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Development of the "Diverted Heck" Reaction for the Synthesis of Five-Membered Rings

Kevin Breitwieser and Peter Chen*

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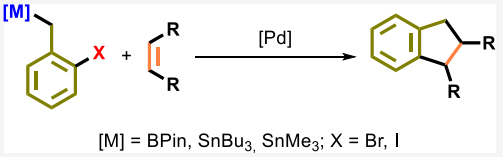
ABSTRACT: The "diverted Heck" reaction has been shown to be a potent method to synthesize cyclopropanes from electron-rich olefins and iodomethyl trifluoroborate. Nevertheless, it is not mechanistically limited to the three-membered rings. The synthesis of five-membered rings using bifunctional substrates with a halide moiety and an organometallic group is described. Furthermore, the reactions of the respective boron and tin-based substrates are further investigated and optimized.



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The "diverted Heck" reaction was developed as an alternative cyclopropanation reaction to the established use of diazomethane,[1] the Simmons–Smith reaction,[2] and the transfer of methylene groups from sulfur ylides (Corey–Chaykovsky reaction).[3] While these reactions are applicable in many cases, they have notable disadvantages. While diazomethane and its precursors are well known for their high toxicity and explosiveness,[4] the Simmons–Smith reaction produces stoichiometric amounts of zinc waste, and depending on the procedure, cationic polymerization can become a major side reaction or the reaction mixture can explode.[5] These methods are furthermore mostly limited to electron-poor and polar olefins.

While the palladium-catalyzed cyclopropanation of olefins using iodomethylstannanes had been reported before (Scheme 1, eq 1), a large excess of the norbornene derivatives was used.[6] However, as this was intended as a trapping experiment and not for synthetic applications, the conditions were not optimized. We subsequently reported the "diverted Heck" reaction, involving the palladium-catalyzed addition of the methylene unit from an iodomethylboron species to an olefin to form a cyclopropane ring (Scheme 1, eq 2).[7] It was shown that this reaction was able to cyclopropanate a wide range of electron-rich olefins and allylic alcohols in good yields up to 98% with a close to 1:1 ratio of the reagent and substrate. The mechanism of this reaction was found to follow the mechanism for the Heck reaction. However, instead of the final β-hydride elimination, an intramolecular transmetalation intervenes. This leads to a palladacyclobutane, which can undergo reductive elimination to form the cyclopropane. The generalized mechanism of the "diverted Heck" reaction is shown in Scheme 2. In the reported case, the organometallic moiety [M] is a trifluoroborate group and the (pseudo)halide X is iodine. They are connected by a methylene group.

In organic synthesis, the formation of carbocycles can be challenging, especially if they are not six-membered rings. As is apparent from the proposed mechanism, unlike carbene insertion reactions, the "diverted Heck" reaction is not strictly limited to the formation of cyclopropanes and should be applicable to all possible ring sizes in principle. In fact, the nickel-catalyzed synthesis of indanes and indenes from *o*-bromobenzyl zinc bromide and alkenes or alkynes has been reported before (Scheme 1, eq 3).[8] The authors propose several possible mechanisms for this reaction, with one of them being strikingly similar to the proposed mechanism for the "diverted Heck" reaction.

However, their method has considerable disadvantages: 3.5 equiv of the zinc reagent is needed for the reaction. In addition, due to the nature of zinc organyls, functional group tolerance is limited compared to reactions with the boron analogues.

This work reports the development of a cyclopentenation reaction based on the "diverted Heck" reaction using bifunctional substrates bearing one halogen moiety as well as an organometallic group based on boron or tin.

EXPERIMENTAL SECTION

General Remarks. Unless otherwise stated, all reactions were carried out under an argon or nitrogen atmosphere using standard Schlenk or glovebox techniques with anhydrous solvents. Solvents and reagents were obtained from abcr, Acros Organics, AlfaAesar, Apollo Scientific, Chemie Brunschwig, Combiblocks, Fluka, Fluorochem, Sigma-Aldrich, TCI, and VWR. Solvents were dried by distillation under nitrogen from sodium (toluene), sodium/benzophenone [diethyl ether, tetrahydrofuran (THF)], sodium/benzophenone/tetraethylene glycol dimethyl ether (TEGDME) (hexane), or magnesium (methanol) before use and were stored under dry

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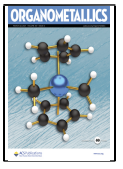

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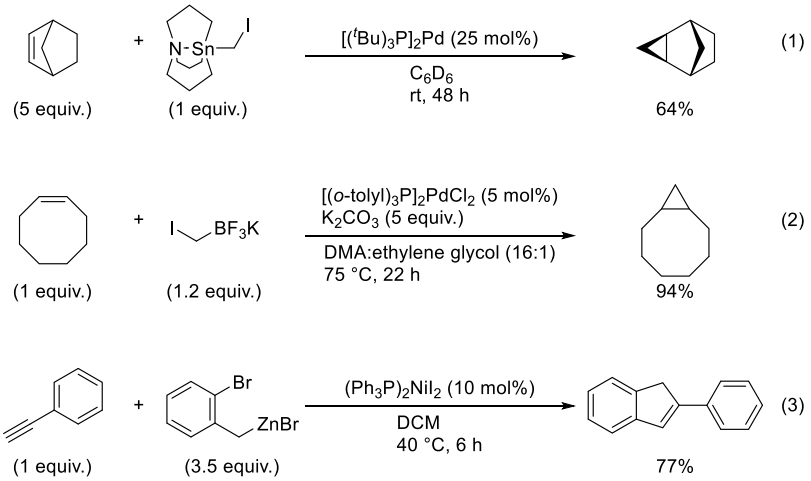
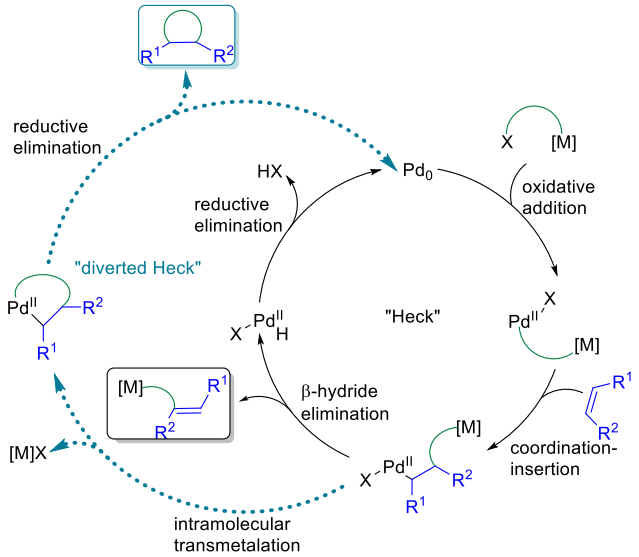
Organometallics 2021, 40, 776–782

Scheme 1. Previously Reported Transition-Metal-Catalyzed Cyclization Reactions Using Reagents Containing a Halogen Moiety and an Organometallic Group



Scheme 2. Proposed Catalytic Cycle for the "Diverted Heck" Cyclization Reaction



X : halogen (Br, I)
[M] : boronic acid derivative or stannyl group

nitrogen. Deuterated chloroform was obtained from Cambridge Isotope Laboratories. Copper(I) iodide and lithium chloride were dried for several hours in high vacuum and stored under dry argon before use. Norbornene was distilled under argon and stored in a nitrogen-filled glovebox before use. Potassium iodomethyltrifluoroborate (>98.0%) was washed with diethyl ether, dried, and stored in a nitrogen-filled glovebox before use. NMR spectra were recorded with a Bruker Avance III 400 MHz, Bruker Neo 400 MHz, or Bruker Neo 500 MHz spectrometer using $CDCl_3$ as a solvent. 500 MHz spectra were recorded by the NMR Service of ETH Zürich. Chemical shifts (δ) are reported in parts per million (ppm) relative to the residual solvent signal for chloroform (7.26 and 77.16 ppm) as an internal reference. ^{13}C, ^{19}F, and ^{31}P spectra were recorded with ^{1}H-decoupling. High-resolution mass spectra were recorded by the Molecular and Biomolecular Analysis Service (MoBiAS) of ETH Zürich using a Bruker maXis ESI-Qq-TOF-MS or Thermo Scientific Q Exactive GC Orbitrap with a direct probe (EI) for mass spectra. Gas chromatography–mass spectrometry (GC–MS) measurements were carried out using a ThermoFinnigan Trace GC + Trace MS and a Supelco Equity-5 30 m × 0.25 mm column with a 0.25 μm film. Gas chromatography-flame ionization detection (GC-FID) measurements were conducted using a Finnigan Focus GC or a Shimadzu GC-2025 with a Thermo Scientific TR-5MS 30 m × 0.25 mm column with a 0.25 μm film. GC-FID quantifications were carried out using calibration curves and undecane as an internal standard.

Representative Cyclopentenation Procedure in *N,N*-Dimethylacetamide/Ethylene Glycol. Inside a nitrogen-filled glovebox, a 9 mL screw-cap vial with an oven-dried magnetic stir bar was charged with K_2CO_3 (80.9 mg, 5.0 equiv) and 0.1 mL of anhydrous ethylene glycol (EG). The mixture was stirred for 10 min. A solution of $[(o\text{-tolyl})_3P]_2PdCl_2$ (4.6 mg, 5 mol %), *o*-bromobenzylboronic acid pinacol ester (41.6 mg, 1.2 equiv), and norbornene (11.0 mg, 1 equiv) in 0.6 mL of *N,N*-dimethylacetamide (DMA) was added. Additional DMA (2 × 0.5 mL) was used to rinse the vials used for transfer and weighing substrates and the catalyst and added to the reaction mixture. The vial was sealed, removed from the glovebox, and heated to 75 °C for 22 h. The mixture was cooled to 0 °C for 10 min, and 5 μL of undecane was added (internal reference). The contents of the vial were extracted with Et_2O (2 × 4 mL) and water (5 mL), and the organic phase was washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered through celite, and analyzed by GC–MS and GC-FID.

Representative Cyclopentenation Procedure for Solvent Screening. Inside a nitrogen-filled glovebox, to a 9 mL screw-cap vial with an oven-dried magnetic stir bar was added a solution of $[(o\text{-tolyl})_3P]_2PdCl_2$ (4.6 mg, 5 mol %), *o*-bromobenzyltributylstannane (64.4 mg, 1.2 equiv), and norbornene (11.0 mg, 1 equiv) in 0.6 mL of DMA. Additional DMA (2 × 0.5 mL) was used to rinse the vials used for transfer and weighing substrates and the catalyst and added to the reaction mixture. The vial was sealed, removed from the glovebox, and heated to 75 °C for 22 h. The mixture was cooled to 0 °C for 10 min, and 5 μL of undecane was added (internal reference). The contents of the vial were extracted with Et_2O (2 × 4 mL) and water (5 mL), and the organic phase was washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered through celite, and analyzed by GC–MS and GC-FID.

Representative Cyclopentenation Procedure with Additives. Inside a nitrogen-filled glovebox, a 9 mL screw-cap vial with an oven-dried magnetic stir bar was charged with CsF (21.3 mg, 1.2 equiv). A solution of $[(o\text{-tolyl})_3P]_2PdCl_2$ (4.6 mg, 5 mol %), *o*-bromobenzyltributylstannane (64.4 mg, 1.2 equiv), and norbornene (11.0 mg, 1 equiv) in 0.6 mL of ^{t}BuOH was added. ^{t}BuOH (2 × 0.5 mL) was used to rinse the vials used for transfer and weighing substrates and the catalyst and added to the reaction mixture. The vial was sealed, removed from the glovebox, and heated to 75 °C for 22 h. The mixture was cooled to 0 °C for 10 min, and 5 μL of undecane was added (internal reference). The contents of the vial were extracted with Et_2O (2 × 4 mL) and water (5 mL), and the organic

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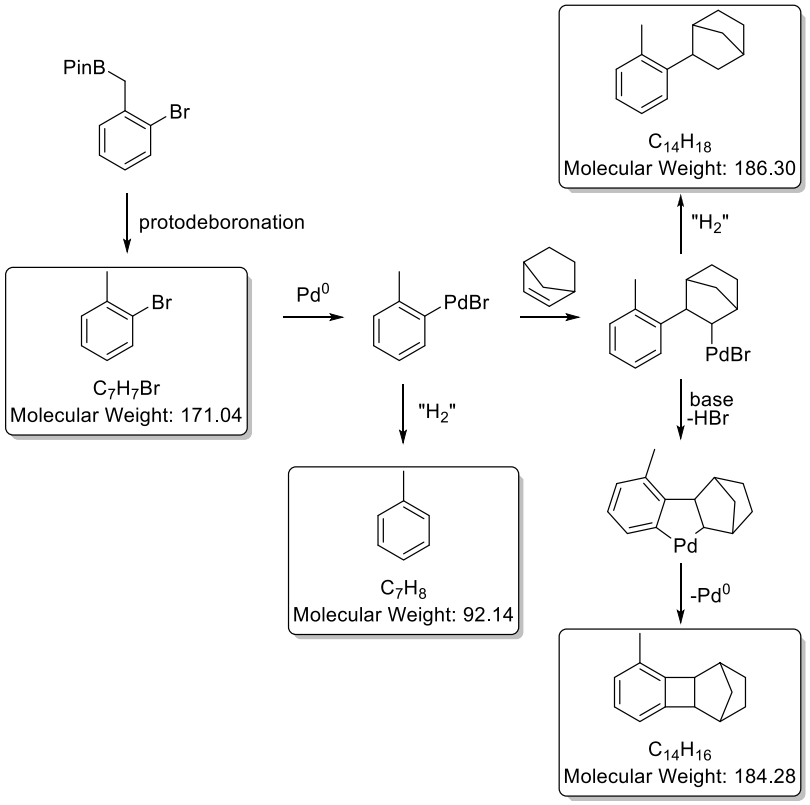
Organometallics 2021, 40, 776–782

Scheme 3. Proposed Mechanism for the Formation of the Four Major Products Observed for the Attempted "Diverted Heck" Reaction of Norbornene and *o*-Bromobenzylboronic Acid Pinacol Ester



phase was washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered through celite, and analyzed by GC−MS and GC-FID.

Representative Procedure for the Isolation of Cyclopentenes. Inside a nitrogen-filled glovebox, an oven-dried 250 mL two-neck flask with an oven-dried magnetic stir bar was charged with CsF (495.2 mg, 1.2 equiv). A solution of $[(o\text{-tolyl})_3P]_2PdCl_2$ (109.7 mg, 5 mol %), *o*-bromobenzyltributylstannane (1499.9 mg, 1.2 equiv), and norbornene (256.5 mg, 1 equiv) in 37.5 mL of ^{t}BuOH was added. The flask was fitted with a glass stopper and glass tap, removed from the glovebox and attached to an argon-filled Schlenk line. The mixture was heated to 75 °C for 22 h. The mixture was cooled to 0 °C and diluted with 75 mL of Et_2O. It was washed with water (2 × 40 mL) and brine (40 mL), dried ($MgSO_4$), and filtered through a pad of silica, washing with additional pentane. The solution was concentrated, and the residue was purified by column chromatography (hexane) twice. The product *exo*-2,3,4,4a,9,9a-hexahydro-1*H*-1,4-methanofluorene was obtained as 58.8 mg (12%) of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23−7.09 (m, 4H), 3.27 (dd, J = 17.1, 10.2 Hz, 1H), 3.15 (d, J = 7.9 Hz, 1H), 2.62 (dd, J = 17.1, 3.4 Hz, 1H), 2.45−2.36 (m, 1H), 2.29 (s, 1H), 2.11 (s, 1H), 1.69−1.50 (m, 2H), 1.48−1.37 (m, 1H), 1.34−1.22 (m, 1H), 1.19−1.08 (m, 1H), 1.06−0.95 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 146.51, 144.95, 126.36, 126.32, 124.62, 124.15, 55.60, 45.02, 43.87, 43.56, 39.47, 32.55, 29.13, 28.96. HRMS (EI) calcd for $C_{14}H_{16}$ $[M]^+$, 184.1247; found, 184.1244.

RESULTS

Investigation of Cyclopentenation with Organoboron Reagents. As the previously described "diverted Heck" cyclopropanation[7] was based on organoboron reagents, it was chosen to use *o*-bromobenzylboronic acid pinacol ester as a model reagent. An aryl halide was chosen as, compared to alkyl halides, it does not undergo nucleophilic substitution reactions with alcoholic solvents (e.g., EG) and because aryl halides undergo faster oxidative addition. Preliminary tests with 3-iodo-2-phenylpropylboronic acid pinacol ester lead to the 1,3-elimination product phenylcyclopropane as the only product visible in GC. This elimination reaction is known to occur under basic conditions.[9] Norbornene was chosen as the model olefin as it shows very high reactivity.[10] Moreover, after migratory insertion, β-hydride elimination (following the "normal" Heck path) is disfavored as it would violate Bredt's rule.[11] The expected "diverted Heck" product is 2,3,4,4a,9,9a-hexahydro-1*H*-1,4-methanofluorene ($C_{14}H_{16}$, m/z = 184). Following the representative cyclopentenation procedure in DMA/EG, GC−MS does detect four major products, these being *o*-bromotoluene, toluene, and hydrocarbons with the formulas $C_{14}H_{18}$ and $C_{14}H_{16}$, the latter matching the target molecule. The molecules $C_{14}H_{16}$ and $C_{14}H_{18}$ are formed through a mechanism described by Catellani and Ferioli,[12] and $C_{14}H_{16}$ can be identified as a benzocyclobutene instead of the desired benzocyclopentenes. While this competing mechanism can be suppressed by replacing the Brønsted base used as an activator for transmetalation with CsF,[13] two other side reactions are observed, these being protodeboronation[14] and transfer hydrogenation. The proposed mechanism for the formation of the observed side products is shown in Scheme 3.

The transfer hydrogenation does not proceed in the absence of a reducing alcohol (e.g., EG and isopropanol),[15] making suppression possible, but the protodeboronation cannot be reduced to a reasonable degree. Even with CsF as an activator and pure DMA as a solvent, next to 9% of the target molecule, 49% *o*-bromotoluene is formed.

To avoid protodemetalation, a system based on the more stable stannanes was investigated.

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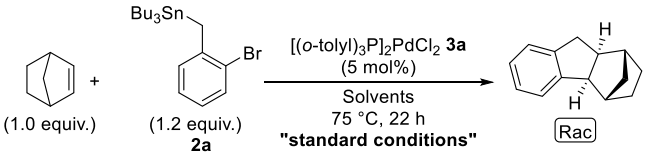
Organometallics 2021, 40, 776−782

Investigation of Cyclopentenation with Organotin Reagents. After only a few test reactions, it was clear that the reagent *o*-bromobenzyltributylstannane is superior to the corresponding boronic acid ester for the reaction. In no case did we see notable formation of *o*-bromotoluene, which was the main issue with the boron reagent. In addition, no activator is necessary for transmetalation. Based on these first successes, optimization of the reaction was carried out. The first parameter optimized was the solvent (Table 1).

Table 1. Solvent Screening for the "Diverted Heck" Cyclopentenation of Norbornene with *o*-Bromobenzyltributylstannane (2a)[a]



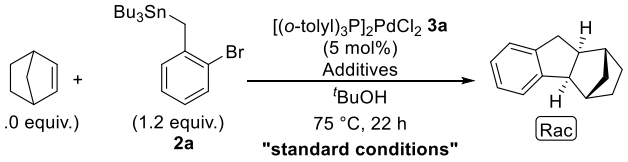
no.	solvent	yield (%)[b]	conv. 2a (%)[b]
1	hexane	2.1	8.8
2	toluene	4.2	16.8
3	fluorobenzene	5.1	28.9
4	THF	0.7	9.6
5	ethyl acetate	4.2	16.4
6	acetone	1.5	7.3
7	DMA	9.1	52.6
8	DMF	13.2	62.4
9	^{t}BuOH	19.2	47.3
10	DMSO	10.2	89.2
11	acetonitrile	3.2	16.7
12	^{i}PrOH	13.7	30.9
13	MeOH	18.2	58.0
14	EG	10.3	62.2
15	water[c]	10.7	23.3

[a]Standard conditions: norbornene (11.0 mg, 1.0 equiv), stannane **2** (64.4 mg, 1.2 equiv), $[(o\text{-tolyl})_3P]_2PdCl_2$ (4.6 mg, 5 mol %), 1.6 mL of the solvent, 75 °C, 22 h. [b]Yields and conversions were evaluated by GC-FID. [c]All components except for the solvent were put into a 9 mL screw-cap vial with a septum cap. The degassed water was added outside of the glovebox through the septum.

Evidently, the reaction works best in polar protic solvents, such as methanol (entry 13) or *tert*-butanol (entry 9), with yields reaching almost 20% in the set of exploratory reactions. Water (entry 15) or EG (entry 14) lead to a much poorer yield, most likely due to phase separation. Polar aprotic and apolar solvents gave worse yields, with only dimethylformamide (DMF) (entry 8) and dimethyl sulfoxide (DMSO) (entry 10) getting higher than 10%. Other solvents, such as acetonitrile (entry 11), acetone (entry 6), THF (entry 4), or toluene (entry 2), lead to yields well below 5%.

Having found a suitable solvent in *tert*-butanol, the application of additive salts was investigated (Table 2). While Brønsted bases were ruled out as they would enable the undesirable C−H activation described before, LiCl, CuI,[16] and CsF[13] are known additives for palladium-catalyzed reactions. Notably, LiCl and CuI addition to the reaction is highly detrimental. 1.2 equiv of LiCl cut the yield of the reaction in half, while even 0.1 equiv of CuI cut the yield by 2/3, with higher loadings being even worse. However, CsF addition is highly beneficial, with 1.2 equiv doubling the yield. Although isopropanol was a worse solvent than *tert*-butanol without an additive, it is superior in combination with CsF, leading to a yield of more than 80% based on the limiting reagent norbornene.

Table 2. Additive Screening for the "Diverted Heck" Cyclopentenation of Norbornene with *o*-Bromobenzyltributylstannane (2a)[a]



no.	additive	yield (%)[b]	conv. 2a (%)[b]
1	none	19.2	47.3
2	LiCl (1.2 equiv)	10.8	>99
3	CuI (0.1 equiv)	6.8	95.9
4	CuI (0.2 equiv)	2.7	3.9
5	CuI (1.2 equiv)	1.4	35.4
6	CsF (1.2 equiv)	64.0	>99
7	CsF (2.4 equiv)	32.3	>99
8	CsF (1.2 equiv) CuI (0.1 equiv)	7.0	21.6
9	CsF (1.2 equiv) CuI (0.2 equiv)	3.6	39.6
10	CsF (2.4 equiv) CuI (0.1 equiv)	3.6	44.8
11	CsF (2.4 equiv) CuI (0.2 equiv)	6.7	53.5
12[c]	CsF (1.2 equiv)	83.1	87.8

[a]Standard conditions: norbornene (11.0 mg, 1.0 equiv), stannane **2a** (64.4 mg, 1.2 equiv), $[(o\text{-tolyl})_3P]_2PdCl_2$ (4.6 mg, 5 mol %), 1.6 mL of ^{t}BuOH, 75 °C, 22 h. [b]Yields and conversions were evaluated by GC-FID. [c]Reaction run in ^{i}PrOH instead of ^{t}BuOH.

With an optimized solvent and additive in hand, the next component to optimize is the stannane itself. There are two functional groups to be modified, these being the stannyl group and the halide (Table 3). Using the corresponding aryl chloride (entry 2) or aryl triflate (entry 4), barely any reaction is noticed, while the reaction proceeds, when the corresponding aryl iodide (entry 3) is used, although the yield is notably lower. The same is true for the benzyl iodide, although in this case, contrary to the aryl halides, the reagent is completely consumed. The trimethylstannane (entry 5) leads to a similar yield as the tributylstannane.

The last component to optimize is the catalyst itself. Accordingly, the same reaction was conducted using several different palladium catalysts with different ligands (Table 4). As is immediately apparent, the reaction strongly favors phosphine complexes. The tested NHC (entry 9) and isocyanide (entry 10) complexes do not lead to any product formation. The same is true for palladium acetate (entry 11) without any added ligand. In the case of tris(*o*-tolyl)phosphine-based ligands, increasing the electron density (entry 2) does not notably change the performance, while the electron-poorer complex (entry 3) leads to a yield increase of 10%. Switching from phosphine to arsine ligands (entry 4) is also detrimental. Comparing the tetrakis(triphenylphosphine) complexes of palladium (entry 5) and nickel (entry 6) also shows that a nickel-catalyzed system, while being slightly less active, could be developed.

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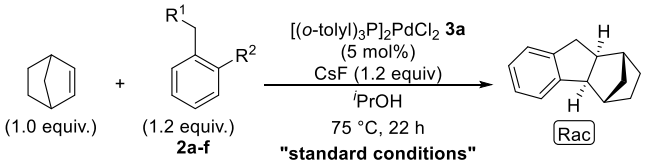
Organometallics 2021, 40, 776−782

Table 3. Reagent Screening for the "Diverted Heck" Cyclopentenation of Norbornene[a]

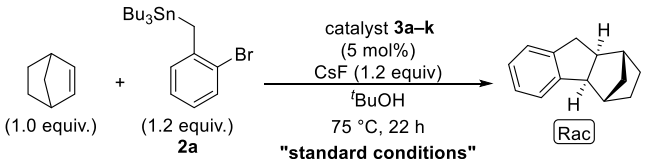


2a: $R^1 = SnBu_3$ $R^2 = Br$
2b: $R^1 = SnBu_3$ $R^2 = Cl$
2c: $R^1 = SnBu_3$ $R^2 = I$
2d: $R^1 = SnBu_3$ $R^2 = OTf$
2e: $R^1 = SnMe_3$ $R^2 = Br$
2f: $R^1 = I$ $R^2 = SnBu_3$

no.	reagent	yield (%)[b]	conv. 2a–f (%)[b]
1	2a	83.1	87.8
2	2b	0.6	28.4
3[c]	2c	36.0	38.2
4	2d	0.0	7.5
5	2e	76.6	94.2
6	2f	24.4	>99

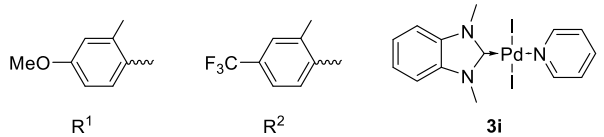
[a]Standard conditions: norbornene (11.0 mg, 1.0 equiv), stannane **2a–f** (1.2 equiv), CsF (21.3 mg, 1.2 equiv), $[(o\text{-tolyl})_3P]_2PdCl_2$ (4.6 mg, 5 mol %), 1.6 mL of ^{i}PrOH, 75 °C, 22 h. [b]Yields and Conversions were evaluated by GC-FID. [c]Reaction was conducted with all volumes and masses of solvents and reagents cut in half.

Table 4. Catalyst Screening for the "Diverted Heck" Cyclopentenation of Norbornene[a]



no.	catalyst	yield (%)[b]	conv. 2a (%)[b]
1	$[(o\text{-tol}_3P)_2PdCl_2]$ (3a)	64.0	>99
2	$[(R^1{}_3P)_2PdCl_2]$ (3b)	68.4	98.3
3	$[(R^2{}_3P)_2PdCl_2]$ (3c)	75.6	91.3
4	$[(o\text{-tol}_3As)_2PdCl_2]$ (3d)	22.4	63.7
5	$[(Ph_3P)_4Pd]$ (**3e**)	35.7	72.5
6	$[(Ph_3P)_4Ni]$ (3f)	30.2	49.6
7	$[(dppf)PdCl_2]$ (3g)	50.8	83.7
8	^{t}BuXPhos Pd G3 (3h)	2.0	89.5
9	**3i**	0.0	<1
10	$[(^t\text{BuNC})_2PdCl_2]$ (3j)	0.0	<1
11	$Pd(OAc)_2$ (3k)	0.0	<1

[a]Standard conditions: norbornene (11.0 mg, 1.0 equiv), stannane **2a** (64.4 mg, 1.2 equiv), CsF (21.3 mg, 1.2 equiv), catalyst **3a–k** (5 mol %), 1.6 mL of ^{t}BuOH, 75 °C, 22 h. [b]Yields were evaluated by GC-FID.



DISCUSSION

Following up on the invention of the "diverted Heck" cyclopropanation, we report the first "diverted Heck" cyclopentenation. While the cyclopropanation uses a boron-based reagent, we show that this is problematic for the cyclopentenation reaction. It was found that competing protodeboronation, C–H activation, and transfer hydrogenation lead to a large number of major side products. While the latter two reactions can be prevented through modification of the reaction conditions, the protodeboronation product remains the major product.

As a result of these stability issues, a tin-based system was developed. While this system immediately showed much better results than the boron-based system, especially only negligible protodestannylation, this system was further optimized. For the solvent optimization, it was found that alcoholic solvents are the best. Tchawou et al.[7] did describe the presence of palladium–alcoholate species during the reaction. It is reasonable to assume that such species are also formed here and are important for the reaction. It should also be noted that unlike for the boron system, reducing alcohols are not problematic. This can be easily explained as while for the boronates protodeboronation did already make transmetalation uncompetitive, in the tin system, the intramolecular transmetalation is possible. In this case, it outcompetes any hydrogen-transfer reaction.

For additives, it was found that CsF notably increases the performance of the system, while LiCl or CuI are detrimental. CsF is believed to facilitate the transmetalation step by either activating the stannane by coordinating to the tin atom or replacing other halides on palladium and enabling the formation of the cyclic transition state as a ligand for tin.

For the choice of the reagent, the aryl bromide proved to be the most efficient. While the aryl chloride was not expected to lead to any improvement due to the much slower oxidative addition,[17] the results for the triflate were not necessarily predictable. It has been shown before that the performance of aryl triflates for palladium-catalyzed reactions is highly variable. While in some cases they are superior to the bromides, they have been reported to be worse than the aryl chlorides in other cases, especially when bulky and electron-rich ligands like P^tBu_3 are employed.[18] Apparently, this is also the case in the system described here. Surprisingly, the aryl iodide forms less product than the bromide, although it should lead to a faster oxidative addition. However, if the oxidative addition is not rate-limiting in the bromide case, no improvement should be expected from this. For the "diverted Heck" cyclopropanation, the migratory insertion and not the transmetalation was found to be rate-limiting.[7] On the other hand, aryl iodides have been found to slow down the transmetalation step of the Stille reaction as less reactive palladium iodide complexes are formed.[19] In both the bromide and the iodide case, the catalyst itself decays before the reaction can completely finish as both starting materials are still present at the end of the reaction. If the catalyst decomposition is more or less independent from the halide, this implies that if a slower transmetalation is rate-determining, less product can be formed until the catalyst decomposes, lowering the overall yield of the reaction. While benzyl iodide **2f** does form the cyclopentenation product as expected, it is less efficient than the aryl bromide or iodide. While benzyl halides are expected to undergo faster oxidative addition than aryl halides,[20] unlike aryl halides, they are susceptible to nucleophilic substitution reactions. Under the reaction conditions (75 °C, alcoholic solvent), ethers should be formed. In fact, among the used reagents, only for the benzyl halide was no trace of it found in GC-FID at the end of the reaction, implying that side reactions occur. It is reasonable that the formed ethers, by still

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Organometallics 2021, 40, 776–782

containing the heavy stannyl group, are not volatile enough to be detected in GC.

For the catalyst choice, it was found that phosphine complexes are vastly preferred. Neither the tested NHC complex nor the isocyanide complex led to any product formation, as did the ligand-free variant with palladium acetate. For the phosphine systems, only **3h** did not form any notable amounts of the product. This is not surprising as an activation of the precatalyst through a base is necessary,[21] which is not possible here. For tris(*o*-tolyl)phosphine-based complexes **3a**–**c**, the difference of performance of the unsubstituted ligand **3a** and the more electron-rich ligand **3b** might not be statistically relevant. Nevertheless, the electron-poor ligand **3c** shows some increased activity. This would match the description for the cyclopropanation that the migratory insertion is rate-limiting as a lower electron density on the catalyst should accelerate this step.[22] While a more weakly binding arsine can also be used, complex **3d** is less efficient. This can be explained with the lower stability of arsine complexes compared to the phosphine complex, leading to faster catalyst decomposition.

Notably, nickel catalyst **3f** is not much less active than the corresponding palladium catalyst **3e**. In fact, it appears to be more selective. This implies that a nickel-catalyzed variant of the "diverted Heck" reaction is possible, although a higher catalyst loading might be needed.

While for the stannane systems no notable side products were visible in GC, certain systems showed a notable discrepancy between yield and conversion, implying that the reagent has to have reacted in a way invisible to GC. The most obvious side reaction is the formation of non-volatile oligomers through Stille coupling as a tin analogue to Suzuki polycondensation.[23] This implies that the intermolecular transmetalation reaction competes with the migratory insertion. The selectivity for Stille coupling or "diverted Heck" reaction therefore depends on the relative rates of these two reactions.

CONCLUSIONS

The first "diverted Heck" cyclopentenation has been reported. It was shown that systems based on benzylboronic acids are not viable. Accordingly, a working tin-based system was designed. It was found that polar-protic solvents and addition of CsF are necessary to optimize the reaction. Phosphine-based catalysts are preferred. While palladium is the metal of choice for this, the possibility for the development of a nickel-based system is shown.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.organomet.1c00025.

Synthesis and experimental details, kinetics, spectra, and calibration curves (PDF)

AUTHOR INFORMATION

Corresponding Author

Peter Chen − *Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule (ETH) Zürich, Zürich CH-8093, Switzerland;* orcid.org/0000-0002-9280-4369; Email: peter.chen@org.chem.ethz.ch

Author

Kevin Breitwieser − *Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule (ETH) Zürich, Zürich CH-8093, Switzerland;* orcid.org/0000-0002-7012-8750

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.organomet.1c00025

Notes

The authors declare no competing financial interest.

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Organometallics 2021, 40, 776−782