Published in final edited form as:

Chemistry. 2018 September 25; 24(54): 14378–14381. doi:10.1002/chem.201803543.

Enantioselective α -Allylation of Acyclic Esters using B(pin)-Substituted Electrophiles: Independent Regulation of Stereocontrol Elements via Cooperative Pd/Lewis Base Catalysis

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Abstract

Cooperation between Lewis base and Pd catalysts enables the direct enantioselective α -functionalization of aryl and vinyl acetic acid esters using a bifunctional B(pin)-substituted electrophile. Critical to the success of this method was the recognition that both catalysts could control the necessary stereochemical aspects; the Lewis base catalyst controls the enantioselectivity of the reaction, while the Pd catalyst regulates alkenylB(pin) configuration. This is the first example of using cooperative catalysis to control both stereochemical features during Pd-catalyzed allylic alkylation.

Keywords

cooperative catalysis; C1-ammonium enolate; palladium; Lewis base, boron

Organoboron reagents enable a raft of transformations and are ubiquitous within organic synthesis.^[1] Exemplifying this, the Pd-catalyzed Suzuki–Miyaura reaction has revolutionized both academic and industrial research as a workhorse for the construction of C(sp²)–C(sp²) bonds.^[2–4] Beyond Pd-catalyzed cross coupling, organoboron reagents are harnessed extensively for stereoselective reagent- and catalyst-controlled homologation reactions, which enable the rapid and modular construction of stereochemically rich 3D-molecular scaffolds.^[5]

The broad reactivity and synthetic utility conferred by organoboron reagents renders methods for their preparation highly desirable. However, while arylboronic acids and esters are easily accessible the corresponding vinylboron species are more challenging to prepare, as control over the alkene geometry is necessary^[6] and their greater susceptibility to protodeboronation can be problematic.^[7] One such method involves the use of bifunctional

Conflict of Interest

The authors declare no conflict of interest.

borylated building blocks, which simultaneously combines catalyzed bond formation with the concomitant incorporation of a synthetically versatile vinylboron moiety (Figure 1a). Walsh and co-workers have investigated the reactivity and utility of B(pin)-substituted electrophiles in Pd-catalyzed allylic alkylation reactions and described the factors governing chemoselective allylic alkylation in preference to potentially competing Suzuki–Miyaura cross coupling.^[8] Building on this seminal work, Pucheault employed (*E*)-B(pin)-substituted enantioenriched secondary allylic acetate in Pd-catalyzed allylic alkylations using malonate nucleophiles giving highly enantioenriched products.^[9] However, there are no reported examples of enantioselective Pd-catalyzed allylic alkylation using B(pin)-substituted electrophiles.

Our laboratory has a long-standing interest in enantioselective transition metal-catalyzed allylic alkylation reactions. These are amongst the most useful and versatile methods for asymmetric C(sp³)-C(sp³) bond formation and central to their versatility is ability to control regio- and stereo-selectivity by altering the steric and electronic profile of the substrate, the metal itself and/or the supporting ligands.^[10] We have recently disclosed a cooperative catalysis platform for asymmetric Pd-catalyzed allylic alkylation.^[11] This process exploits C1-ammonium enolates as catalytically accessible ester enolate equivalents that are stereodefined and chiral by virtue of a chiral amine Lewis base, and provide a potentially general approach to the α -alkylation of aryl and vinyl acetic acid esters.

Motivated by the synthetic potential of bifunctional reagents and attracted to the aforementioned versatility of vinylboronic esters, we sought to combine our cooperative catalysis framework with B(pin)-substituted electrophiles as an expansive means for the rapid construction of enantioenriched molecular scaffolds via programmed elaboration (Figure 1b). Key to the development of this process would be identification of suitable catalyst/ligand system to control not only electrophile reactivity and avoid competing unproductive processes such as protodeboronation, but also afford sufficient control of over alkene geometry.^[12] We expected our cooperative catalysis framework would be perfectly suited to this challenge as the supporting ligands on Pd can be tuned and modified without compromising enantiocontrol, which resides with the Lewis base catalyst.^[10] Herein, we disclose an operationally simple cooperative catalysis protocol for the asymmetric α -allylation of linear esters using B(pin)-substituted electrophiles to provide versatile and highly enantioenriched products that can be further elaborated in orthogonal fashion.

We began by assessing the compatibility of (*E*)-B(pin)-substituted allyl mesylate **1** as an electrophilic partner in the allylation of pentafluorophenyl (Pfp) acetic ester **2**. We have previously described the high reactivity and superior levels of enantiocontrol of Birman's benzotetramisole (BTM)^[13] Lewis base catalyst during related cooperative regimes and thus sought to establish the effect of the supporting phosphine ligands on Pd(0).^[11] Using Xantphos we were delighted to observe high yields of the expected allylated product **3a** (Table 1, Entry 1) with encouraging levels of *E/Z* selectivity and excellent levels of enantioinduction. Further assessment of common bidentate ligands (Entries 2–5) identified ($\pm$)-BINAP as superior in its governance of alkene stereochemistry. Assessment of a representative range of common monodentate phosphines offered more modest levels of control of alkene stereochemistry (Entries 6–9). Notably, superb levels of enantioselectivity

were excellent independent of the ligand employed, which only affected the alkene geometry. Having identified BINAP as the most effective ligand (Entry 5) we then assessed the effect of the reaction solvent (Entries 10–12) and obtained the product **3a** with excellent levels of enantiocontrol but as a single (*E*)-alkene isomer in 1,4-dioxane (Entry 11). Finally, and in respect of BINAP being chiral, we sought to establish its capacity to further enhance the enantioselectivity of the reaction in an additive manner.

Employing (*S*)-BINAP in combination with (*S*)-BTM resulted in a very small but measurable enhancement in enantioselectivity due to a stereoreinforcing *matched* effect (Entry 13). Using the antipodal (*R*)-BINAP with (*S*)-BTM resulted in the equivalent *mismatched* outcome where enantioselectivity was slightly diminished (Entry 14). Finally, the control reaction employing the achiral Lewis base DHPB in combination with (*R*)-BINAP gave equivalent levels of slightly enantioenriched **3a** (Entry 15). Thus, using enantiopure BINAP as a supporting ligand for Pd is insufficient to render this process enantioselective. However, although BTM controls the absolute stereochemistry of the bond forming event we have observed a slight amplification of enantioselectivity using (*S*)/(*S*) or (*R*)/(*R*) pairings.

With fully optimized conditions in hand, the nucleophile scope of the reaction was assessed (Scheme 1). Aryl acetates were broadly competent nucleophiles and provided products in high isolated yields, as single (*E*)-vinylB(pin) isomers and with high levels of enantioselectivity. Of particular note is the tolerance of halogens, with no competing Suzuki–Miyaura reaction observed.^[14] Vinyl acetic acid Pfp esters were also competent nucleophiles although provided products with slightly lower levels of enantioselectivity. Finally, and in line with our earlier studies on 2-substituted allyl electrophiles, changing the ligand to P(2-thienyl)₃ enabled the 2-substituted B(pin) electrophile to be engaged (**3q**).^[11a]

We had initially chosen the pinacol boronate for evaluation as it is easily incorporated, robust and does not readily protodeboronate, and it can be readily diversified. Nonetheless, we sought to evaluate the reactivity and of other commonly encountered boron moieties (Table 2). Switching the nucleofugal group from mesylate to *t*-butylcarbonate resulted in lower enantioselectivity (90:10 er) and appreciable amounts of protodeboronation (Entries 1 & 2). The corresponding neopentylglycolboronic ester was ineffective in the reaction, with significant protodeboronation observed (Entries 3 & 4), as was the vinylBF₃K/*t*-butylcarbonate (Entry 5). Finally, the B(MIDA)/*t*-butyl carbonate provided the desired product in diminished yield relative to the B(pin) albeit as a single (*E*)-alkene isomer and in good enantioselectivity (Entry 6).^[15]

Having demonstrated the generality of our protocol, we sought to validate the synthetic utility of the (*E*)-B(pin)-substituted allyl mesylate **1** as a bifunctional reagent by combining our enantioselective C(sp³)–C(sp³) bond formation with subsequent chemoselective functionalizations (Scheme 2). Enantioselective alkylation of 4-bromonaphthyl acetic acid Pfp ester **4** gave methyl ester **5**. Thereafter, the vinylB(pin) could be chemoselectively elaborated in the presence of the bromide. First the B(pin) was converted, via the BF₃K salt, to the corresponding vinylB(neo) **6** without erosion of enantioselectivity. This permits the incorporation of other vinylboron moieties that are incompatible with or ineffective in the

alkylation reaction (cf. Table 2). The vinylB(pin) could also be engaged in chemoselective C–O bond formation to give **7**. Finally, and inspired by the prized orthogonality provided by the Suzuki–Miyaura cross coupling reaction, we independently elaborated both the bromide and B(pin) moieties. Chemoselective modification of the B(pin) and bromide handles was possible via sequential Suzuki–Miyaura (**8**) and Buchwald–Hartwig amination reactions (**9**), respectively. Reversing the order of functionalization was demonstrated by Heck reaction on the bromide (**10**) followed by Suzuki–Miyaura cross coupling using the vinylB(pin) (**11**). In each of these processes the high levels of enantioselectivity were preserved.

In summary, we have developed a cooperative catalysis-based Lewis base/Pd method for the direct α -functionalization of aryl and vinyl acetic acid Pfp esters using a B(pin)-substituted allyl mesylate electrophile. Critical to the success of this method was the recognition that both catalysts could control the necessary stereochemical aspects; the Lewis base catalyst controls the enantioselectivity of the reaction, while the Pd catalyst regulates alkenylB(pin) configuration. This is the first example of using Lewis base/Pd cooperative catalysis to control both stereochemical features in Pd-catalyzed allylic alkylation reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We gratefully acknowledge Indiana University and NIH-NIGMS (R01GM121573), for generous financial support. This project was partially supported by the IU Vice Provost for Research through the Research Equipment Fund.

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- [15]. Despite significant effort, we were unable to prepare the corresponding BF₃K and B(MIDA) mesylates in pure form.³

Figure 1.

(a) Bifunctional borylated building blocks (b) Cooperative catalysis to independently control stereochemical elements of α -allylation with B(pin)-substituted electrophiles

Scheme 1.
Nucleophile Scope.

Scheme 2. Chemoselective product elaboration:

[a] Standard conditions (Table 1) then add MeOH, DMAP, $i\text{Pr}_2\text{NEt}$, 50 °C 18 h; [b](i) KHF_2 , $\text{H}_2\text{O}/\text{MeOH}$, 50 °C 4 h, (ii) neopentyl glycol, K_2CO_3 , MeCN, Me_3SiCl , rt 3 h; [c] $\text{Cu}(\text{OAc})_2$, NEt_3 , allyl alcohol, rt, 24 h; [d] 4-iodobenzonitrile, $\text{Pd}(\text{dppf})\text{Cl}_2$ (6.5 mol%), K_3PO_4 ; THF/ H_2O , rt 18 h; [e] N -Boc-piperazine, $\text{Pd}(\text{OAc})_2$ (4 mol%), XPhos (8 mol%), Cs_2CO_3 , toluene, 100 °C, 17 h; [f] methyl acrylate, $\text{Pd}(\text{OAc})_2$ (5 mol%), SPhos (10 mol%), $i\text{Pr}_2\text{Et}$, 1,4-dioxane, 100 °C, 17 h; [g] 4-iodobenzaldehyde, $\text{Pd}(\text{dppf})\text{Cl}_2$ (10 mol%), K_3PO_4 , THF/ H_2O , rt, 18 h. DMAP = N,N -dimethylaminopyridine, dppf = 1,1'-ferrocenediyl-bis(diphenylphosphine), SPhos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, XPhos = 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl.

Table 1.

Reaction Optimization.

Entry ^a	PR ₃	(mol%)	solvent	Yield [%] ^b	E:Z ^c	er ^d
1	Xantphos	10	THF	79	6:1	94:6
2	DPEphos	10	THF	36	3:1	94:6
3	dppf	10	THF	38	4:1	94:6
4	dppp	10	THF	0	--	--
5	(<i>a</i>)-BINAP	10	THF	75	15:1	93:7
6	P(2-furyl) ₃	20	THF	80	5:1	94:6
7	P(2-thienyl) ₃	20	THF	90	6:1	93:7
8	P(<i>p</i> -OMePh) ₃	20	THF	0	--	--
9	PCy ₃	20	THF	0	--	--
10	(<i>a</i>)-BINAP	10	PhCH ₃	20	15:1	98:2
11	(<i>a</i>)-BINAP	10	Dioxane	75	20:1	97:3
12	(<i>a</i>)-BINAP	10	CH ₂ Cl ₂	0	--	--
13	(<i>S</i>)-(-)-BINAP	10	Dioxane	75	20:1	98:2
14	(<i>R</i>)-(+)-BINAP	10	Dioxane	75	20:1	94:6
15 ^e	(<i>R</i>)-(+)-BINAP	10	Dioxane	75	20:1	53:47

(*S*)-BTM

DHPB

[a] Reactions performed on a 0.1 mmol scale. [b] Yields determined by ¹H NMR by comparison with an internal standard (1,2,4,5-tetramethylbenzene). [c] Determined by integration of the relevant alkene peaks in the ¹H NMR spectrum of the crude material. [d] determined by chiral HPLC analysis in comparison to the racemate. [e] Reaction conducted using DHPB as the Lewis base catalysts.

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[d] determined by chiral HPLC analysis in comparison to the racemate.

[e] Reaction conducted using DHPB as the Lewis base catalysts.

Table 2.

Evaluation of other boron substituents and leaving groups.

Entry ^a	[B]	X	Yield [%] ^b	PDB(%)	E:Z ^c	er ^d
1	B(pin)	OMs	78	0	>20:1	97:3
2	B(pin)	OCO ₂ tBu	60	20	>20:1	90:10
3	B(neo)	OMs	0	45	--	ND
4	B(neo)	OCO ₂ tBu	0	83	--	ND
5	BF ₃ K	OCO ₂ tBu	0	--	--	--
6	B(MIDA)	OCO ₂ tBu	50	0	>20:1	94:6

[B] =

B(pin)

B(neo)

B(MIDA)

[a] Reactions performed on a 0.1 mmol scale. [b] Yields determined by ¹H NMR by comparison with an internal standard (1,2,4,5-tetramethylbenzene). [c] Determined by chiral HPLC analysis. [d] 24 h reaction time. [e] Isolated yield. PDB = protodeboronated product, Pfp = pentafluorophenyl, Ms = methanesulfonyl.

[a] Reactions performed on a 0.1 mmol scale.

[b] Yields determined by ¹H NMR by comparison with an internal standard (1,2,4,5-tetramethylbenzene).

[c] Determined by chiral HPLC analysis.

[d] 24 h reaction time.

[e] Isolated yield. PDB = protodeboronated product, Pfp = pentafluorophenyl, Ms = methanesulfonyl.