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Nickel-Catalyzed Cross-Couplings of Benzylic Pivalates with Arylboroxines: Stereospecific Formation of Diarylalkanes and Triarylmethanes

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Supporting Information

ABSTRACT: We have developed a stereospecific nickel-catalyzed cross-coupling of benzylic pivalates with arylboroxines. The success of this reaction relies on the use of $Ni(cod)_2$ as the catalyst and NaOMe as a uniquely effective base. This reaction has broad scope with respect to the arylboroxine and benzylic pivalate, enabling the synthesis of a variety of diarylalkanes and triarylmethanes in good to excellent yields and ee's.

Diarylalkanes and triarylmethanes are important molecules in organic synthesis and pharmaceutical development.[1] A highly efficient and direct route to these valuable chiral compounds is the metal-catalyzed cross-coupling of a benzylic electrophile with an organometallic reagent.[2] Such couplings have been accomplished in both enantioselective and enantiospecific fashion.[3−5] Of particular note, the Jarvo group has demonstrated that nickel-catalyzed cross-couplings of enantioenriched benzylic ethers with Grignard reagents occur with excellent levels of chirality transfer.[6] Jarvo's work highlights the convenience of using readily available enantioenriched benzylic alcohol derivatives as starting materials. However, a limitation to the state of the art in this field is the requirement for highly nucleophilic coupling partners (Grignard or organozinc reagents), which restricts the range of functional groups that are compatible with these reactions. To our knowledge, no enantioselective couplings of benzylic electrophiles with the more mild organoboranes are yet known, and stereospecific couplings with boronic reagents to deliver these products are rare.[7−11] The ability to employ organoboranes as coupling partners would lead to greatly expanded scope and functional group tolerance within this important class of reactions.

Recognizing the wide accessibility of enantioenriched benzylic alcohol derivatives and the advantage of using mild and functional-group-tolerant organoborane coupling partners, we sought to develop a stereospecific cross-coupling of these reagents. Within our research program focused around the development of cross-coupling reactions of nontraditional electrophiles, we have been drawn to the use of pivalate substrates for aryl C−O bond activation.[12,13] We envisioned that the use of benzylic pivalates would enable the desired nickel-catalyzed coupling of enantioenriched benzylic alcohol derivatives with organoborane coupling partners (Scheme 1). Herein we report the stereospecific, high-yield cross-coupling of benzylic pivalates with arylboroxines in the presence of a simple nickel(0) catalyst. This cross-coupling leads to a wide variety of diarylalkanes and triarylmethanes.

Scheme 1. Stereospecific Coupling of Benzylic Pivalates with Arylboroxines

We selected the cross-coupling of pivalate **1a**, which is readily prepared with >99% ee,[14] as our model reaction for optimization. Given the precedent for activation of benzylic C−O bonds[5e,f,6] and our prior experience in Suzuki cross-couplings of benzylic electrophiles,[8a] we anticipated that a Ni(0) catalyst supported by an electron-rich phosphine ligand would enable this transformation. However, with $Ni(cod)_2$/PCy_3 (cod = 1,5-cyclooctadiene, Cy = cyclohexyl) as the catalyst system and phenylboronic acid as the coupling partner, we observed low yields of the desired product **2** using a variety of bases commonly employed in Suzuki cross-couplings (Table 1, entries 1 and 2). β-Hydride elimination was also observed under these reaction conditions. However, when NaOMe was employed as the base, **2** was formed in 78% yield (entry 3). Further optimization showed that the use of PCy_2Ph as the ligand resulted in 93% yield (entry 4), but **2** was formed with only 54% ee under these conditions. In contrast, much higher chirality transfer was obtained without a detrimental effect on the yield when $Ni(cod)_2$ alone was used as the catalyst (93% ee; entry 5). Notably, the absolute configuration of the major enantiomer was the opposite when the phosphine ligand was not employed. When a greater amount of boronic acid and lower reaction temperature (70 °C) were used, a greater extent of chirality transfer was observed without a significant drop in yield (entry 6). The nature of the counterion of the methoxide base had a significant impact on the reaction outcome. With KOMe, the product was formed with lower ee (entry 7), and no reaction occurred with LiOMe (entry 8). These results suggest that the solubility of the base is important; with more base in solution (as occurs with KOMe), a lower product ee was observed, but LiOMe may not have been soluble enough in PhMe to promote the reaction. This hypothesis is consistent with our solvent studies: with more polar solvents, lower product ee's were observed.[14] By increasing the concentration of the reaction mixture, we obtained an 87% yield of **2** with

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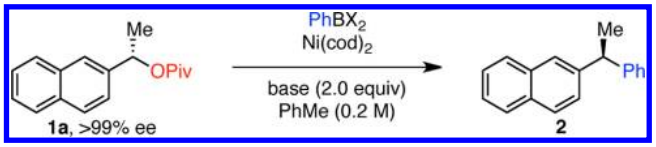
Table 1. Optimization of the Cross-Coupling Reaction[a]



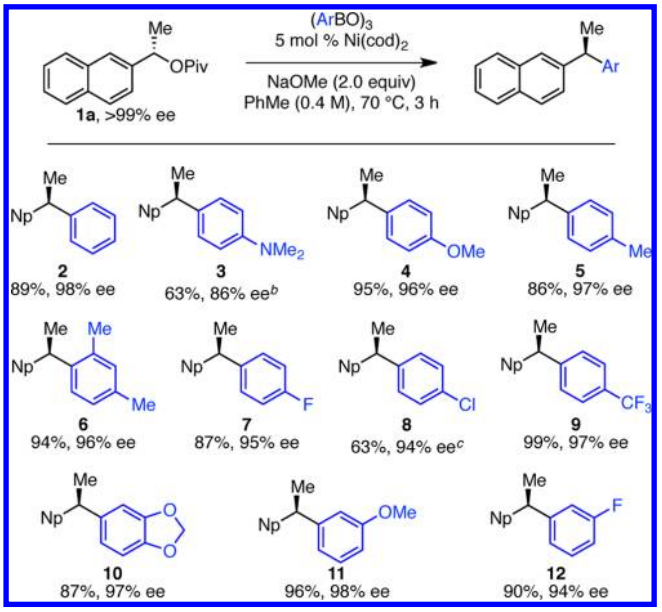
entry	mol % Ni	$PhBX_2$ (equiv)	base	T (°C)	yield (%)[b]	ee (%)[c]
1[d]	10	$PhB(OH)_2$ (3.0)	CsF	100	14	n.d.[e]
2[d]	10	$PhB(OH)_2$ (3.0)	K_3PO_4	100	14	n.d.[e]
3[d]	10	$PhB(OH)_2$ (3.0)	NaOMe	100	78	n.d.[e]
4[f]	10	$PhB(OH)_2$ (2.0)	NaOMe	100	93	54 (*R*)
5	10	$PhB(OH)_2$ (2.0)	NaOMe	100	99	93 (*S*)
6	10	$PhB(OH)_2$ (3.0)	NaOMe	70	83	99 (*S*)
7	10	$PhB(OH)_2$ (3.0)	KOMe	70	74	69 (*S*)
8	10	$PhB(OH)_2$ (3.0)	LiOMe	70	0	n.d.[e]
9[g]	5	$PhB(OH)_2$ (2.5)	NaOMe	70	87	98 (*S*)
10[g]	**5**	**$(PhBO)_3$ (0.83)**	**NaOMe**	**70**	**98**	**97 (*S*)**
11[g,h]	5	$(PhBO)_3$ (0.83)	NaOMe	70	59	94 (*S*)
12[g]	0	$PhB(OH)_2$ (2.5)	NaOMe	70	0	n.d.[e]
13[g]	0	$(PhBO)_3$ (0.83)	NaOMe	70	0	n.d.[e]

[a]Conditions: pivalate **1a** (0.10 mmol, 1.0 equiv), $PhBX_2$, $Ni(cod)_2$, and base (2.0 equiv) in PhMe (0.2 M), unless otherwise noted. [b]Determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c]Determined by chiral HPLC. The absolute configurations of the major enantiomers are shown in parentheses. [d]Performed with racemic **1a**. PCy_3 (24 mol %) was added. [e]n.d. = not determined. [f]PCy_2Ph (22 mol %) was added. [g]0.4 M. [h]1.0 equiv of H_2O was added.

excellent chirality transfer using $PhB(OH)_2$ and only 5 mol % $Ni(cod)_2$ (entry 9). Nearly quantitative yield was observed when phenylboroxine was employed as the coupling partner under these conditions (entry 10). Although the difference in yield was not particularly significant for this model reaction, as we examined other arylboronic reagents, we generally observed better yields and higher levels of chirality transfer with boroxines, indicating that water likely has a detrimental effect on this reaction. Indeed, the addition of H_2O (1.0 equiv) to the reaction mixture resulted in diminished yield and chirality transfer (entry 11).[14] Finally, we performed control reactions in the absence of $Ni(cod)_2$ and found that no cross-coupling occurred with either phenylboronic acid or phenylboroxine (entries 12 and 13). In these reactions, pivalate **1a** was recovered quantitatively with >99% ee.

Under our optimized conditions (Table 1, entry 10), we observed broad scope with respect to the arylboroxine (Scheme 2).[15] High yields and excellent chirality transfer were observed with both electron-rich and electron-poor aryl groups. Furthermore, a wide range of functional groups were tolerated, including amino (**3**), ether (**4**), fluoro (**7**, **12**), chloro (**8**), trifluoromethyl (**9**), and acetal (**10**) functionalities. The formation of chloride **8** is particularly impressive and highlights the advantage of using a boronic coupling partner and the

Scheme 2. Scope of Boroxines[a]



[a]Conditions: pivalate **1a** (0.20 mmol, 1.0 equiv), boroxine (0.83 equiv), $Ni(cod)_2$ (5 mol %), and NaOMe (2.0 equiv) in PhMe (0.4 M) at 70 °C for 3 h, unless otherwise noted. Average isolated yields of duplicate experiments (±0–2%) and average ee's of duplicate experiments (±0–1%) as determined by chiral HPLC are reported. [b]10 mol % $Ni(cod)_2$, 90 °C, 12 h. [c]40 °C, 24 h.

mildness of these reaction conditions. Increased steric hindrance on the aryl fragment was well-tolerated, as demonstrated by the formation of product **6** in 94% yield with 96% ee. By comparison of product **5** to an authentic sample recently prepared in our laboratory,[8a] we confirmed the absolute configuration of this product, demonstrating that this reaction occurs with overall inversion of configuration at the benzylic stereocenter. The absolute configurations of the other products were assigned by analogy.

Variation of the pivalate partner led to a variety of diarylalkane and triarylmethane products in good to excellent yields and enantiospecificities (Table 2). In the formation of diarylalkanes, increased steric bulk of the alkyl substituent (R) was well-tolerated, giving excellent levels of chirality transfer in the cross-coupling reaction (entries 1–4). Notably, even pivalate **1c** with a bulky isobutyl substituent underwent the reaction (entry 4). The coupling of diaryl-substituted pivalate **1d** also proceeded in excellent yields to deliver triarylmethanes **17** and **18** with good levels of chirality transfer (entries 5 and 6). A variety of functional groups on the naphthyl fragment were well-tolerated. The coupling of 6-methoxynaphthyl-substituted pivalate **1e** gave diarylethane **19** in 87% yield with 93% ee (entry 7). In particular, the successful couplings of ester- and nitrile-substituted pivalates **1f** and **1g** highlight the increased functional group tolerance enabled by the use of an arylboroxine coupling partner (entries 8 and 9). The couplings of benzylic pivalates with aryl groups other than 2-naphthyl were also successful. The reaction of 1-naphthyl-substituted pivalate **1h** gave diarylethane **22** in 73% yield with 85% es (entry 10). We hypothesize that the slightly lower level of chirality transfer in this case may be due to the increased steric hindrance arising from ortho substitution on the aromatic group. Both electron-rich and electron-poor heteroaromatics underwent the desired coupling (entries 11 and 12). Finally, we

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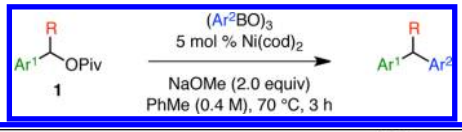
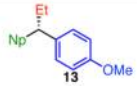
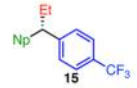
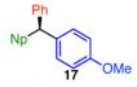
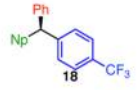
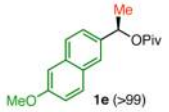
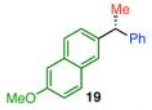
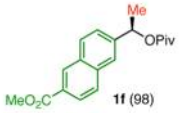
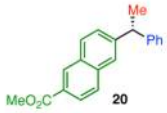
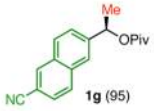
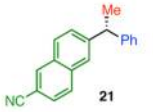
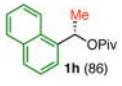
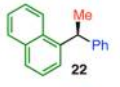
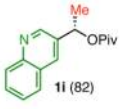
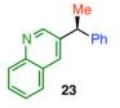
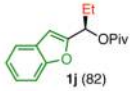
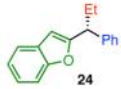
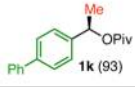
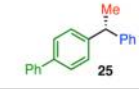
Table 2. Scope of Pivalates[a]



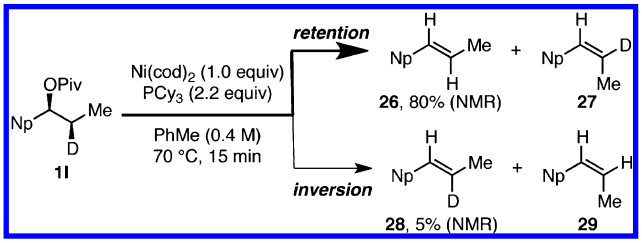
entry	1 (% ee)[b]	Product	yield (%)[c]	ee (%)[d]	es (%)[e]
1[f,g]	 1b (>99)	 13	71	94	≥94
2[g]	 1b (>99)	 14	93	97	≥97
3[g]	 1b (>99)	 15	94	96	≥96
4[h]	 1c (93)	 16	72	91	98
5[f,i]	 1d (>99)	 17	85	86	≥86
6[f,i,j]	 1d (>99)	 18	96	80	≥80
7[k]	 1e (>99)	 19	87	93	≥93
8	 1f (98)	 20	84	94	96
9	 1g (95)	 21	45	89	94
10	 1h (86)	 22	73	73	85
11	 1i (82)	 23	94	58	71
12[l,m]	 1j (82)	 24	49	72	88
13[f,m,n]	 1k (93)	 25	33	84	90

[a]Conditions: pivalate (0.20 mmol, 1.0 equiv), boroxine (0.83−1.3 equiv), $Ni(cod)_2$ (5 mol %), and NaOMe (2.0 equiv) in PhMe (0.4 M) at 70 °C for 3 h, unless otherwise noted. [b]Determined by chiral HPLC. [c]Average isolated yields of duplicate experiments (±0−2%), unless otherwise noted. [d]Average ee's of duplicate experiments (±0−1%), as determined by chiral HPLC, unless otherwise noted. [e]% es = enantiospecificity = [(ee of product)/(ee of starting material)] × 100%. [f]10 mol % $Ni(cod)_2$. [g]80 °C. [h]12 h. [i]90 °C. [j]Results of a single experiment. [k]50 °C. [l]32 °C. [m]24 h. [n]100 °C.

were pleased to observe that the cross-coupling of biphenyl-substituted pivalate proceeded with 90% es (entry 13). The diminished yield in this case clearly demonstrates the importance of the aryl group in the oxidative addition of nickel to the pivalate.

We hypothesize that this reaction proceeds via oxidative addition of the nickel catalyst to the benzylic C−O bond, with subsequent transmetalation and reductive elimination delivering the C−C bond of the arylated product. In an effort to understand the stereochemical outcome of the oxidative addition, we attempted a series of β-hydride elimination experiments using deuterated pivalate **1l** (Scheme 3).[16] If the

Scheme 3. β-Hydride Elimination Experiment



oxidative addition occurs with retention of configuration at the benzylic carbon, then products **26** and/or **27** will result. However, if inversion of configuration occurs upon oxidative addition, then products **28** and/or **29** will be observed. We first attempted to induce β-hydride elimination using stoichiometric $Ni(cod)_2$. However, we observed no reaction, even at reaction temperatures of up to 130 °C. In contrast, when a phosphine ligand was added, facile β-hydride elimination was observed. With PCy_3, an 80% yield of styrene **26** and a 5% yield of styrene **28** were observed after only 15 min at 70 °C (Scheme 3). These results are consistent with the conclusion that the predominant pathway for oxidative addition proceeds with retention of configuration at the benzylic carbon when a phosphine-supported nickel catalyst is used. Although it seems somewhat surprising that the C−D bond was selectively cleaved to form **26**, this result is likely due to the significant steric hindrance between the naphthyl and methyl groups in the transition state leading to product **27**. As shown in entry 4 of Table 1 and in the Supporting Information, the cross-coupling occurs with overall retention of configuration with phosphine-supported nickel catalysts, suggesting that the transmetalation and reductive elimination also occur with retention of configuration. Such retention of configuration during transmetalation and reductive elimination is well-precedented with similar organometallic intermediates.[16,17] However, retention of configuration upon oxidative addition of a benzylic electrophile is rare and suggests that the oxidative addition may be more complicated with this catalyst system. In contrast, when only $Ni(cod)_2$ was used without any phosphine ligand, we observed overall inversion of configuration at the benzylic carbon, suggesting that the oxidative addition step likely occurs with inversion of configuration via an S_N2 pathway under these conditions.

In summary, we have developed a stereospecific nickel-catalyzed cross-coupling of enantioenriched benzylic pivalates with arylboroxines. The successful development of this reaction depended on the identification of $Ni(cod)_2$ as the optimal catalyst and NaOMe as a uniquely effective base. This reaction has broad scope with respect to the arylboroxine and benzylic

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pivalate, enabling the synthesis of a variety of diarylalkanes and triarylmethanes with good to excellent levels of chirality transfer. Our current efforts are directed toward expanding the versatility and scope of this cross-coupling reaction as well as deepening our mechanistic understanding to enable rational improvements in the catalyst system.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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