

Stereospecific, Ligand-Free Synthesis of All-Carbon Quaternary Stereocenters from Tertiary Benzylic Carboxylates

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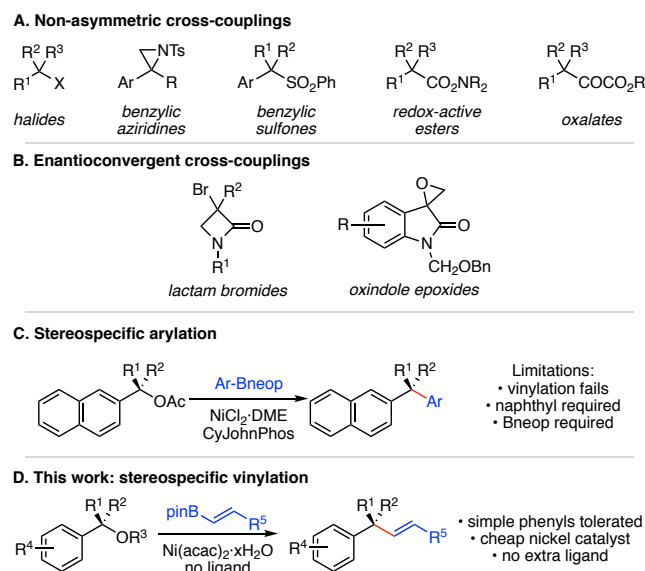
Supporting Information Placeholder

ABSTRACT: Nickel-catalyzed, stereospecific cross-couplings via activation of secondary C–O bonds has been well developed in the past few years. Meanwhile, stereospecific cross-couplings of tertiary electrophiles have been rarely explored. Herein, we describe a nickel-catalyzed, ligand-free Suzuki-Miyaura vinylation, using easily prepared, highly enantioenriched tertiary benzylic carboxylates to install all-carbon quaternary stereocenters in high yields and ee's. In addition to allowing stereospecific vinylation of these substrates for the first time, this method overcomes the longstanding requirement for a naphthyl group on the benzylic carboxylate.

Harnessing tertiary electrophiles in transition metal-catalyzed carbon–carbon (C–C) bond formation is one of the longstanding challenges in modern chemistry.¹ Because these transformations would deliver valuable, all-carbon quaternary centers, which are widespread in natural products and other bioactive compounds,² tremendous effort has been directed towards this goal.^{3,4} The challenge of such cross-couplings are two-fold; significant steric hindrance must be overcome, and stereochemistry must be controlled. With respect to overcoming the steric challenge, unactivated alkyl halides are well-developed tertiary electrophiles.⁵ Other tertiary electrophiles have also been demonstrated, such as benzylic aziridines,⁶ benzylic sulfonates,⁷ redox-active esters,⁸ and unactivated tertiary alkyl oxalates⁹ (Scheme 1A). However, in terms of stereocontrol, only a few, limited methods are known, particularly for non-allylic substrates.¹⁰ Namely, Fu and Zhang have developed enantioconvergent cross-couplings of tertiary lactam bromides¹¹ and oxindole epoxides¹², respectively (Scheme 1B). The strict requirements for the substrate structure in these reactions belies the difficulty in controlling the stereochemistry in cross-couplings of tertiary electrophiles. In an alternative strategy, we developed a stereospecific Suzuki-Miyaura arylation of enantioenriched tertiary benzylic acetates (Scheme 1C).¹³ However, as excited as we were to form benzylic quaternary stereocenters using this NiCl₂·DME/CyJohnPhos catalyst, we were sharply aware of its limitations. Although vinylboronates are often more reactive than their aryl counterparts, we surprisingly observed no

reaction when the arylation conditions were applied to vinylboronates. The arylation was also sensitive to the steric bulk of the boronate ester. Neopentyl glycol esters (Bneop) were required, because the more common pinacol esters (Bpin) resulted in lower yields, thus limiting the convenience of this method. In addition to these major limitations in the nucleophilic coupling partner, the scope of benzylic acetates was limited to those with naphthyl (or naphthyl-like) substituents. In fact, only one substrate lacked such substitution, and it was a dibenzylic substrate. Notably, this requirement for a naphthyl group or dibenzylic activation plagues stereospecific cross-couplings as a whole, including those of secondary electrophiles.¹⁴⁻¹⁹

Scheme 1. Tertiary Electrophiles in Cross-Couplings



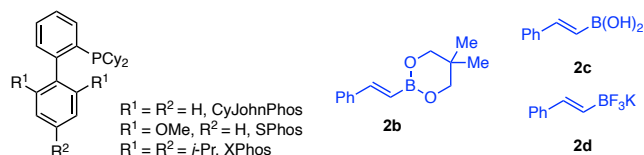
Due to these limitations, the importance of all-carbon quaternary stereocenters, and the high utility of vinyl substituents for further elaboration, we now report a stereospecific, nickel-catalyzed cross-coupling of tertiary benzylic carboxylates (Scheme 1D). To enable this vinylation, a new catalyst system – one unsupported by any added ligand – was discovered. This new catalyst system not only enabled the vinylation; it also resulted in unprecedented scope in the tertiary benzylic

carboxylate, allowing even substrates with simple phenyl substituents to be used.

We selected the cross-coupling of tertiary acetate **1a** and vinyl boronate ester **2a** for optimization studies (Table 1). Under similar conditions as our previous arylation (NiCl₂·DME, CyJohnPhos), we saw only trace desired product **3** (entry 1). A broad investigation of ligands showed that bulkier Buchwald-type ligands gave better yields, with XPhos providing 80% yield (entries 2–3). However, we observed even better yield in the absence of ligand (entry 4). This surprising result was mechanistically intriguing and offered an opportunity to develop an inexpensive and simple catalyst. Indeed, we were able to use an even cheaper nickel catalyst, Ni(acac)₂·xH₂O,²⁰ by changing the base from NaOMe to LiOt-Bu (entries 5–6). Control experiments (entries 7–8) showed that both nickel and base were required. Additionally, the corresponding vinyl Bneop (**2b**) worked (entry 9). However, use of boronic acid **2c** resulted in no product (entry 10), and only 34% yield was observed with trifluoroborate **2d** (entry 11).

Table 1. Optimization^a

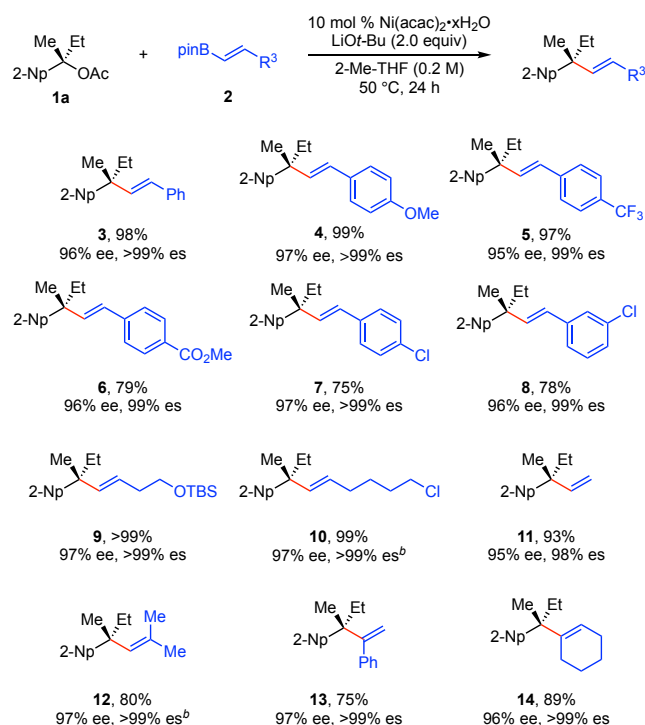
entry	Ni/L	base	yield (%) ^b	ee (%) ^c	es (%) ^d
1	NiCl ₂ ·DME/ CyJohnPhos	Na-OMe	<5	n.d. ^e	n.d.
2	NiCl ₂ ·DME/ SPhos	Na-OMe	7	96	99
3	NiCl ₂ ·DME/ XPhos	Na-OMe	80	96	99
4	NiCl ₂ ·DME	Na-OMe	>99	97	>99
5	Ni(acac) ₂ ·xH ₂ O	Na-OMe	91	93	96
6	Ni(acac) ₂ ·xH ₂ O	LiOt-Bu	>99	97	>99
7	none	LiOt-Bu	0	n.d.	n.d.
8	Ni(acac) ₂ ·xH ₂ O	none	0	n.d.	n.d.
9 ^f	Ni(acac) ₂ ·xH ₂ O	LiOt-Bu	86	96	99
10 ^g	Ni(acac) ₂ ·xH ₂ O	LiOt-Bu	0	n.d.	n.d.
11 ^h	Ni(acac) ₂ ·xH ₂ O	LiOt-Bu	34	92	95



^a Conditions: **1a** (0.10 mmol), **2a** (2.0 equiv), Ni source (10 mol %), ligand (20 mol %), base (2.0 equiv), 2-Me-THF (0.2 M), 50 °C, 24 h, unless otherwise noted. ^b Determined by ¹H NMR analysis 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 n.d. = not determined. ^f **2b** in place of **2a**. ^g **2c** in place of **2a**. ^h **2d** in place of **2a**.

Under the optimized conditions (Table 1, entry 6), we observed a broad scope with respect to the vinyl boronate ester (Scheme 2). Vinyl groups with both aryl (**3–8**) and alkyl groups (**9–14**) can be incorporated. Electron-rich (**4**) and electron-poor (**5, 6**) aryl substituents worked well. Compatibility with a range of functional groups was also observed. Noteworthy examples include an ester (**6**), aryl chlorides (**7, 8**), a TBS-protected alcohol (**9**), and an alkyl chloride (**10**), which offer opportunities for further elaboration. Notably, a tremendous range of vinyl substitution is tolerated, enabling synthesis of monosubstituted alkene **11**, 1,1-disubstituted alkenes **12** and **14**. Notably, these more substituted alkenes are not accessible via an allylic arylation.²¹ In all cases, the stereochemical fidelity was exceptional.

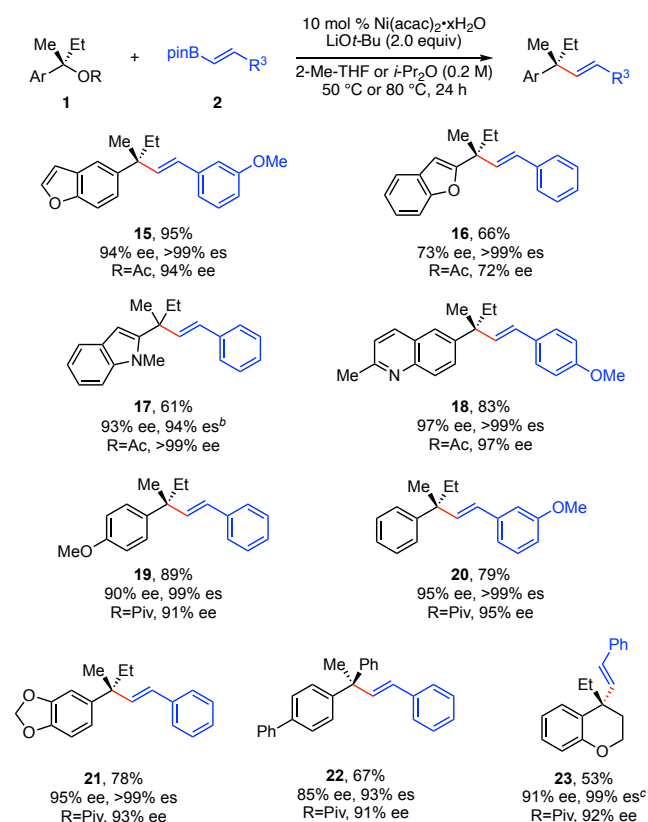
Scheme 2. Scope of the Vinyl Boronate Ester



^a Conditions: **1a** (0.40 mmol), **2** (2.0 equiv), Ni(acac)₂·xH₂O (10 mol %), LiOt-Bu (2.0 equiv), 2-Me-THF (0.2 M), 50 °C, 24 h. Average isolated yields (±3%) and ee's (±1%, determined by HPLC or SFC analysis using a chiral stationary phase) of duplicate experiments. ^b 80 °C.

With respect to the scope of tertiary benzylic esters, we were particularly interested in substrates with heteroaryl and non-naphthyl aryl groups, because these substrates failed under our previous arylation conditions (Scheme 3). Excitingly, heteroaryl substitution is well tolerated, as evidenced by the efficient formation of benzofurans **15** and **16**, indole **17**, and quinoline **18**. For substrates with non-naphthyl groups, we observed low yields when we employed benzylic acetates as substrates. However, we also observed decomposition of these tertiary benzylic acetates upon purification, leading us to question whether they were simply decomposing under the reaction conditions, particularly if they underwent slower oxidative addition than naphthyl-substituted **1a**. By changing to a more stable pivalate group, we were able to break through the limitation of naphthyl-like substrates. Using pivalates and increasing the reaction temperature to 80 °C enabled efficient cross-couplings of simple phenyl-substituted esters (**19–21**). Additionally, more sterically hindered quaternary centers (**22**, **23**) were also accessible. The ability to incorporate heteroaryls and non-naphthyl substituents dramatically expands the utility of this method.

Scheme 3. Ester Scope



^a Conditions: **1a** (0.40 mmol), **2** (2.0 equiv), Ni(acac)₂·xH₂O (10 mol %), LiOt-Bu (2.0 equiv), 2-Me-THF (0.2 M), 50 °C or

i-Pr₂O (0.2 M), 80 °C, 24 h. Average isolated yields (±4%) and ee's (±2%, determined by HPLC or SFC analysis using a chiral stationary phase) of duplicate experiments, unless otherwise noted. ^b Unknown absolute configuration. ^c Single run.

In terms of mechanism, we hypothesize that this reaction proceeds via a Ni^{0/II} catalytic cycle, starting with oxidative addition via an S_N2'-like attack of a Ni⁰ species on the benzylic carboxylate.^{14,17} The overall reaction proceeds with stereoretention,²² consistent with oxidative addition through a closed transition state with the carboxylate directing Ni⁰ to the ortho position of the aryl ring. Subsequent transmetalation and reductive elimination delivers product and completes the catalytic cycle. However, it is unclear what species supports the nickel intermediates, particularly Ni⁰, because no additional ligand is needed. One possible supporting ligand is 1,3-butadiene, which we have observed in low yields and likely form during the reduction of Ni(acac)₂.¹⁵ However, based on precedent for electron-poor alkenes as ligands for Ni⁰,²³ the vinylboronate ester or product may also serve as ligand.²⁴ Further studies are needed to determine what species is the active catalyst and why this catalyst offers the unprecedented ability to activate non-naphthyl substrates.

In summary, these new conditions enable unparalleled scope in the benzylic carboxylate and the use of widely commercially available vinylboronate esters. Notably, these reactions rely only on inexpensive Ni(acac)₂·xH₂O as catalyst; no additional ligand is needed. Exploration of the mechanism, especially the nature of the active catalyst, and efforts to expand the use of this highly active catalyst system are ongoing in the lab.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website. Experimental details and data (PDF)

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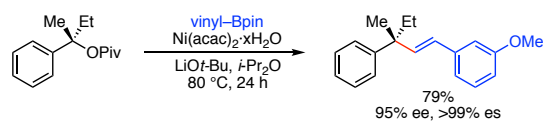
We thank NIH (R01 GM111820, R35 GM131816) and the University of Delaware for fellowships (C.H.B., A.D.D.). Data were acquired at UD on instruments obtained with assistance of NSF and NIH funding (NSF CHE0421224, CHE1229234, CHE0840401, and CHE1048367; NIH P20 GM104316, P20 GM103541, and S10 OD016267). We thank Lotus Separations, LLC, for assistance with SFC.

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- heteroaryls and simple, non-naphthyl aryls tolerated
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