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Enantioselective 1,1-Arylborylation of Alkenes: Merging Chiral Anion Phase Transfer with Pd Catalysis

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Abstract

A palladium-catalyzed three-component coupling of *a*-olefins, aryldiazonium salts, and bis-(pinacolato)diboron affords direct access to chiral benzylic boronic esters. This process is rendered highly enantioselective using an unprecedented example of cooperative chiral anion phase transfer and transition-metal catalysis.

Benzylic boronic esters are attractive building blocks for complex biologically active natural products and pharmaceuticals as they participate in several well-established stereospecific transformations that forge C–O, C–N, or C–C bonds.[1] Accordingly, there has been significant interest in developing new enantioselective methods that afford these motifs. Examples of catalytic enantioselective hydroboration,[2] allylic borylation,[3] conjugate borylation,[4] reductive transformations of vinyl boronates[5] and 1,2-diborylation of aromatic imines and styrenes have been reported.[6] Furthermore, several enantioselective borylation reactions utilizing stoichiometric amounts of chiral auxiliaries have been disclosed.[7] Recently, several methods have been reported that rely on transformations of 1,1-diborylated alkanes. For example, Hall[8] and Yun[9] have reported the preparation of enantioenriched 1,1-diborylated alkanes that undergo chemoselective coupling to provide highly enantioenriched benzylic organoboronates (Figures 1a and 1b). In a related contribution, Morken and co-workers have disclosed an enantioselective Suzuki reaction of 1,1-diboronates to provide highly enriched boronic esters (Figure 1c).[10] While these methods ultimately access valuable enantioenriched benzylic boronates, they require a multistep synthetic sequence. From the perspective of synthetic divergence and step-economy, an ideal transformation would involve one-step installation of both the boronate and aryl functional groups (Figure 1d).

Inspired by seminal examples of Pd-catalyzed 1,1-diarylation from Sigman and co-workers,[11,12] we envisioned direct formation of 1,1-arylborylated products (9) from unactivated olefins (7) via a three-component Heck–Matsuda arylation/Miyuara borylation cascade reaction (Figure 1d). In these initial reports, efficient 1,1-difunctionalization required "ligand-free" conditions, as efforts to induce enantioselectivity through application of chiral ligands attenuated the desired three-component reaction pathway.[12] Cognizant of this limitation, we were intrigued by the possibility of providing enantioinduction via a chiral ion-pairing strategy. While the intermediacy of non-cationic Pd(0) species presented a challenge due to the lack of continuous Coulombic attraction between the chiral anion and a cationic metal center, we hypothesized that a chiral anion phase-transfer (CAPT) strategy[13-15] could enable association of a chiral anion with the key cationic Pd(II) intermediates involved in the enantiodetermining step. In this scenario, an insoluble aryldiazonium salt (**11**, Figure 2) would undergo phase transfer to provide soluble, chiral ion pair **12**.[16,17] Oxidative addition of the Pd(0) species followed by migratory insertion of the olefinic coupling partner would yield chiral Pd complex **14**. Sequential β-hydride elimination and reinsertion steps would yield enantioenriched benzylic Pd complex **15** that is poised to undergo transmetalation and subsequent reductive elimination to provide the desired benzylic boronic ester. Importantly, the non-cationic Pd(0) species generated in this process can be reoxidized by soluble diazonium chiral ion pair **12** to regenerate the chiral Pd(II) species **13**. In this Communication we report the successful execution of this methodological hypothesis through the single-step 1,1-arylbor-ylation of α-olefins, with high levels of enantioselectivity achieved via implementation of a CAPT strategy.

Given the lack of precedent for this transformation, we sought to provide proof-of-principle with the development of a non-stereoselective 1,1-arylborylation of α-olefins. We were pleased to find that a room-temperature THF suspension of catalytic $Pd_2(dba)_3$, phenyldiazonium tetrafluoroborate, allyl methyl carbonate, and bis(pinacolato)diboron smoothly provided racemic boronate **16** in 72% yield (Table 1). Both electron-rich (**17**) and electron-poor aryldiazonium salts (**18**) proved competent in the transformation of allyl methyl carbonate to provide boronic esters **17** and **18** in 90% and 71% yield, respectively. Use of *ortho*-substituted aryldiazonium cations also provided the product in good yield (**19**). Notably, utilization of homoallylic carbonates (**20**), as well as protected allylic amines, furnished the borylated products in good to excellent yields (**21,22**). Further, a nitrile-substituted substrate underwent smooth arylborylation in 99% yield, demonstrating that substrates containing chelating groups did not impede the reaction (**23**). As an important demonstration of scope, electron poor alkenes were also effective under our reaction conditions, providing the arylborylated products **24–26**, albeit in diminished yields.[18]

Having provided proof-of-principle for a single-step 1,1-arylborylation reaction, we began work toward rendering the process enantioselective via CAPT. Utilizing allyl methyl carbonate and phenyldiazonium tetrafluoroborate, an extensive study of reaction conditions was undertaken. In initial experiments, nonpolar solvents such as hexanes provided poor conversion (Table 2, entry 1), while THF allowed for excellent conversion albeit with poor enantioselectivity (entry 2). Et_2O was identified as optimal, furnishing the product in 33% ee and 45% yield (entry 3).[19] Examination of commonly employed CAPT catalysts (**27–29**)

identified TCyP (**27**) as superior in terms of enantioselectivity, providing the desired product in 88% ee (entry 5). Further, Na_3PO_4 provided the highest yield of the bases examined, furnishing the product in 36% yield (entry 7). Finally, addition of exogenous dibenzylideneacetone (dba) derivatives[20] (**30**) improved the efficiency of the reaction, with *m*-CF$_3$-dba (**30b**) allowing for retention of enantioselectivity, providing the product in 39% yield and 90% ee (entry 9).[21]

With optimized conditions in hand, we examined the aryldiazonium scope. Utilizing allyl methyl carbonate we found that aryldiazonium salts functionalized with a methoxy group at the *meta*- or *para*-positions provided products in synthetically useful yields and good to excellent enantioselectivities (Table 3a, **32** and **33**). Alkyl substitution of the *para*- or *meta*-positions also provided highly enantioenriched benzylic boronic ester products (**34–37**). Finally, substitution with a vinyl group at the *para*-position afforded enriched boronic ester (**38**) in 40% yield and 98% ee.

In addition to protected allylic alcohols, *α,β*-unsaturated esters were utilized as an alternative olefinic precursor for the enantioselective transformation (Table 3b). Notably, use of *m*-CF$_3$-dba (**30b**) was not required to achieve useful yields and high enantioselectivities with acrylate coupling partners. Utilization of phenyldiazonium tetrafluoroborate allowed for formation of *β,β*-arylborylated ester **40** in 47% yield and 89% ee. The aryl moiety of the diazonium salt was tolerant of substitution of the *para*-position with heteroatom or alkyl functional groups, providing a variety of *β,β*-arylborylated esters in synthetically useful yields and excellent enantioselectivities (**41–44**).

In conclusion, we have disclosed a modular and step-economical method for the direct preparation of chiral benzylic boronates from terminal alkenes. Furthermore, this process was rendered enantioselective through the use of a chiral anion phase-transfer strategy. We expect the coupling of CAPT and Pd catalysis to have broad implications, as it provides an alternative strategy for achieving enantioinduction in "ligandless" reaction manifolds where chiral ancillary ligands have a deleterious effect.[22]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

REFERENCES

(1). (a) Hall, DG. Boronic Acids. 2nd ed.. Wiley-VCH; Weinheim: 2011. (b) Crudden CM, Edwards D. Eur. J. Org. Chem. 2003:4695.

(2). (a) Carroll AM, O'Sullivan TP, Guiry PJ. Adv. Synth. Catal. 2005; 347:609.(b) Smith SM, Takacs JM. J. Am. Chem. Soc. 2010; 132:1740. [PubMed: 20092272] (c) Corbera R, Mszar NW, Hoveyda AH. Angew. Chem., Int. Ed. 2011; 50:7079.

(3). (a) Guzman-Martinez A, Hoveyda AH. J. Am. Chem. Soc. 2010; 132:10634. [PubMed: 20681681] (b) Park JK, Lackey HH, Ondrusek BA, McQuade DT. J. Am. Chem. Soc. 2011; 133:2410. [PubMed: 21291218]

(4). Calow AD, Whiting A. Org. Biomol. Chem. 2012; 10:5485. [PubMed: 22717773]

(5). (a) Ding J, Lee JCH, Hall DG. Org. Lett. 2012; 14:4462. [PubMed: 22894652] (b) Morgan JB, Morken JP. J. Am. Chem. Soc. 2004; 126:15338. [PubMed: 15563134] (c) Lee JCH, Hall DG. J. Am. Chem. Soc. 2010; 132:5544. [PubMed: 20355729]

(6). (a) Kliman LT, Mlynarski SN, Morken JP. J. Am. Chem. Soc. 2009; 131:13210. [PubMed: 19702329] (b) Hong K, Morken JP. J. Am. Chem. Soc. 2013; 135:9252. [PubMed: 23763463]

(7). (a) Matteeon DS, Sadhu KM, Ray R, Peterson ML, Majumdar D, Hunt GD, Jemthi PK, Teai DJS, Erdik B. Pure Appl. Chem. 1988; 57:1741.(b) Beckmann E, Desai V, Hoppe D. Synlett. 2004; 13:2275.(c) Beenen MA, An C, Ellman JA. J. Am. Chem. Soc. 2008; 130:6910. [PubMed: 18461938] (d) Scott HK, Aggarwal VK. Chem.—Eur. J. 2011; 17:13124. [PubMed: 22052475]

(8). Lee JCH, McDonald R, Hall DG. Nat. Chem. 2011; 3:894. [PubMed: 22024887]

(9). Feng X, Jeon H, Yun J. Angew. Chem., Int. Ed. 2013; 52:3989.

(10). Sun C, Potter B, Morken JP. J. Am. Chem. Soc. 2014; 136:6534. [PubMed: 24564423]

(11). (a) Saini V, Sigman MS. J. Am. Chem. Soc. 2012; 134:11372. [PubMed: 22765909] (b) Liao L, Jana R, Urkalan KB, Sigman MS. J. Am. Chem. Soc. 2011; 133:5784. [PubMed: 21449562]

(12). Saini V, Liao L, Wang Q, Jana R, Sigman MS. Org. Lett. 2013; 15:5008. [PubMed: 24047468]

(13). (a) Rauniyar V, Lackner AD, Hamilton GL, Toste FD. Science. 2011; 334:1681. [PubMed: 22194571] (b) Lackner A, Samant A, Toste FD. J. Am. Chem. Soc. 2013; 135:14090. [PubMed: 24025122] (c) Neel AJ, Hehn JP, Tripet PF, Toste FD. J. Am. Chem. Soc. 2013; 135:14044. [PubMed: 24025163] (d) Yang X, Phipps RJ, Toste FD. J. Am. Chem. Soc. 2014; 136:5225. [PubMed: 24684209] (e) Zi W, Wang Y-M, Toste FD. J. Am. Chem. Soc. 2014; 136:12864. [PubMed: 25203796]

(14). (a) Hamilton GL, Kang EJ, Mba M, Toste FD. Science. 2007; 317:406.(b) Mukherjee S, List B. J. Am. Chem. Soc. 2007; 129:11336. [PubMed: 17715928] (c) Rauniyar V, Wang ZJ, Burks HE, Toste FD. J. Am. Chem. Soc. 2011; 133:8486. [PubMed: 21561153] (d) Jiang G, Halder R, Fang Y, List B. Angew. Chem., Int. Ed. 2011; 50:9752.

(15). (a) Phipps RJ, Hamilton GL, Toste FD. Nature Chem. 2012; 4:603. [PubMed: 22824891] (b) Brak K, Jacobsen EN. Angew. Chem., Int. Ed. 2013; 52:534.(c) Mahlau M, List B. Angew. Chem., Int. Ed. 2013; 52:518.

(16). Nelson HM, Reisberg SH, Shunatona HP, Patel JS, Toste FD. Angew. Chem., Int. Ed. 2014; 53:5600.

(17). Nelson HM, Patel JS, Shunatona HP, Toste FD. Chem. Sci. 2015; 6:170. [PubMed: 25485073]

(18). Unfunctionalized alkenes afforded the product in lower yields. For example, 1-octene underwent arylborylation in 37% yield. In the enantioselective reaction, the desired product was obtained in trace amounts, and the corresponding sytrene constituted the primary product.

(19). The major byproduct in the enantioselective arylborylation reaction of both the allylic alcohol and acrylate substrates was the corresponding styrene. Unlike the non-enantioselective reaction in THF solvent, use of Et$_2$O solvent and phase-transfer catalyst results in significant termination via β-hydride elimination.

(20). The dba derivatives utilized in this study were prepared according to the procedure outlined in the following report: Kapdi AR, Whitwood AC, Williamson DC, Lynam JM, Burns MJ, Williams TJ, Reay AJ, Holmes J, Fairlamb IJS. J. Am. Chem. Soc. 2013; 135:8388. [PubMed: 23701049]

(21). While the role of dba derivatives in improving the efficiency of this process has not been rigorously investigated, and direct ligand exchange between Pd$_2$(dba)$_3$ and m-CF$_3$-dba has not been observed under the reaction conditions, we attribute this effect to stabilization of unobservable Pd species along the catalytic cycle.

(22). For an alternative approach to the use of chiral anions in palladium catalysis with achiral cationic ancillary ligands, see: Ohmatsu K, Ito M, Kunieda T, Ooi T. J. Am. Chem. Soc. 2013; 135:590. [PubMed: 23270455] Ohmatsu K, Yoshiyuki H, Ooi T. Chem. Sci. 2014; 5:3645. Ohmatsu K, Ito M, Kunieda T, Ooi T. Nat. Chem. 2012; 4:473. [PubMed: 22614382]

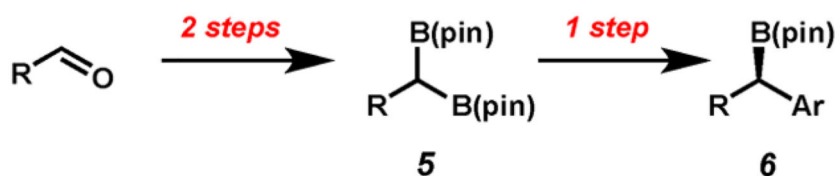a) Hall, *Nature Chem.*, **2011**
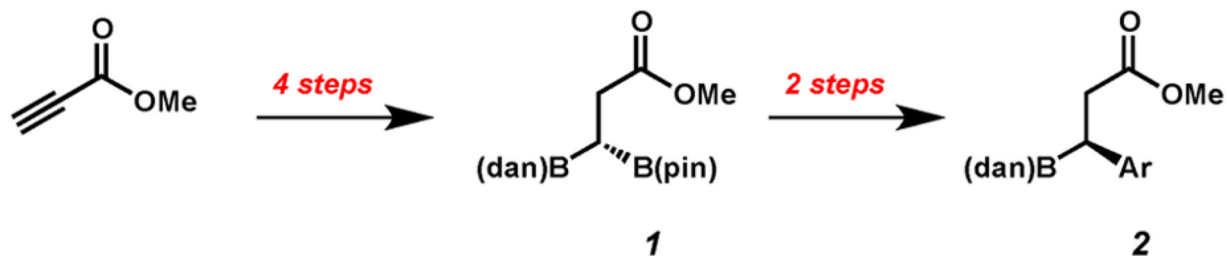
b) Yun, *Angew. Chem., Int. Ed.*, **2013**
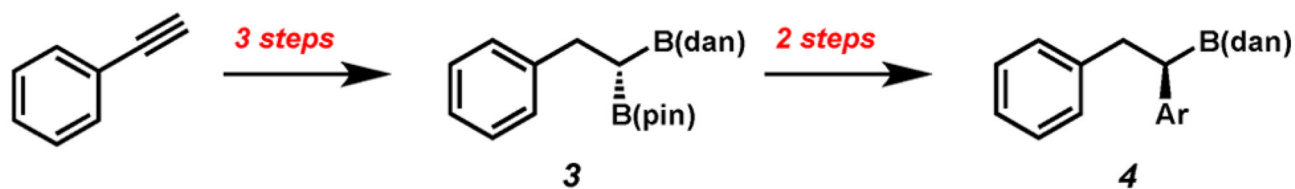
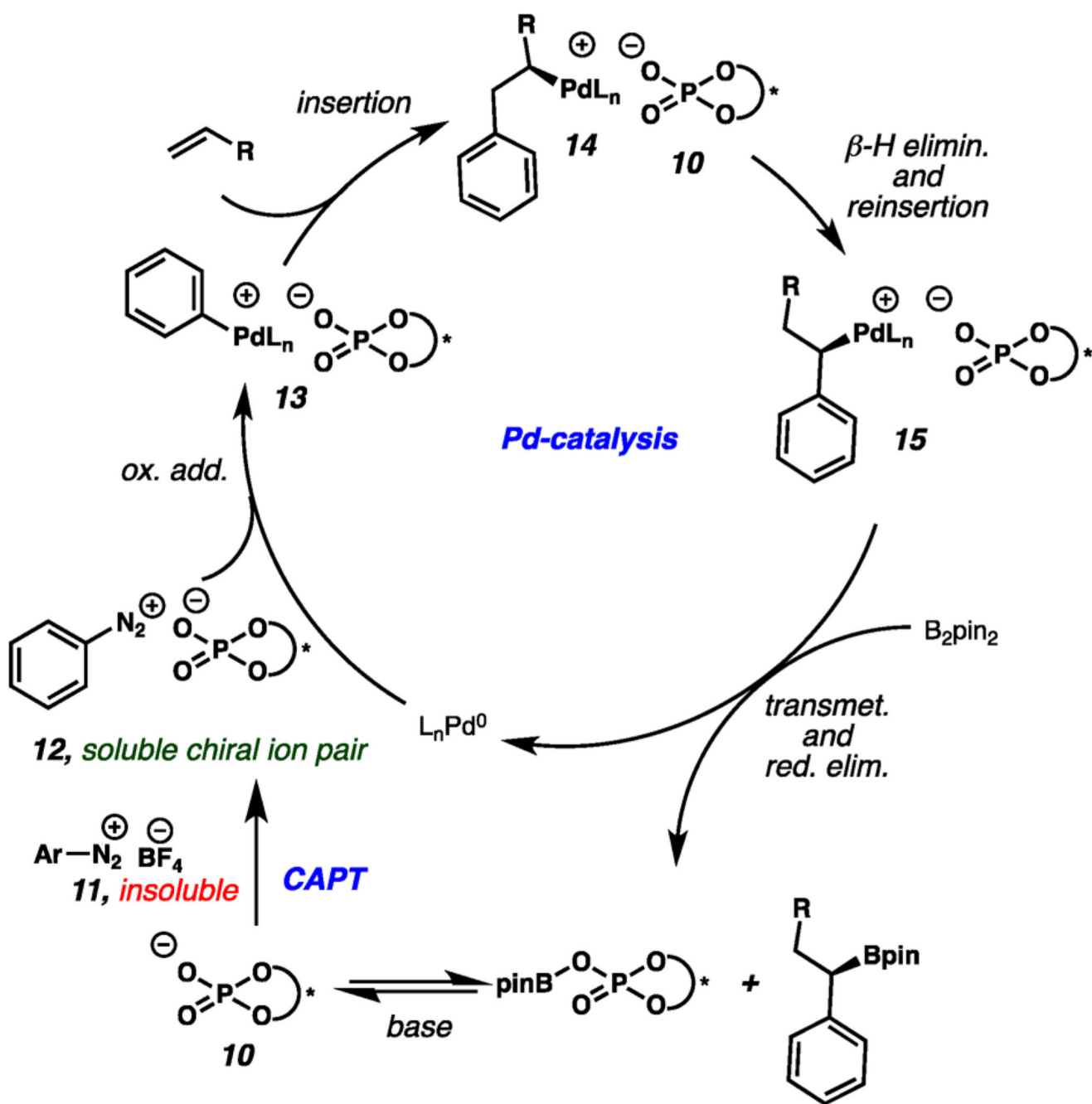c) Morken, *J. Am. Chem. Soc.*, **2014**

d) *this work*

Figure 1.
Recent examples of multistep enantioselective 1,1-arylborylation by (a) Hall and co-workers, (b) Yun and co-workers, (c) Morken and co-workers, and (d) the single-step 1,1-arylborylation reported herein. dan = 1,8-diaminonaphthalene; pin = pinacolato.

Figure 2.
Proposed dual catalytic cycle for Pd-CAPT 1,1-arylborylation.

Table 1

Non-enantioselective Scope[a,b]
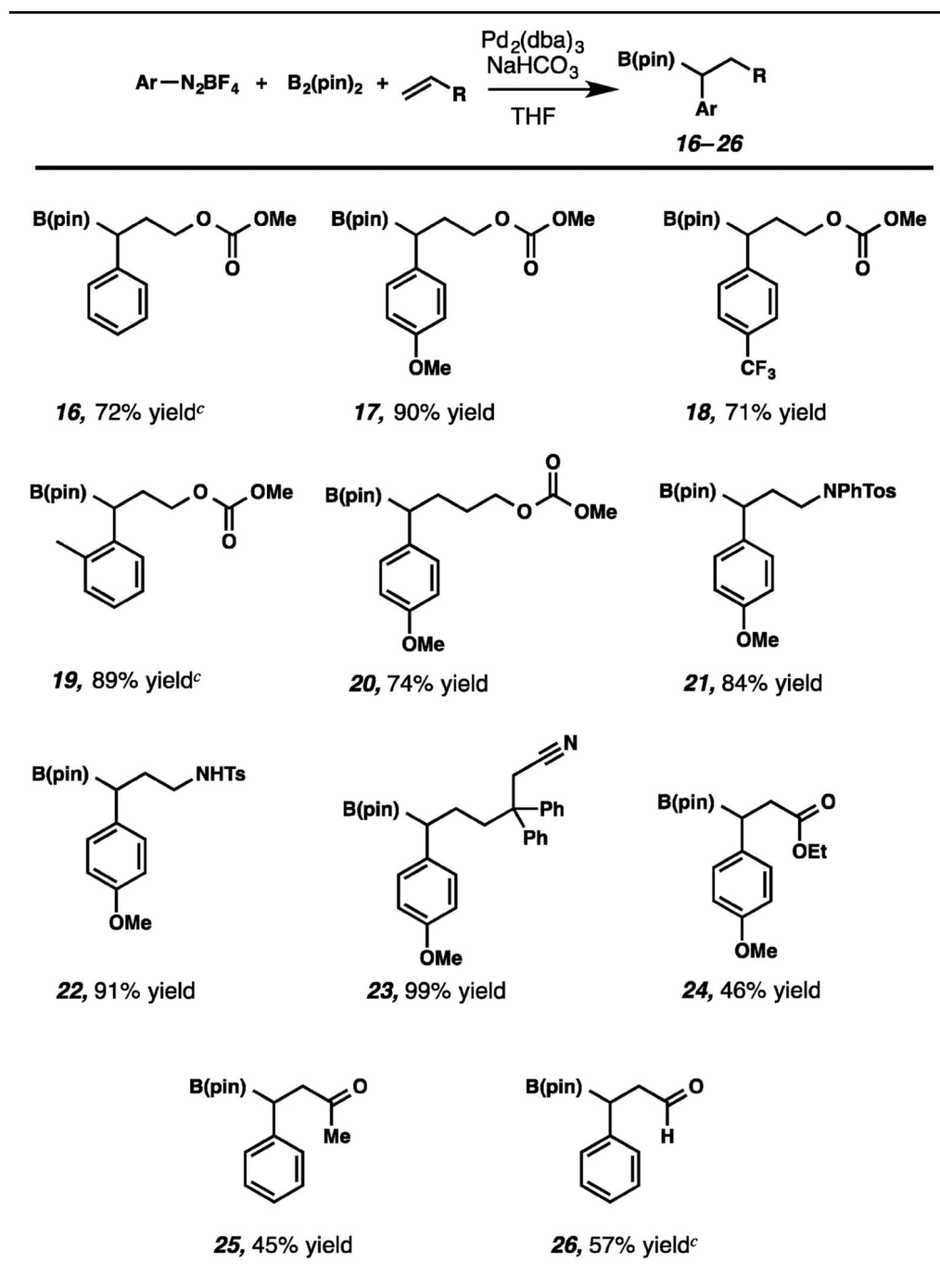
a Conditions: ArN$_2$BF$_4$ (1 equiv), B$_2$(pin)$_2$ (1.2 equiv), Pd$_2$(dba)$_3$ (0.025 equiv), alkene (1 equiv), THF, 25 °C, 2–8 h.
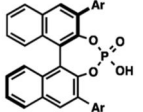
b Isolated yields.

^{c}NMR yield.
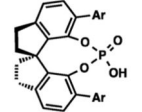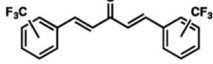
Table 2

Optimization of Enantioselective 1,1-Arylborylation[a,b]
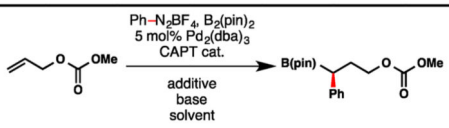
entry	cat.	solvent	base	additive	ee (%)	yield (%)
1	28	hexanes	NaHCO$_3$	–	–	<5
2	28	THF	NaHCO$_3$	–	<5	72
3	28	Et$_2$O	NaHCO$_3$	–	33	45
4	29	Et$_2$O	NaHCO$_3$	–	<5	14
5	27	Et$_2$O	NaHCO$_3$	–	88	25
6	27	Et$_2$O	K$_2$CO$_3$	–	94	25
7	27	Et$_2$O	Na$_3$PO$_4$	–	93	26
8	27	Et$_2$O	Na$_3$PO$_4$	30a	70	40
9	27	Et$_2$O	Na$_3$PO$_4$	30b	90	39

[a]Enantiomeric excess determined by chiral phase HPLC.

[b]Yield determined by ^{1}H NMR utilizing dimethyl sulfone as an internal standard.

Table 3

Enantioselective Scope[a,b]

a)

Ar–N$_2$BF$_4$, B$_2$(pin)$_2$
5 mol% Pd$_2$(dba)$_3$
10 mol% TCyP (27)
16 mol% m-CF$_3$-dba(30)

Na$_3$PO$_4$, Et$_2$O

31 → (pin)B / Ar

32–38

32, 36% yield
84% ee

33, 58% yield
87% ee

34, 46% yield
84% ee

35, 32% yield
96% ee

36, 50% yield
85% ee

37, 50% yield
88% ee

38, 40% yield
98% ee

b)

Ar–N$_2$BF$_4$, B$_2$(pin)$_2$
5 mol% Pd$_2$(dba)$_3$
10 mol% TCyP (27)
Na$_3$PO$_4$, Et$_2$O

39 → 40–44

40, 47% yield
89% ee

41, 40% yield
97% ee

42, 33% yield
98% ee

43, 44% yield
84% ee

44, 29% yield
98% ee

[a] Enantiomeric excess determined by chiral phase HPLC.

[b] Yield determined by ^{1}H NMR utilizing dimethyl sulfone as an internal standard.