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Palladium-catalysed carboborylation for the synthesis of borylated indanes

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Abstract. A palladium catalysed carboborylation reaction for the synthesis of borylated indanes has been investigated. This reaction proceeds in good yields with an achiral catalyst, and is tolerant of substitution on the aryl ring, although sensitivity to the substitution of the alkene was observed. Initial studies towards an enantioselective version of this reactions were undertaken, identifying phosphoramidites as a promising ligand class. This allowed for the synthesis of chiral indane and indolone products with moderate levels of enantioselectivity.

Keywords: Borylation, cascade cyclisation, palladium catalysis, anion capture

The rapid and efficient generation of molecular complexity is a major goal of organic chemistry and catalysis. To this end, identifying processes which allow for the formation of new carbon-carbon bonds while also controlling the formation of stereochemistry is highly desirable. One fundamental process that meets this need is the catalytic carbopalladation of alkenes.[1] This process forms a new C-C bond, generates up to two new stereocentres and generates a new σ-alkyl-palladium complex in one step.

In the Mizoroki-Heck reaction,[2] the prototypical example of catalytic carbopalladation, the stereochemical information formed during this step is subsequently lost through a β-hydride elimination process. Thus, a number of groups have looked at strategies to intercept the σ-alkyl-palladium complex formed by alkene carbopalladation with nucleophiles, allowing for the difunctionalisation of alkenes and the formation of new stereocentres. These processes have been termed "anion capture cascades" (Figure 1a).[3]

In these cascade processes, β-hydride elimination can be avoided by utilising 1,1-disubstituted alkenes, which lack a hydrogen at the β-position following carbopalladation. Alternatively, β-hydride elimination can be suppressed through stereoelectronic control of the reactive intermediates[4] or through ligand control.[5]

The σ-alkyl-palladium complex is a versatile intermediate for palladium catalysed cascade reactions. The σ-alkyl-palladium complex was utilised successfully in the seminal work by Larock, who employed hydride as a nucleophile in a Pd-catalysed reductive cyclisation reaction.[6] This chemistry has since proven to be quite robust and tolerable of many cross coupling partners including cyanide,[7] iodine[8] as well as boronates[9] and carbon-based nucleophiles[10] (Figure 1b).

Despite such progress, the majority of *enantioselective* palladium-catalysed anion capture cascades have utilised hydride reduction,[4, 11] C-H functionalisation of heteroarenes,[12] Heck coupling,[13] Suzuki-type coupling or Sonagashira coupling[14] in the final step. A number of dearomative Heck-type couplings have been reported,[15] including Lautens' enantioselective dearomatization/borylation of indoles,[15c] highlighting the potential of borylation reactions in enantioselective anion capture cascades.

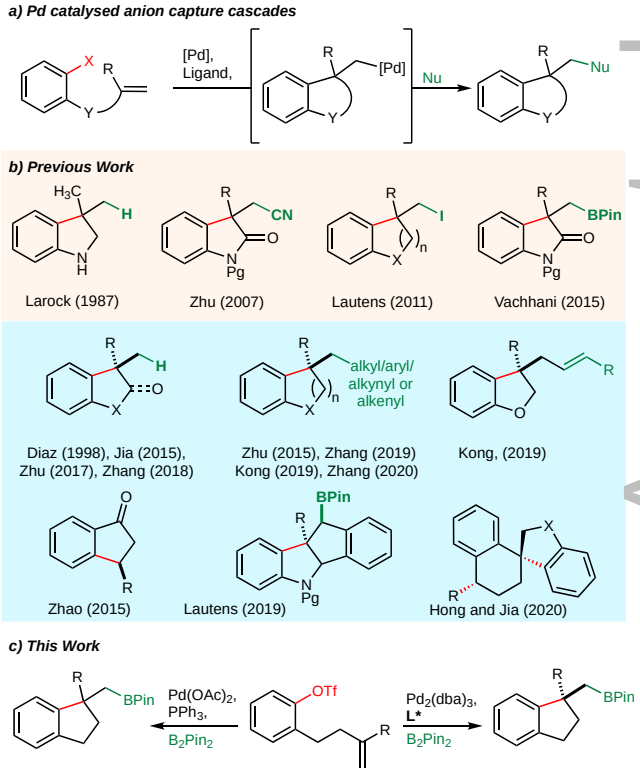

Figure 1. Pd catalysed anion capture cascades

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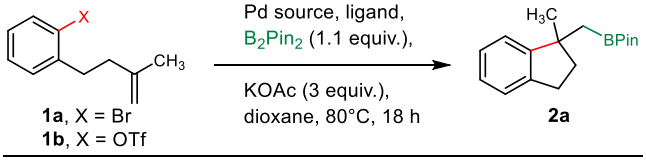
Alkyl organoboronates are valuable compounds in organic chemistry, due to their flexible use in cross-coupling chemistry and functional group interconversion.[16] The practical use of organoboronates has increased with advancements in Pd and Pt catalysis, with di-borylation,[17] silyl-borylation[18] and carbo-borylation methods becoming available.[19] The synthetic advantages of boronates includes their stability to air and moisture as well as the vast array of transformations which enable their use as synthons in the synthesis of drugs and natural products. In 2015, Vachhani and Van der Eycken demonstrated a borylative cascade cyclisation to form oxindoles.[9] To our knowledge, the only enantioselective carbo-borylation reactions of intercepted σ-alkyl-palladium complexes have been reported by Tong for the synthesis of 3,3-disubstituted tetrahydropyridines[20] and Lautens for the dearomative cyclisation of indoles.[15c] Herein, we report a palladium catalysed carboborylation reaction for the synthesis of borylated indanes, providing rapid access to these valuable synthons (Figure 1, c).

We began our study by examining the cascade cyclisation/borylation of aryl bromide **1a**. We were initially pleased to see that treatment of **1a** with $PdCl_2$ (10 mol%) in the presence of B_2Pin_2 and KOAc in dioxane at 80 °C provided a 25% yield of the desired cyclised product **2a** (Table 1; Entry 1).

While the use of a bis-phosphine ligand with $PdCl_2$ or $Pd_2(dba)_3$ gave no improvement in yield (Entries 2 and 3) the combination of dppf or PPh_3 and $Pd(OAc)_2$ gave the desired product in good yields (Entries 4 and 5). Given the ready availability of PPh_3 we chose to proceed with this ligand for further studies. The reaction was also found to proceed just as well when the aryl triflate **1b** was used (Entry 6). Further studies were conducted with this psuedohalide due to easy access to the starting materials.

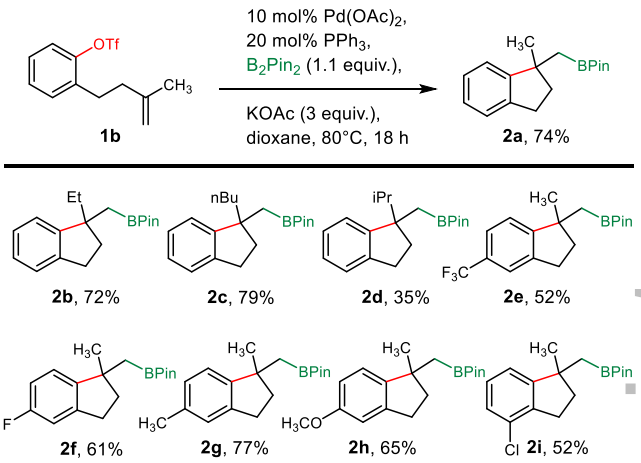
Table 1. Optimisation of the carboborylation of **1**.



Entry	Pd source[a]	Substrate	Ligand[a]	Yield[d]
1	$PdCl_2$	**1a**	-	25%
2	$PdCl_2$	**1a**	dppf	18%
3	$Pd_2(dba)_3$[b]	**1a**	dppf	<5%
4	$Pd(OAc)_2$	**1a**	dppf	77%
5	$Pd(OAc)_2$	**1a**	PPh_3[c]	74%
6	$Pd(OAc)_2$	**1b**	PPh_3[c]	74%

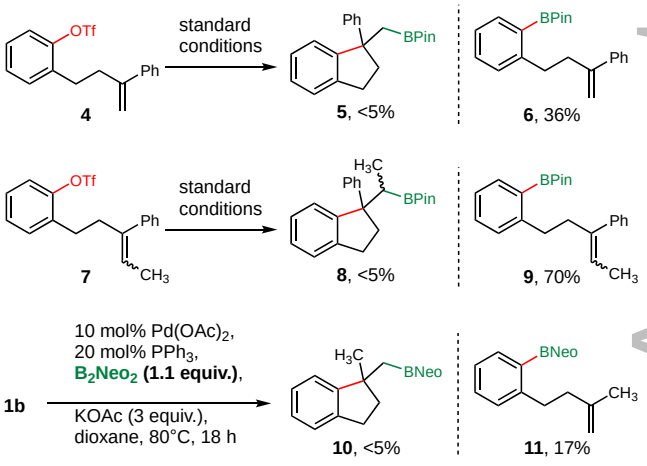
[a]10 mol%. [b]5 mol%. [c]20 mol%. [d]Isolated yield.

With optimised conditions in hand, we investigated the scope of this reaction by varying the substituents at the aryl and olefinic positions. The reaction was found to be tolerant to substitution of the olefin methyl group for ethyl and butyl groups (Scheme 1, **2b,c**) while the bulkier iPr group (**2d**) gave a considerably reduced yield of 35%. Substitution of the aryl ring with both electron-withdrawing (**2e,f,i**) and electron-donating groups (**2g,h**) was well tolerated under these conditions.



Scheme 1. Examples of alkene carboborylation

We next investigated the cascade cyclisation/ borylation of substrates with an aryl-substituted alkene (Scheme 2). Unfortunately, when the aryltriflate **4** was subjected to the standard conditions the cyclised product **5** was not observed; only the direct borylation product **6** was isolated in 36% yield. In addition, the trisubstituted alkene substrate **7** also delivered the direct borylation product 9, rather than the indane **8**. The use of an alternative borylating agent was attempted, using bis(neopentyl glycolato)diboron with the standard substrate **1b**. Under these conditions, the cyclised product **8** was not observed, with the arylboronate **9** isolated in 17% yield.

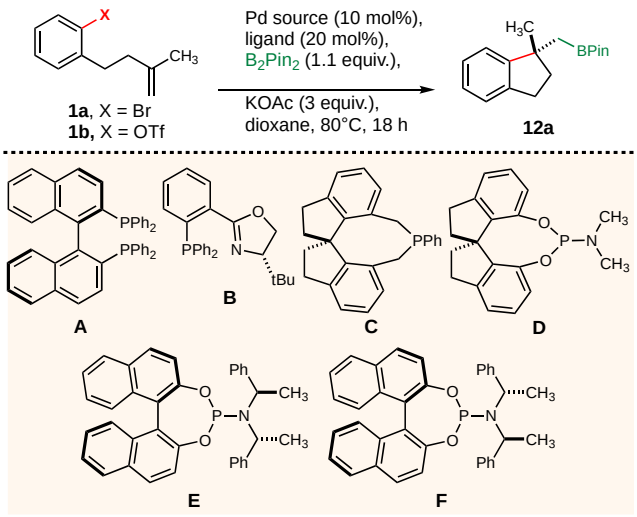


Scheme 2. Attempted carboborylation of aryl alkenes

Studies into the enantioselective synthesis of 3,3-disubstituted indanes by carboborylation were also conducted. (See SI for full optimisation table.) Initially, the bromide **1a** was treated with

$Pd(OAc)_2$, (*R*)-BINAP (**A**), B_2Pin_2 and KOAc in dioxane. This provided the product **12a** in low yield and poor enantioselectivity (Table 2, Entry 1). The use of (*S*)-tBu-PHOX ligand (**B**) resulted in no reaction, while the monodentate ligands (*R*)-SITCP (**C**) and (*R*)-SIPHOS (**D**) gave the indane **12a** with negligible enantioselectivity (Entries 2-4). The addition of silver salts to this reaction was attempted, as formation of the cationic palladium intermediate has been associated with higher enantioselectivity in Heck reactions[21] (Entry 5). This resulted in reduced yield and poor enantioselectivity. Switching the substrate to triflate **1b** gave a modest increase in enantioselectivity (Entry 6), which could be further increased through the use of the phosphoramidite (*R*,*S*,*S*)-PE-Monophos, providing indane **12a** in 58% yield and 80:20 e.r.

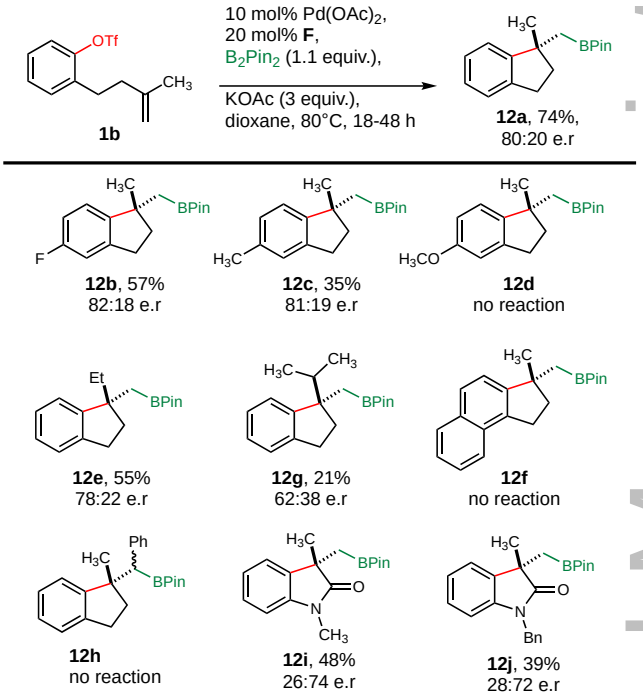
Table 2. Optimisation of enantioselective carboborylation.



Entry	Pd source	Substrate	Ligand	Yield[a] (e.r)[b]
1	Pd(OAc)	**1a**	**A**	32%(52:48)
2	$Pd(OAc)_2$	**1a**	**B**	N/R
3	$Pd(OAc)_2$	**1a**	**C**	68%(45:55)
4	$Pd(OAc)_2$	**1a**	**D**	69%(45:55)
5[c]	$Pd(OAc)_2$	**1a**	**D**	49%(54:46)
6	$Pd(OAc)_2$	**1b**	**D**	62%(70:30)
7[d]	$Pd_2(dba)_3$	**1b**	**E**	53%(66:34)
8[d]	$Pd_2(dba)_3$	**1b**	**F**	58%(80:20)

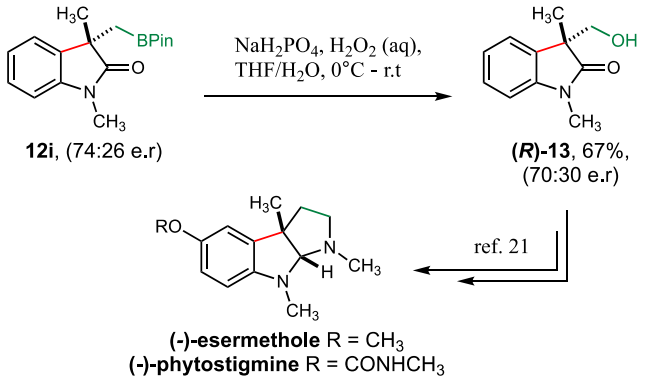
[a] Isolated yield. [b] e.r determined by chiral HPCL; N/R = no reaction. [c] 1 equiv. of Ag_2CO_3 added [d] 5 mol% cat. loading.

Having determined reasonable reaction conditions for the enantioselective carbo-borylation reaction, a small scope was investigated (Scheme 3). With these enantioselective conditions, the reaction was found to be much more sensitive to the electronic nature of the aryl group. Whilst the electron-withdrawing *p*-F substituted **12b** gave comparable yields to the parent reaction (58%, 82:18 e.r), the electron-donating *p*-CH_3 substrate **12c** performed much worse (35%, 81:19 e.r) and *p*-OCH_3 (**12d**) did not react at all. The Et substituted alkene substrate **12e** gave a comparable yield and enantioselectivity (55%, 78:22 e.r), while the iPr substituted gave reduced yield of 21% (**12g**). The naphthyl substrate **12f** and the trisubstituted olefin **12h** resulted in no reaction. Finally, enantioselective carbo-borylation was attempted for the synthesis of chiral oxindoles. Although oxindoles **12f** and **12g** were synthesised successfully under the conditions, the enantioselectivities of the products were reduced slightly when compared to the parent reaction.



Scheme 3. Examples of enantioselective carboborylation

The absolute configuration of the major enantiomer of compounds **12a-j** was assigned by oxidation of the borylated oxindole **12i** to the known alcohol **(*R*)-13** (Scheme 4). Comparison of the optical rotation of **(*R*)-13** ($[\alpha]_D$ = -4.0, lit $[\alpha]_D$ = -8.5, >99:1 e.r) and the chiral HPLC data (see SI) with the reported values[22] confirmed the (*R*)- configuration of this product. The alcohol **(*R*)-13** has been previously reported as an intermediate in the synthesis of natural products (-)-esermethole and (-)-phytostigmine,[23] offering a potential new route to this class of alkaloids.



Scheme 4. Oxidation and assignment of configuration

In summary, we have reported the intramolecular Pd-catalysed carboborylation cascade for the synthesis of 3,3-disubstituted indanes using B_2Pin_2. It was observed that the reaction was tolerant of variable electronics at the aryl substituent and sensitive to substitution around the olefin. When the B_2Neo_2 dimer was used, selectivity towards the non-cyclised Miyaura borylation product was observed. Finally, the first enantioselective Pd-catalysed carboborylation for the synthesis of chiral indanes has been successfully reported in moderate yields and enantioselectivity.

Experimental Section

Experimental procedure for enantioselective carboborylation of **1b**.

To a dry round-bottom flask was added $Pd_2(dba)_3$ (7.2 mg 0.05 equiv.) and (*R,S,S*)-PE-Monophos (17 mg, 0.2 equiv.) and the flask purged with N_2 gas for 10 minutes. The contents of the flask were dissolved in 1 mL dry and degassed dioxane and allowed to stir for 30 min until the solution turned from purple to yellow. The solution was transferred to a pre-purged 10 mL reaction vial containing B_2Pin_2 (46 mg, 1.1 equiv.) and dry KOAc (47 mg, 3 equiv.). Aryltriflate **1b** (39 µL, 0.16 mmol) was then added to the reaction mixture via micro syringe and the reaction was warmed to 80°C for 16 hours. The reaction was then cooled, diluted with EtOAc and filtered. The extract was concentrated and purified via flash column chromatography (40% CH_2Cl_2/hexanes) to give the product (25 mg, 74% yield) as a clear oil.

R_f = 0.17 (20% CH_2Cl_2/hexanes); IR υ_{max} (neat) 3070, 2977, 2933, 2866, 1477, 1449, 1354, 1318, 1269, 1213, 1142, 968, 880, 847, 756, 727; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19-7.09 (m, 4H), 2.93-2.84 (m, 2H), 2.12 (ddd, J = 7, 8, 12.5 Hz, 1H), 1.94 (ddd, J = 6, 8, 12.5 Hz, 1H), 1.31 (s, 3H), 1.26 (d, J = 15 Hz, 1H), 1.20 (d, J = 7 Hz, 12H), 1.12 (d, J = 15 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.6, 146.4, 136.3, 131.1, 129.3, 125.2, 109.9, 83.5, 41.8, 35.0, 25.0, 22.6.

Chiral HPLC was performed on a Chiralpak AD-H column, eluted in 99.5:0.5 hexane:iPrOH at 1 ml/min, t_1 = 4.49 (major enantiomer), t_2 = 4.92 (minor enantiomer); er = 80:20. $[\alpha]_D^{23}$ = -10.9° (c = 1.30, CH_2Cl_2).

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COMMUNICATION

Palladium-catalysed carboborylation for the synthesis of borylated indanes

Andrzej Zieba and Joel F. Hooper

The interception of σ-alkyl-palladium complexes in catalysis is a powerful strategy for the generation of molecular complexity. We have demonstrated a palladium catalysed carboborylation reaction for the synthesis of borylated indanes, which proceeds in good yields and moderate enantioselectivity.