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Communication

Overcoming the Naphthyl Requirement in Stereospecific Cross-Couplings to Form Quaternary Stereocenters

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Cite This: J. Am. Chem. Soc. 2021, 143, 8608−8613
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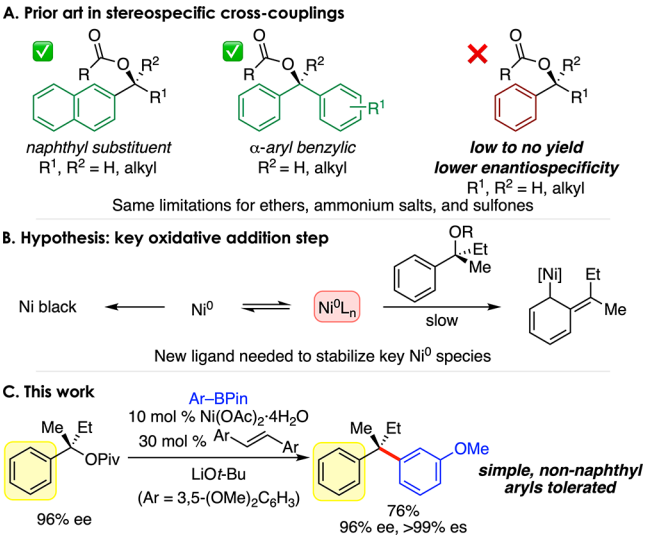
ABSTRACT: The use of a simple stilbene ligand has enabled a stereospecific Suzuki−Miyaura cross-coupling of tertiary benzylic carboxylates, including those lacking naphthyl substituents. This method installs challenging all-carbon diaryl quaternary stereocenters in good yield and ee and represents an important breakthrough in the "naphthyl requirement" that pervades stereospecific cross-couplings involving enantioenriched electrophiles.

Given their prevalence in bioactive natural products, pharmaceuticals, and small molecules, the asymmetric synthesis of all-carbon quaternary stereocenters remains an important challenge.[1] Despite advances in the formation of these fully substituted centers in allylic systems and proximal to carbonyls,[2] asymmetric formation of this motif in other scenarios is highly limited, especially for diaryl quaternary stereocenters.[3] We envisioned that a stereospecific cross-coupling would be a potentially powerful approach to this motif, particularly if an alcohol derivative were employed as the substrate. Alcohols and their derivatives are attractive substrates because of the high incidence of C−O bonds and alcohols in natural products and pharmaceuticals as well as simple starting materials.[4] Indeed, C(sp^3) cross-coupling through C−O bond cleavage has been demonstrated to forge various bonds, including C−C,[5] C−B,[6] C−N,[7] and C−P.[8] Among these, stereospecific cross-couplings using enantioenriched alcohol derivatives offer a potentially powerful method for asymmetric synthesis because the alcohol precursors are easily accessible in high enantiopurity,[9] the reactions often proceed with high stereochemical fidelity, and many of the products are otherwise challenging to synthesize asymmetrically.[10]

However, nickel-catalyzed stereospecific cross-couplings of benzylic electrophiles suffer from significant restrictions on the substrate structure, limiting their utility and prompting us to reconsider our approach to catalyst design.[11] To obtain high yields and stereochemical fidelities, substrates must be substituted with naphthyl groups or specific heteroaryls (Scheme 1A, left).[12] Exceptions to this so-called "naphthyl requirement" are generally only possible for α-aryl benzylic electrophiles, in which the C−O bond benefits from additional activation from a second aryl group (Scheme 1A, middle).[10d,13] For other benzylic electrophiles, the naphthyl requirement is ubiquitous. It is observed for all nickel-catalyzed stereospecific cross-couplings of benzylic electrophiles, including ethers,[12a] ammonium salts,[14] and sulfones,[15] regardless of the coupling partner (Scheme 1A).[16] Low yields and stereochemical fidelities are observed with substrates with phenyl and substituted phenyl substituents (Scheme 1A, right), preventing the application of this strategy to the synthesis of a vast array of valuable diarylalkanes with tertiary or quaternary benzylic stereocenters.

Scheme 1. Naphthyl Requirement in Stereospecific Cross-Couplings



We hypothesized that the low reactivity of phenyl-substituted electrophiles is due to a prohibitively difficult oxidative addition. The naphthyl requirement is consistent with oxidative addition via an S_N2' mechanism that breaks the aromaticity of the aryl substituent (Scheme 1B).[17] The dearomatization energy of the phenyl group appears to be too high for previous catalysts.[18] Traditionally, a difficult

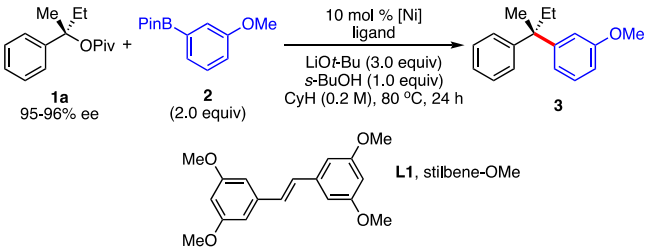
Received: April 13, 2021
Published: June 1, 2021

https://doi.org/10.1021/jacs.1c03898
J. Am. Chem. Soc. 2021, 143, 8608−8613

oxidative addition would be addressed by the use of an electron-rich, bulky phosphine ligand to lower the activation barrier of that step.[19] However, the use of such ligands had already met its limit. Even with the use of CyJohnPhos, a naphthyl-like group was required in our previous conditions, perhaps because of the steric requirements of oxidative addition to a bulky substrate.[10e] We also recognized that slow oxidative addition would necessitate efficient stabilization of the Ni(0) catalyst species to prevent catalyst death. We thus broadly considered potential ligands that could stabilize the key Ni(0) state but not shut down the oxidative addition reactivity. This search led us to consider alkenes that could stabilize the Ni(0) species and readily dissociate if needed for the oxidative addition.[20] Here we show that the use of a simple stilbene additive gives a new, surprisingly active catalyst system for the Suzuki–Miyaura arylation of tertiary pivalates (Scheme 1C). These conditions overcome the naphthyl requirement in the formation of highly enantioenriched diaryl quaternary stereocenters, dramatically increasing the utility of this reaction for the synthesis of valuable products.

The cross-coupling of 2-phenylbutan-2-yl pivalate (**1a**) and 3-methoxyphenylboronic acid pinacol ester (**2**) was chosen as the model reaction. After extensive optimization, we found that 94% yield and 96% ee (>99% es) could be achieved in the presence of 30 mol % stilbene **L1** as well as 10 mol % $Ni(OAc)_2{\cdot}4H_2O$, LiO*t*-Bu, and *s*-BuOH (Table 1, entry 1). This high yield and level of stereochemical fidelity are unprecedented in stereospecific cross-couplings of non-naphthyl-substituted substrates. As expected, control experiments showed that Ni is required (entry 2). However, a variety of Ni(II) salts can be employed (entries 3–5).[21] On the other hand, the use of $Ni(COD)_2$ resulted in only 45% yield in the presence of **L1** (entry 6). Notably, despite its supporting diene ligand, $Ni(COD)_2$ alone was a poor catalyst, giving only 18% yield (entry 7). This difference between **L1** and COD highlights the unique nature of the stilbene in this cross-coupling. The unique nature of **L1** is also seen in our ligand studies. The addition of **L1** seems to predominantly affect the yield of the reaction; without **L1**, 43% yield with 91% ee is observed (entry 8). This effect is also observed with $Ni(OTf)_2$, where the reaction without **L1** gives 16% yield with 90% ee (entry 9), and the addition of even 5 mol % **L1** increases the yield substantially (entries 10–12). Although other stilbenes have a similar effect,[22] the replacement of **L1** with other common ligands for Ni-catalyzed cross-couplings results in little to no yield (entries 13–17). Notably, the use of alkyl phosphines, such as PCy_3 and CyJohnPhos, resulted in β-hydride elimination, whereas no β-hydride elimination was observed with **L1**. Replacing **L1** with other alkenes used in Ni catalysis, such as styrenes, fumarates, and dienes, also failed to provide the beneficial effect of **L1**.[20,22] Additional control experiments demonstrated that LiO*t*-Bu is required (entry 18), and a strong dependence on the countercation was observed. The alcohol additive is also necessary to achieve high yields (entry 19), although this effect was not particularly sensitive to the alcohol structure.[22,23] Additionally, nonpolar solvents were best, with much lower yields observed in solvents such as 2-methyltetrahydrofuran (33%) and MeCN (0%).[22] This strong solvent dependence may suggest that the efficiency of this reaction is diminished if the solvent can competitively coordinate to the Ni species or that nonpolar solvents may promote beneficial π–π interactions. Finally, higher yields are achieved with the pivalate leaving group than with a Boc-protected alcohol. In addition, we have found that benzylic acetates lacking an extended aryl substituent are often unstable; the analogous pivalates are more robust, offering great ease in handling and avoiding decomposition under the cross-coupling conditions. Notably the reaction proceeds with stereoretention, similarly to our previous cross-couplings to form quaternary stereocenters.[10e]

Table 1. Optimization[a]



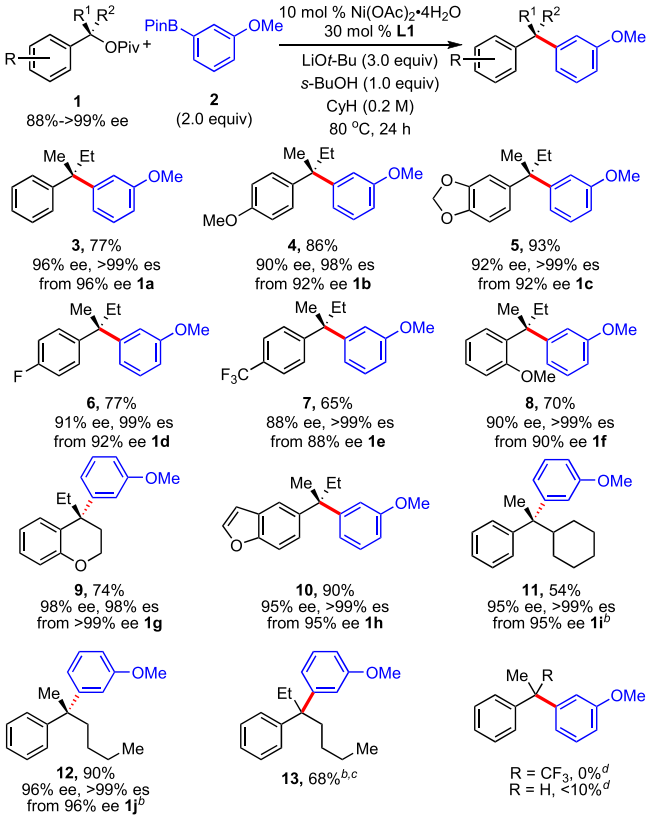
entry	[Ni]	L (mol %)	other deviation	yield (%)[b]	ee (es[c]) (%)[d]
1	$Ni(OAc)_2{\cdot}4H_2O$	**L1** (30)	–	94	96 (>99)
		Impact of [Ni]			
2	–	**L1** (30)	–	0	n.d.
3	$Ni(OAc)_2{\cdot}4H_2O$	**L1** (10)	–	88	96 (>99)
4	$Ni(TMHD)_2$[f]	**L1** (10)	–	87	92 (97)
5	$Ni(OTf)_2$	**L1** (10)	–	84	95 (99)
6	$Ni(COD)_2$	**L1** (10)	–	45	95 (99)
7[e]	$Ni(COD)_2$	(0)	–	18	n.d.
		Impact of the Ligand			
8	$Ni(OAc)_2{\cdot}4H_2O$	(0)	–	43	91 (95)
9	$Ni(OTf)_2$	(0)	–	16	90 (94)
10	$Ni(OTf)_2$	**L1** (5)	–	78	95 (99)
11	$Ni(OTf)_2$	**L1** (10)	–	84	95 (99)
12	$Ni(OTf)_2$	**L1** (30)	–	90	96 (>99)
13[e]	$Ni(OAc)_2{\cdot}4H_2O$	PPh_3 (30)	–	0	n.d.
14[e]	$Ni(OAc)_2{\cdot}4H_2O$	PCy_3 (30)	–	<5	n.d.
15[e]	$Ni(OAc)_2{\cdot}4H_2O$	bipy (30)	–	0	n.d.
16[e]	$Ni(OAc)_2{\cdot}4H_2O$	phen (30)	–	0	n.d.
17[e]	$Ni(OAc)_2{\cdot}4H_2O$	terpy (30)	–	0	n.d.
		Additional Control Experiments			
18	$Ni(OAc)_2{\cdot}4H_2O$	**L1** (30)	w/o LiO*t*-Bu	0	n.d.
19	$Ni(OAc)_2{\cdot}4H_2O$	**L1** (30)	w/o *s*-BuOH	36	95 (99)

[a]Conditions: **1a** (0.10 mmol), **2** (2.0 equiv), [Ni] (10 mol %), ligand, LiO*t*-Bu (3.0 equiv), *s*-BuOH (1.0 equiv), CyH (0.2 M), 80 °C, 24 h, unless noted otherwise. [b]Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c]es = $(ee_{product})/(ee_{starting\ material})$. [d]Determined by HPLC using a chiral stationary phase. n.d. = not determined. [e](±)-**1a**. [f]TMHD = 2,2,6,6-tetramethyl-3,5-heptanedionate.

Under these optimized conditions, we observed high yields and stereochemical fidelity across a range of pivalates (Scheme 2). Substrates with both electron-rich (**4**, **5**) and electron-poor (**7**) aryl groups were tolerated. The electron-poor examples were particularly noteworthy, as they do not benefit from the lower dearomatization energies that electron-donating substituents can provide.[18c] Even product **7** with a strong electron-

https://doi.org/10.1021/jacs.1c03898
J. Am. Chem. Soc. 2021, 143, 8608–8613

Scheme 2. Pivalate Scope[a]

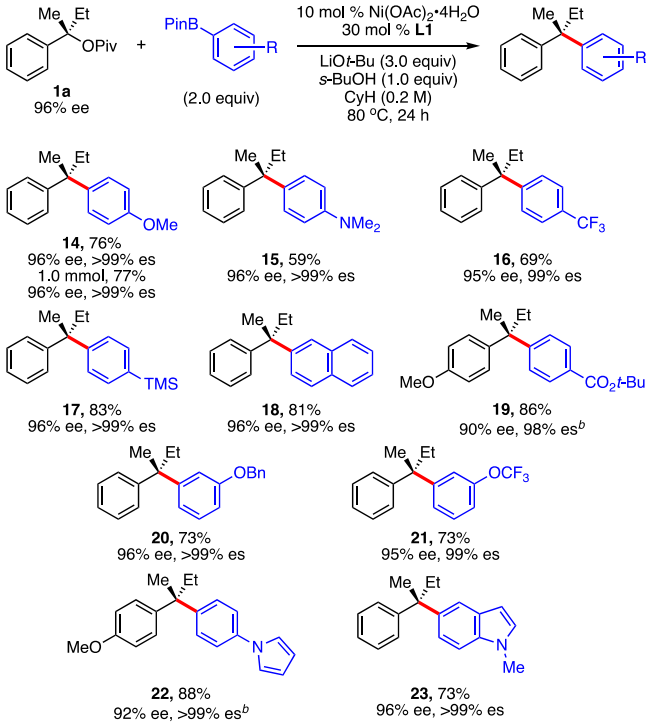


[a]Conditions: pivalate **1** (0.40 mmol), ArBpin (2.0 equiv), $Ni(OAc)_2 \cdot 4H_2O$ (10 mol %), **L1** (30 mol %), LiO*t*-Bu (3.0 equiv), *s*-BuOH (1.0 equiv), CyH (0.2 M), 80 °C, 24 h. Average isolated yields (±4%) and ee's (±1%, determined by HPLC analysis using a chiral stationary phase) of duplicate experiments are shown. [b]Single experiment. [c]Enantiomers could not be resolved. [d](±)-**1** was used.

withdrawing *p*-trifluoromethylphenyl group was formed; a high yield with such an electron-poor aryl substituent is unprecedented for these stereospecific cross-couplings. Steric encumbrance was also tolerated, as demonstrated by the bulky *o*-anisole substituent in product **8**. With respect to heterocycles, both chromane (**9**) and benzofuran (**10**) were well-tolerated in the pivalate. A variety of alkyl substituents were also accommodated on the benzylic carbon (R^1, R^2). Notably, cyclic substrates could be used, making quaternary stereocenters in rings (**9**) accessible. Bulkier alkyl substituents could also be used (**9**, **11**−**13**), although somewhat diminished yields were observed for branched alkyl groups (**11**). However, trifluoromethyl substitution shut down the reaction, and secondary benzyl pivalates resulted in only trace product, perhaps because of the incompatibility of the acidity of the benzylic proton under these basic conditions. Further studies will address these limitations. Nonetheless, for all of the products formed, excellent levels of stereochemical fidelity were observed.

On the arylboronate ester side, a wide scope was also observed (Scheme 3). Both electron-rich (**14**, **15**) and electron-poor (**16**, **19**, **21**) arylboronates reacted in high yield and stereochemical fidelity. Notably, the cross-coupling to form **14** gave nearly identical results when performed on a 1 mmol scale. Various functional groups can be used, including trimethylsilyl (**17**), a polycyclic aromatic hydrocarbon (**18**), a

Scheme 3. Arylboronate Ester Scope[a]



[a]Conditions: pivalate **1a** (0.40 mmol), ArBpin (2.0 equiv), $Ni(OAc)_2 \cdot 4H_2O$ (10 mol %), **L1** (30 mol %), LiO*t*-Bu (3.0 equiv), *s*-BuOH (1.0 equiv), CyH (0.2 M), 80 °C, 24 h. Average isolated yields (±10%) and ee's (±0%, determined by HPLC analysis using a chiral stationary phase) of duplicate experiments are shown. [b]**1b** (92% ee) was used.

tert-butyl ester (**19**), a benzyl aryl ether (**20**), and a trifluoromethyl ether (**21**). Heterocycles, including pyrrole (**22**) and indole (**23**), also worked as well. However, lower yields were observed with ortho substituents (45% yield with *o*-tolylboronic ester), and alkenes, alkynes, and protic functional groups were not tolerated.[22]

With respect to the mechanism, we are intrigued by the role that stilbene **L1** plays in the reaction. With the hypothesis that the cross-coupling of non-naphthyl-substituted electrophiles has been traditionally limited by a difficult oxidative addition, we assume that the presence of **L1** must influence that step.[20,24] To probe the role of **L1**, we studied the kinetic profile of the reaction of pivalate (±)-**1a** and 3,4,5-trimethoxyphenylboronic ester, which had greater solubility than other boronic esters. As before, we observed a significant difference in the yield when **L1** is present; the reaction without **L1** barely proceeds (Figure 1A). Surprisingly, however, a significant induction period was observed in both the presence and absence of **L1**, with the shortest induction period observed for 30 mol % **L1**. Our efforts to eliminate this induction period via activation of the boronic ester, reduction of the Ni(II) precatalyst, and addition of byproducts to test for autocatalysis failed.[22] We also observed that the identity of the stilbene additive does not affect the reaction profile (Figure 1B), and no trend between stilbene substitution and stereochemical fidelity is apparent.[22] We also observed >90% recovery of **L1** in the cross-coupling. These results, as well as the fact that the primary impact of **L1** is on the yield and the increase in es is modest (95 to >99% es), suggest that **L1**'s primary role may be in the formation of the active catalyst as a ligand. **L1** may also

https://doi.org/10.1021/jacs.1c03898
J. Am. Chem. Soc. 2021, 143, 8608−8613

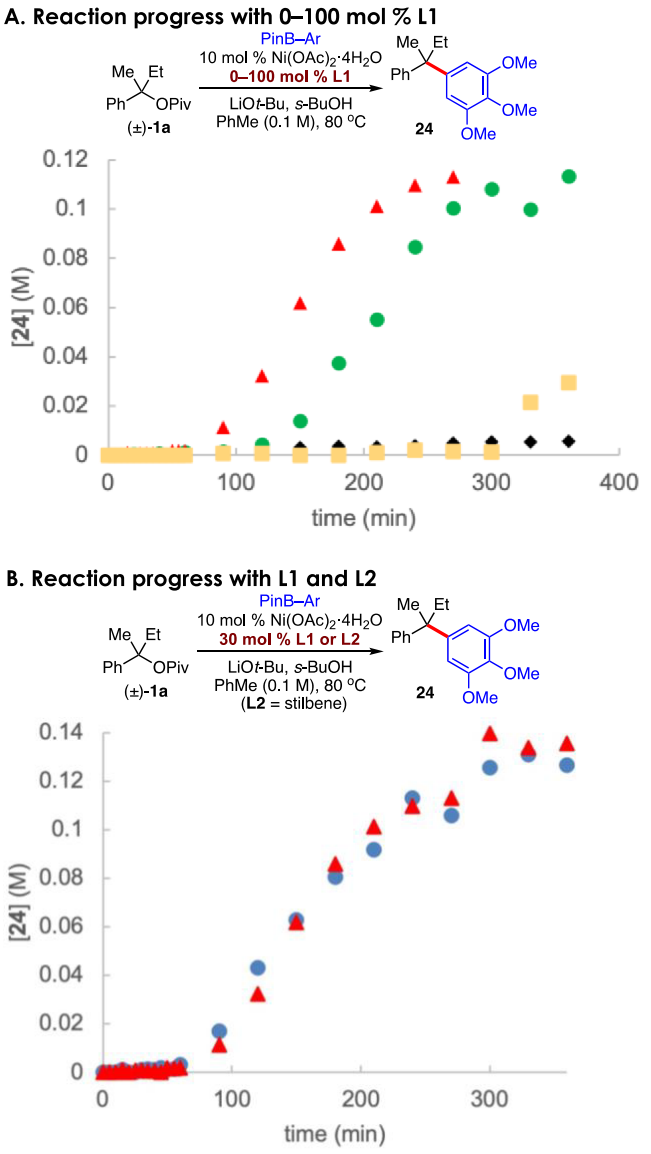


Figure 1. (A) Comparison of reaction progress in the presence of varying amounts of **L1**: black ◆, 0 mol % **L1**; green ●, 10 mol % **L1**; red ▲, 30 mol % **L1**; yellow ■, 100 mol % **L1**. (B) Comparison of reaction progress with **L1** (red ▲) and **L2** (stilbene, blue ●).

serve additional roles: the observation that 100 mol % **L1** is worse than 30 mol % **L1** (see Figure 1A) suggests that **L1** may have an inhibitory effect, perhaps by driving Ni(0) off the catalytic cycle into a reservoir. In addition, **L1** may serve an important role in preventing β-hydride elimination by blocking the necessary open coordination site on the Ni(II) intermediate. Indeed, these latter possibilities would explain why more tightly binding and more electron-deficient alkenes fail to promote this cross-coupling; the fluxional nature of the Ni/stilbene coordination may be important to traverse the catalytic cycle.[25] Ongoing studies are directed toward a thorough investigation of these possibilities as well as determining how the alcohol additive promotes the reaction.

In summary, we have discovered novel conditions for the nickel-catalyzed stereospecific Suzuki–Miyaura cross-coupling. With the identification of a stilbene as a supporting ligand, we have overcome the longstanding requirement for a naphthyl substituent in stereospecific cross-couplings of benzylic electrophiles. With this methodology, we can now utilize an unprecedented scope of enantioenriched tertiary pivalates to deliver all-carbon quaternary stereocenters in high yields and stereochemical fidelities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c03898.

Experimental details and data (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank NIH (R01 GM111820, R35 GM131816). Data were acquired at UD on instruments obtained with the 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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