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Ni-Catalyzed Borylative Diene-Aldehyde Coupling: The Remarkable Effect of $P(\text{SiMe}_3)_3$

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Abstract

The nickel-catalyzed reaction of carbonyls and dienes was accomplished in a regio- and stereo-selective fashion employing a stoichiometric amount of bis(pinacolato)diboron. In the presence of $P(\text{SiMe}_3)_3$, this reductive coupling furnishes allyl boronic esters which are regioisomeric to those obtained with PCy_3 as the ligand. The coupling product may be subject to oxidation, which furnishes the derived 1,3-diol, or allylation with an additional aldehyde, which furnishes the derived 1,6-diol in a stereoselective fashion.

Rapid construction of complex molecules with high regio- and stereoselectivity is a central objective in organic synthesis. In this regard, reactions that result in the formation of multiple new bonds and that establish multiple stereocenters are particularly valuable.¹ To address this topic, we recently initiated studies on the borylative coupling of unsaturated substrates.² In one manifestation of this strategy, we examined the Mori-Tamaru Ni-catalyzed coupling of aldehydes and dienes,^{3,4} but employed bis(pinacolato)diboron ($\text{B}_2(\text{pin})_2$) as the reducing agent. In the presence of PCy_3 as an ancillary ligand for nickel, reaction product **3** (Scheme 1) is furnished as a single constitutional and stereoisomer. In accord with mechanistic studies by Ogoshi,⁵ it is likely that this reaction occurs by a pathway involving oxidative cyclometalation to give **1**; subsequent transmetalation would furnish **2** and reductive elimination to connect C1 with the boryl ligand would release **3** from the catalyst. We considered that other ligands might alter the regioselectivity of the reductive elimination by connection of C3 and the boryl group, and thereby furnish allylboronate **4** as the reaction product. The structural features of compound **4** – three contiguous stereocenters, an α -chiral allylboronate,⁶ and a functional group pattern that maps onto polyketides – made this a compelling inquiry. In this report, we describe a remarkable turnover in regioselectivity of the borylative diene/aldehyde coupling when PCy_3 is replaced with $P(\text{SiMe}_3)_3$.

Initial exploratory studies focused on the nickel catalyzed reaction between one equivalent each of 1,3-pentadiene, benzaldehyde, and $\text{B}_2(\text{pin})_2$. While PCy_3 and $P(t\text{-Bu})_3$ both promoted formation of terminal boronate **3** (analysis after oxidative workup with hydrogen peroxide), other alkyl and aryl phosphines, triaminophosphines, and simple phosphites were

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Supporting Information Available: Characterization and procedures. This information is available free of charge through the internet at <http://pubs.acs.org>.

either ineffective or resulted in poor selectivity (Table 1). *However, when commercially available $P(\text{SiMe}_3)_3$ was employed, compound 4 was observed with excellent selectivity.*

In addition to compound 4, by-products comprising two aldehydes and one diene, or two dienes and one aldehyde, were also observed. Reasoning that reaction of 4 with unreacted aldehyde might compete with the catalytic process at later stages of reaction and deliver some of these by-products, the concentrations of $\text{B}_2(\text{pin})_2$ and pentadiene were increased. This strategy furnished optimal conditions for this three-component process. As depicted in Table 2, upon oxidation the borylative coupling reaction converts benzaldehyde and 1,3-pentadiene to the derived 1,3-diol with >20:1 diastereoselectivity.⁷ Examination of other substrates revealed that, in general, the reaction is effective for aromatic and heteroaromatic aldehydes and generally delivers the 1,3-diol with excellent regio- and stereocontrol. To determine whether this transformation might apply to more common synthetic building blocks, the aliphatic aldehydes in entries 8–12 were also studied. These experiments suggest that the reaction can be effective with both linear and branched aliphatic aldehydes; additionally, a simple α -chiral aldehyde was found to react with Felkin selectivity thereby opening the possibility for asymmetric synthesis (entry 12).

As alluded to in the introduction, general structure 4 possesses an α -chiral allylic boronate, a motif that often engages in highly selective carbonyl allylation reactions. To probe the capacity for structures such as 4 to participate in stereoselective allylations, benzaldehyde and 1,3-pentadiene were subjected to borylative coupling and, after 12 hours, isobutyraldehyde was added to the reaction mixture. This single-pot reaction sequence delivered 1,6-diol 9 (Scheme 2) in good yield, as a single regioisomer, and with excellent levels of 1,5-stereoiduction (>20:1 d.r.) and olefin stereocontrol. Considering the olefin configuration in the reaction product, it appears plausible that boronate 7 reacts with isobutyraldehyde by way of transition structure 8 with the α -substituent occupying a pseudoequatorial position.⁸

$P(\text{SiMe}_3)_3$ is a relatively unknown ligand in transition metal catalysis⁹ and the reversal in regioselectivity when it is used in place of PCy_3 or $P(t\text{-Bu})_3$ deserves comment. Data in Table 1 reveal that smaller ligands may favor formation of 4 (entries 7 and 8 versus entries 2 and 3), which might suggest that $P(\text{SiMe}_3)_3$ simply serves as a precursor to PH_3 (reaction with adventitious moisture).¹⁰ However, *in situ* ^{31}P NMR analysis of reactions in the presence of $P(\text{SiMe}_3)_3$ shows that most of the ligand remains unmodified (^{31}P $\delta = -251.4$ ppm) over the course of the catalytic reaction.¹¹ The fact that the cone angle of $P(\text{SiMe}_3)_3$ is similar to that of $P(t\text{-Bu})_3$ (178° versus 182°)¹² suggests that the difference in regioselectivity observed with these ligands may arise from electronic rather than steric differences. While the ^{13}C NMR chemical shift¹³ and IR analysis (A_1 CO stretching frequency) of $(\text{Me}_3\text{Si})_3\text{PNi}(\text{CO})_3$ suggest that $P(\text{SiMe}_3)_3$ and trialkylphosphines are electronically similar ligands, analyses by both Bartik¹⁴ and Helm¹⁵ indicate that $P(\text{SiMe}_3)_3$ can act as an electron acceptor. Thus a tentative hypothesis is that the large cone angle of $P(\text{SiMe}_3)_3$, combined with an ability to act as an electron acceptor, may facilitate reductive elimination of 4 from 2, prior to allyl isomerization required for formation of 3.¹⁶

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.

Scheme 2.

Table 1

Effect of Ligand On the Ni-Catalyzed Diborylative Coupling.

entry	ligand	5:6	% yield ^a	d.r. ^b
1	none	>20:1	39	1:1
2	PCy ₃	>20:1	69	>20:1
3	P(<i>t</i> -Bu) ₃	>20:1	71	6:1
4	PPh ₃	>20:1	63	5:1
5	P(NMe ₂) ₃	>20:1	16	>20:1
6	P(OEt) ₃	>20:1	40	4:1
7	PEt ₃	1:2	34	2:1
8	PMe ₃	1:3	55	4:1
9	P(SiMe ₃)	1:12	45	>20:1

^(a) Isolated yield of major product.^(b) d.r. of major product.

Table 2Ni(cod)₂/P(SiMe₃)₃-Catalyzed Diborylative Coupling.

entry	aldehyde	product	d.r. ^a	% yi
1			>20:1	67
2			>20:1	73
3			>20:1	64

entry	aldehyde	product	d.r. ^a	% yi
4			>20:1	57
5			>20:1	57

entry	aldehyde	product	d.r. ^a	% yi
6			>20:1	55
7			>20:1	55
8			>20:1	58
9			>20:1	50
10			>20:1	45

entry	aldehyde	product	d.r. ^a	% yi
11			>20:1	37
12			6:1 ^d	49

(^a) Determined by ¹H NMR analysis of unpurified reaction mixture.

(^b) Isolated yield of purified material. Value is an average of two experiments.

(^c) Run with 1.1 equiv of diene and 1.2 equiv of B₂(pin)₂.

(^d) Ratio refers to Felkin:anti Felkin selectivity. Reaction for 24 h.