graphical Abstract

All-carbon quaternary stereocenters are prevalent in natural products and other bioactive molecules.¹ A powerful approach for the synthesis of all-carbon quaternary stereocenters is an allylic substitution reaction.^{1e, 2} Such a reaction not only delivers the desired stereocenter, but also includes a versatile alkene substituent that provides multiple opportunities for further elaboration.³ Recognizing the potential of such an approach, many elegant enantioselective additions to allylic electrophiles have been developed to deliver quaternary stereocenters substituted with terminal alkenes (**2**, Scheme 1A).⁴ In contrast, methods to prepare enantioenriched products with quaternary stereocenters and *internal* alkenes (**5**) are

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Notes

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Supporting Information

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more limited, particularly for acyclic allylic electrophiles.⁵ In particular, only two arylations have been reported towards this motif, both with exceptional stereochemical fidelity (Scheme 1B). Kobayashi has developed a stereospecific addition of aryl cuprates to allylic picolimates.⁶ Morken has taken an umpolung approach with a stereospecific, palladium-catalyzed cross-coupling of allylic boronate esters with aryl halides.⁷

As we considered an efficient and convenient approach to the synthesis of quaternary stereocenters substituted with internal alkenes, we were inspired to combine the best aspects of these two methods in a new nickel-catalyzed reaction. We were attracted to allylic alcohol derivatives for their ease of preparation in highly enantioenriched form. In addition, we sought to identify conditions that would enable catalytic use of the metal, as well as an aryl boron species, due to their convenience and broad functional group tolerance.⁸ Based on our previous Suzuki–Miyaura cross-coupling of allylic pivalates to set tertiary stereocenters,⁹ as well as our efforts with benzylic carboxylates to set tertiary and quaternary stereocenters,¹⁰ we envisioned that a nickel-based catalyst would enable the desired transformation. Herein, we report a stereospecific, nickel-catalyzed cross-coupling of allylic pivalates with arylboroxines to deliver products equipped with quaternary stereocenters and internal alkenes (Scheme 1C). This reaction boasts mild reaction conditions, broad tolerance of functional groups and heterocycles, and high yields and ee's.

We selected the cross-coupling of secondary pivalate **6a**, readily prepared in 96% ee,¹¹ and *m*-methoxyphenylboroxine for optimization. Under our previous conditions for the formation of tertiary stereocenters,^{9a} we observed high yield, but poor stereochemical fidelity (entry 1). The use of a more electron-rich phosphine ligand resulted in a moderate increase in enantiospecificity (es, entry 2). To maximize the convenience of this transformation, we investigated the use of an air-stable Ni(II) salt under these conditions and found that Ni(OTf)₂ provided even higher es, albeit in diminished yield (entry 3). Further examination of ligand revealed that use of bisphosphine dppf led to 93% es, but only 30% yield with considerable decomposition of the starting material (entry 4). We hypothesized that the wide bite angle of dppf may be important for high es, but that the potential redox activity of the ferrocene may also be the cause of starting material decomposition.¹² Dppb, which has a similar bite angle to dppf but a floppier backbone, resulted in only 79% es (entry 5).¹³ However, the use of the more rigid BISBI resulted in high yield and es (entry 6).¹⁴ Additional improvements in yield and es were realized by switching to NiCl₂·DME, lowering the catalyst loading, and reducing the reaction temperature (entries 7–8). Although even higher stereochemical fidelity is achieved at room temperature, the yield is significantly diminished (entry 9). In addition, control experiments demonstrate that nickel is required for the cross-coupling (entries 10–11). The use of Ni(cod)₂ instead of NiCl₂·DME resulted in quantitative yield, but lower stereochemical fidelity (entry 12). The use of aryl boronic acid in place of arylboroxine results in lower yields with significant hydrolysis of pivalate.¹⁵ The use of other leaving groups led to lower stereochemical fidelity; with an acetate leaving group, significant hydrolysis was observed.¹⁵

Under the optimized conditions (Table 1, entry 8), a variety of arylboroxines underwent cross-coupling (Scheme 2). Both electron-rich (**9–11**, **18**, **19**) and electron-poor (**8**, **13–17**) aryl groups can be used. In general, higher stereochemical fidelity is observed with more

electron-rich arylboroxines, but good to excellent es was observed in every case. For arylboroxines with limited solubility in MeCN, elevated temperature (70 °C) was used to ensure complete conversion. A range of functional groups, including ethers (**8**, **10**), anilines (**9**), dioxolane (**11**), trifluoromethyl (**13**), ketones (**14**), esters (**15**), amides (**16**), and nitriles (**17**), were well tolerated. In addition, heteroaryl boroxines can be used in this chemistry, as shown by efficient formation of indole **18** and benzofuran **19**.

We also investigated the scope with respect to the allylic pivalate (Scheme 3). A variety of aryl substituents (Ar¹) can be used, including those with ortho, meta, and para substitution; the highest stereochemical fidelities are observed with electron-poor aryl substituents (**22**, **23**, **24**). For strongly electron-rich aryl substituents, such as *p*-methoxyphenyl, significant decomposition and little desired product were observed, likely due to the greater reactivity of the allylic pivalate. The reaction is somewhat sensitive to changes in the alkyl substituents (R¹, R³), but good yields and high stereochemical fidelity were observed with bulkier (*t*Bu) or functionalized alkyl groups (**28**, **29**, **30**). Similarly to the arylboroxine, a variety of functional groups and heterocycles are well tolerated, as shown by silyl ethers **21** and **30**, nitrile **22**, and trifluoromethyl **23**, pyridine **24**, benzofuran **25**, and epoxide **29**. The absolute configuration of product **27** was determined to be *S* by oxidative cleavage to known carboxylic acid **31** and comparison to the reported optical rotation (eq 1).^{7a, 16} This result shows that this arylation proceeds with stereoinversion, consistent with our other cross-couplings in MeCN.^{9b}

(1)

To probe the influence of the alkene geometry on the stereochemical outcome, we compared the reactions of geraniol-derived (*E*)-**6mm** to nerol-derived (*Z*)-**6mm** (Scheme 4). Arylation of (*E*)-**6mm** proceeded in high yield with excellent stereochemical fidelity. Slightly lower yield and stereochemical fidelity was observed with (*Z*)-**6mm**. Lower stereochemical fidelity was also observed with other (*Z*)-alkenes.¹⁵ Notably, opposite absolute configuration was observed from the arylations of (*E*)- vs. (*Z*)-**6m**, highlighting the importance of the alkene geometry on the stereochemical outcome.

With respect to the mechanism, we propose oxidative addition to give a π -allyl nickel complex, transmetalation, and reductive elimination to deliver product **8** with stabilizing conjugation of the alkene by the phenyl group.¹⁷ This pathway is analogous to that proposed in our allylic arylation and borylation to deliver tertiary stereocenters.⁹ Formation of a π -allyl nickel complex is also consistent with both regioisomers of starting material delivering the same regioisomer of product.¹⁵ The oxidative addition can proceed either via a closed transition state (TS1 or TS2, Scheme 5) or open transition state (TS 3 or TS4). In both open

and closed pathways, the transition states differ by whether Ni adds to the *re* or *si* face of the alkene, one of which is disfavored by developing 1,3-diaxial or A^{1,3} interactions. Formation of (*S,E*)-**8** as the major product suggests that this reaction largely proceeds via open TS3, in which nickel adds from the opposite face of the allylic system as the pivalate leaving group and developing A^{1,3} interactions are minimized. We have previously observed that MeCN can favor such open transition states by coordinating the nickel catalyst and blocking pivalate coordination.^{9b} In addition, Jarvo has proposed that bulky *N*-heterocyclic carbene ligands can also disrupt coordination of the leaving group to nickel;^{10c} potentially, bidentate BISBI may play a similar role. Further experiments are needed to determine if one or both these interactions are relevant here.

In summary, we have developed a stereospecific, nickel-catalyzed Suzuki–Miyaura cross-coupling of allylic pivalates with arylboroxines to deliver highly enantioenriched allyl arenes with benzylic quaternary stereocenters and internal alkenes. The enantioenriched allylic pivalates are readily prepared, and a variety of functional groups can be incorporated on both the allylic pivalate and the arylboroxine. Further, the catalyst system is comprised of commercially available and air-stable Ni(II) salt and BISBI ligand. Efforts to expand the scope of this transformation are ongoing in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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17. When the phenyl substituent is replaced by an alkyl group, low regioselectivity is observed in the arylation.

A. Prior Art: Terminal Alkene Products **B. Prior Art: Arylation to Deliver Internal Alkene Products** **C. This Work:** **Scheme 1.**

Preparation of allylic quaternary stereocenters via allylic substitution

Scheme 2. Scope of aryl boroxines^a

^a Conditions: pivalate **6a** (98% ee, 0.40 mmol, 1.0 equiv), boroxine (1.5 equiv), $NiCl_2 \cdot DME$ (2 mol %), BISBI (2 mol %), NaOMe (3.0 equiv), MeCN (0.4 M), 50 °C, 16 h. Average isolated yields ($\pm 9\%$) and ee's ($\pm 2\%$, determined by HPLC analysis using a chiral stationary phase) of duplicate reactions. es = $(ee_{\text{product}})/(ee_{\text{starting material}})$. ^b 70 °C.

Scheme 3. Scope of allylic pivalates

^a Conditions: pivalate **6** (98% ee, 0.40 mmol, 1.0 equiv), boroxine (1.5 equiv), $\text{NiCl}_2\cdot\text{DME}$ (2 mol %), BISBI (2 mol %), NaOMe (3.0 equiv), MeCN (0.4 M), 50 °C, 16 h. Average isolated yields ($\pm 5\%$) and ee's ($\pm 2\%$, determined by HPLC analysis using a chiral stationary phase) of duplicate reactions. es = $(\text{ee}_{\text{product}})/(\text{ee}_{\text{starting material}})$. ^b 70 °C. ^c Single experiment. ^d Pivalate **6** of unknown configuration. ^e Contaminated with 4% of $\text{S}_{\text{N}}2$ product.

Scheme 4.

Effect of alkene geometry on stereochemical outcome

Scheme 5.
Rationale for stereoinversion

Table 1

Optimization^a

entry	[Ni] (mol %)	ligand (mol %)	t (°C)	yield (%) ^b	% ee (%) ^{c,d}
1	Ni(cod) ₂ (5)	BnPPPh ₂ (11)	70	90	54 (56)
2	Ni(cod) ₂ (5)	PCy ₃ (11)	70	95	64 (67)
3 ^e	Ni(OTf) ₂ (5)	PCy ₃ (11)	70	56	75 (79)
4 ^e	Ni(OTf) ₂ (5)	dppf (5)	70	30	89 (93)
5 ^e	Ni(OTf) ₂ (5)	dppb (5)	70	48	75 (79)
6 ^{f,g}	Ni(OTf) ₂ (5)	BISBI (5)	70	87	90 (95)
7 ^{g,h}	NiCl ₂ -DME (5)	BISBI (5)	70	93	87 (91)
8 ^{g,h,i}	NiCl ₂ -DME (2)	BISBI (2)	50	96	91 (95)
9 ^{g,h,j}	NiCl ₂ -DME (2)	BISBI (2)	rt	28	95 (99)
10	–	–	70	0	–
11	–	BISBI (2)	70	0	–
12 ^{g,h,i,k}	Ni(cod) ₂ (2)	BISBI (2)	50	>95	66 (68)

^a Conditions: pivalate **6a** (96% ee, 0.10 mmol, 1.0 equiv), *m*-methoxyphenylboroxine (1.0 equiv), [Ni], ligand, NaOMe (2.0 equiv), MeCN (0.4 M), 3 h, unless noted otherwise.^b Determined by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard.^c Determined by HPLC analysis using a chiral stationary phase.^d es = (ee-product)/(ee-starting material).^e KOMe (2.0 equiv) in place of NaOMe.^f KOMe (3.0 equiv).^g (ArBO)₃ (1.5 equiv).

6a (97% ee),

k,
24 h.

i,
16 h.

h NaOMe (3.0 equiv).