

Summer Scholar Report

Enantioselective One-pot Carbozincation Negishi Cross-Coupling Cascade Reaction

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Abstract:

Geminal bimetallic reagents have been widely used and extensively studied in organic synthesis. Their unique reactivity allows them to be involved in an array of transformations that build up complexity with high efficiency and stereoselectivity. α -Borylzinc compounds have been shown to undergo crosscoupling reactions with aryl or alkenyl electrophiles. Herein, we describe a new method for the enantioselective synthesis of α -borylzinc compounds by a nickel(II) catalyzed carbozincation of alkenyl boronates with organozinc compounds. To explore its synthetic utility, the α -borylzinc product was directly subjected to Pd-catalyzed cross-coupling with an arylhalide. This reaction could be accomplished in a one-pot synthesis with high stereospecificity.

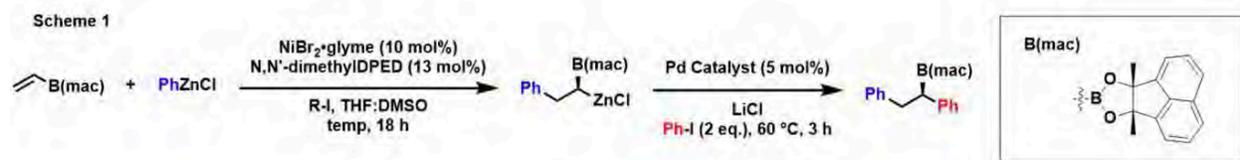
Introduction:

Geminal bimetallic reagents have been widely used and extensively studied in the domain of organic synthesis[1]. Their unique reactivity allows them to be involved in an array of transformations that build up complexity with high efficiency and stereoselectivity.

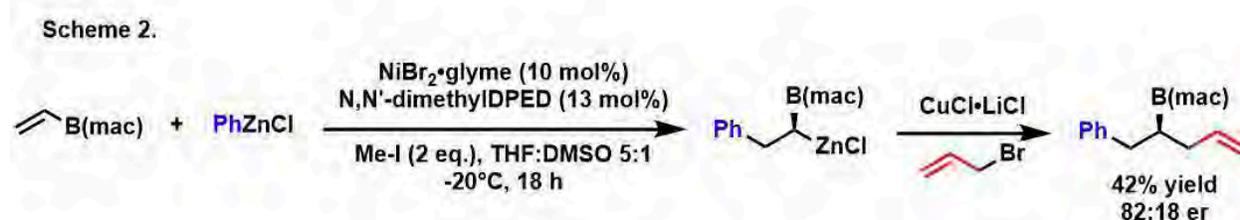
Previously in the Morcken Lab, we probed the synthetic utility of geminal bis(boronates) by the development of a series of reactions, including enantioselective cross-coupling reaction with aryl[2] or alkenyl[3] electrophiles, alkylation reactions[4], boron-Wittig reactions[5] and [2+2] cycloaddition reactions[6].

α -Borylzinc compounds has been shown to undergo cross-coupling reaction with aryl or alkenyl electrophiles[7]. However, the synthesis of α -borylzinc compounds has so far been restricted to the insertion of zinc powder into α - haloboronic esters[8] and zinc-halogen exchange[9]. Both methods require α -haloboronic esters as substrates, which limited the utility of this class of reagent in organic synthesis.

Herein, we describe a new method for the enantioselective synthesis of α -borylzinc compounds by a nickel(II) catalyzed addition of organozinc reagents to alkenyl boronates.



To explore its synthetic utility, the α -borylzinc compound was directly cross-coupled with an aryl-halide catalyzed by Pd(II) species in a one-pot synthesis (Scheme 1).



Results and Discussion:

Initial Investigation

Previously, our group optimized conditions for the carbozincation reaction and evaluated the enantioselectivity of the reaction. We also showed that a Cu(I) mediated allylic substitution could apply to the intermediate compound (Scheme 2). Therefore, the same conditions were used here for the carbozincation reaction. We started our investigation by conducting the carbozincation reaction at -20°C with *n*-butyl iodide as an oxidant. Subsequent cross coupling with iodobenzene, catalyzed by commercially available bis(triphenylphosphine)palladium(II) dichloride at 60°C , afforded desired product with 42% yield and 62:38 er (Table 1, entry 1). The enantioenrichment is significantly lower than what was observed with Cu(I) mediated allylation reaction (75:25 er). We attributed the diminished selectivity to racemization of α -borylalkyl zinc reagent which might occur at the elevated temperature of the cross-coupling reaction compared to the allylation.

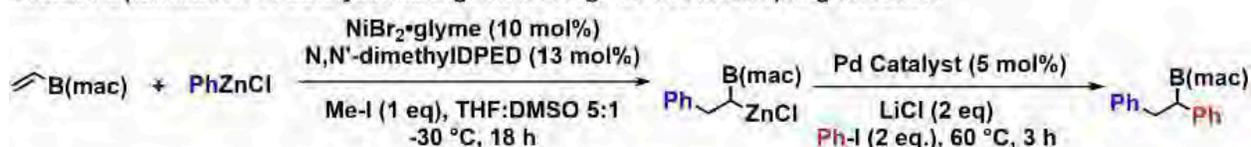
Thus, we examined additives which may either facilitate the cross-coupling reaction or might inhibit the racemization. Addition of more DMSO did not help the selectivity (entry 2). Though ZnCl_2 as an additive gave lower selectivity, LiCl, which has been shown to promote the transmetalation during Negishi cross-coupling reaction [10], led to increased enantioselectivity (entry 3 and 4). Our previous studies also found out that using methyl iodide instead of *n*-butyl iodide as an oxidant would improve the selectivity in the carbozincation reaction.

However, two equivalents of methyl iodide seemed to hamper the cross-coupling reaction, resulting in diminished yield (entry 5). We hypothesized that methyl iodide may poison the palladium catalyst by forming an unreactive methyl complex. Indeed, we saw a boost in yield when only one equivalent of methyl iodide was used (entry 6). In order to study the rate of the cross-coupling reaction and the racemization of α -borylalkyl zinc intermediate during the reaction, three reactions were set up in parallel where the cross-coupling reaction was run for 30, 60 and 180 minutes at 60 °C, respectively (entry 7-9). It was observed that the reaction was completed within one hour and, based on the enantioenrichment, the α -borylalkyl zinc reagent was slowly racemizing during the reaction (70:30 er vs 67:33 er).

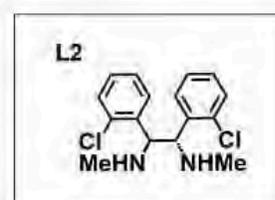
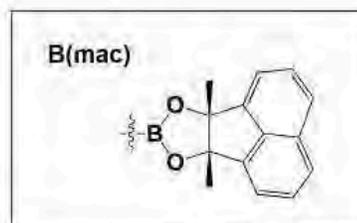
Table 1. Initial Investigation

Entry	R-I	Temperature(°C)	Additive	Reaction Time	yield	e.r.
1	2 eq. nBul	-20	none	12 hours	42%	62:38
2	2 eq. nBul	-20	DMSO (2 ml)	12 hours	39%	62:38
3	2 eq. nBul	-20	2 eq. ZnCl ₂	12 hours	46%	56:44
4	2 eq. nBul	-20	2 eq. LiCl	12 hours	45%	71:29
5	2 eq. MeI	-20	none	12 hours	10%	69:31
6	1 eq. MeI	-30	2 eq. LiCl	3 hours	36%	79:21
7	2 eq. nBul	-20	2 eq. LiCl	30 min	34%	70:30
8	2 eq. nBul	-20	2 eq. LiCl	1 hour	46%	67:33
9	2 eq. nBul	-20	2 eq. LiCl	3 hours	47%	67:33

Table 2. Optimization of Catalyst and Ligand for Negeshi Cross-Coupling Reaction



Entry	Pd Catalyst	yield	e.r.
1	(Ph ₃ P) ₂ PdCl ₂	36%	79:21
2	Pd(OAc) ₂ + SPhos	41%	76:24
3	Pd(OAc) ₂ + RuPhos	34%	77:23
4 ^a	Pd(OAc) ₂ + CPhos	31%	79:21
5 ^{ac}	Pd(OAc) ₂ + DPPF	10%	64:36
6 ^b	Pd(OAc) ₂ + PCy ₃	29%	79:21
7 ^a	Pd(OAc) ₂ + P(<i>o</i> -Tol) ₃	42%	80:20
8 ^b	Pd(OAc) ₂ + P(<i>o</i> -Tol) ₃	16%	83:17
9 ^{ad}	Pd ₂ (dba) ₃ + P(<i>o</i> -Tol) ₃	22%	81:19



- a) 0.5 eq. of Me-I was used instead of 1 eq.
 b) L2 was used instead of N,N'-dimethyl DPED
 c) 0.06 eq. of ligand was used instead of 0.1 eq.
 d) The cross-coupling reaction was ran at 40 °C instead of at 60 °C

We then investigated a variety of palladium catalysts and ligands for the Negeshi cross-coupling reaction. Bis(triphenylphosphine)palladium(II) dichloride at 60 °C afforded desired product with 36% yield and 79:21 er (Table 2, entry 1). Using palladium acetate with SPhos ligand gave a higher yield but slightly lower selectivity (entry 2), while CPhos or RuPhos ligand did not enhance the selectivity either (entry 3-4). Using a bidentate ligand (DPPF) gave a diminished yield and selectivity (entry 5). Tricyclohexylphosphine gave comparable selectivity but lower yield (entry 6). Using 0.5 equivalents of methyl iodide and tri(*o*-tolyl)phosphine boosted the yield of the reaction to 42% while retaining good enantioselectivity (entry 7). The use of L2 instead of (S)-N,N'-Me-DPED in the first step also gave improved selectivity (83:17 er) though the yield was diminished (entry 8). Changing the palladium source to tris(dibenzylideneacetone) dipalladium(0) and lowering the cross-coupling reaction temperature to 40°C diminished the yield and did not have significant impact on the selectivity (entry 9).

In summary, we developed an enantioselective carbozincation of vinyl boronic esters that is followed by one-pot palladium catalyzed cross coupling reaction. The process occurs with synthetically useful yield and enantioselectivity. Further studies to understand detailed mechanism, to optimize the reaction conditions and to broaden the scope of the reaction is underway.

References:

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