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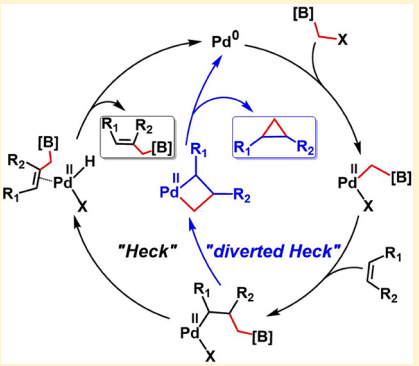
Mechanism-Based Design and Optimization of a Catalytic Electrophilic Cyclopropanation without Diazomethane

Augustin A. S. W. Tchawou, Mihai Raducan, and Peter Chen*

Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule (ETH) Zürich, CH-8093 Zürich, Switzerland

Supporting Information

ABSTRACT: Iodomethylboron compounds, either the trifluoroborate or a boronic ester, cyclopropanate electron-rich olefins and unprotected allylic alcohols with Pd catalysts according to a novel, designed catalytic cycle. Proposed intermediates in a "diverted Heck" mechanism are observed by means of spectroscopic studies and by isolation and X-ray crystallographic characterization, which together with reaction kinetics point to a separation of rate-determining and product-determining steps, and a mechanism-based optimization of the yield, selectivity, and scope of the catalytic electrophilic cyclopropanation. The reaction with crystalline, air-stable, nonhygroscopic, and nontoxic reagents provides an alternative to Simmons–Smith-type reactions, as well as cyclopropanation procedures that require the use of diazomethane.



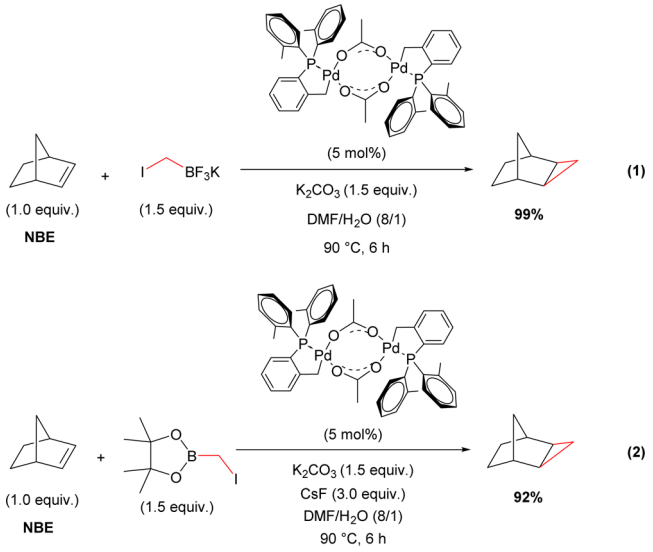
The synthetic preparation of cyclopropanes commonly requires the use of a Simmons–Smith-type cyclopropanation[1] or the metal-catalyzed decomposition of diazo compounds.[2] Alternative preparative pathways reported for nucleophilic cyclopropanations include organocatalysis,[3] the Michael initiated ring closure (MIRC) reaction,[4] or palladium catalysis[5] to produce cyclopropanes. These approaches, however, are mostly limited to electron-deficient or polar olefins. The necessity of developing a safer and catalytic electrophilic strategy for the cyclopropanation of electron-rich alkenes therefore exists.

Palladium-catalyzed carbon–carbon bond formation via cross-coupling chemistry has shown an enormous synthetic potential in organic synthesis and has become widely used in research, in both academia and industry.[6] The mechanisms have been extensively investigated over the past few decades. Key elementary steps common to the major palladium-catalyzed carbon–carbon bond-forming reactions include oxidative addition, transmetalation, and reductive elimination. The coupling partner associated with the Mizoroki–Heck-type[7] reaction is an alkene, whereas for the other major coupling methods (e.g., Suzuki,[8] Negishi,[9] Sonogashira,[10] Hiyama,[11] Stille,[12] etc.) an organometallic reagent is utilized.

Combining the principles featured in these palladium-based cross-coupling reactions, we recently disclosed a catalytic route for the cyclopropanation of norbornene (NBE) using a commercially available iodomethylboron species as the methylene transfer agent.[13] We found that in DMF/H_2O in a 8/1 ratio at 90 °C, the Herrmann–Beller catalyst,[14] widely used in the Heck reaction, was particularly efficient in converting norbornene (NBE) into the corresponding tricyclo(3.2.1.$0^{2,4}$)-octane in the presence of potassium iodomethyltrifluoroborate (ICH_2BF_3K), with potassium carbonate acting as a base (Scheme 1, eq 1). Using iodomethylboronic acid pinacol ester (ICH_2Bpin) instead of ICH_2BF_3K together with cesium fluoride under the same conditions led to the formation of the cyclopropane in 92% yield (Scheme 1, eq 2).

In that original work, other electron-rich alkenes, such as cyclooctene (COE), showed low conversion and poor

Scheme 1. Previously Reported Pd-Catalyzed Methylenation of NBE using Iodomethylboron Species



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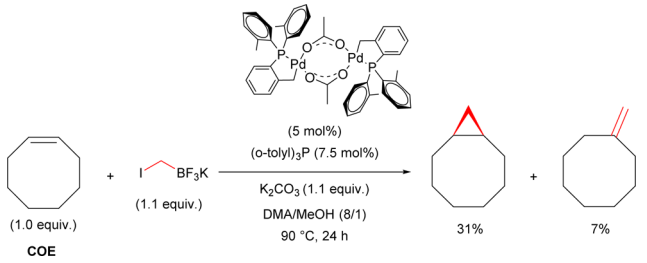
selectivity for the desired cyclopropanation products over what we identified to be β-hydride elimination products (Scheme 2). Major questions concerning the mechanism by which the reaction is taking place remained open.

Scheme 2. Previously Reported Pd-Catalyzed Methylenation of COE using Iodomethyltrifluoroborate



We report here experimental evidence for the "diverted Heck" mechanism proposed in our earlier work and the mechanism-based improvement in yield and substrate scope for the palladium-catalyzed cyclopropanation of electron-rich olefins, including strained and unstrained substrates, sterically hindered olefins, and allylic alcohols.

EXPERIMENTAL SECTION

General Remarks. Unless otherwise stated, all reactions were carried out under an argon or N_2 atmosphere using standard Schlenk or glovebox techniques with anhydrous solvents. Solvents and reagents were acquired from Aldrich, Fluka, Acros Organics, ABCR Chemicals, and TCI. Deuterated solvents were obtained from Amar Chemicals. Extra molecular sieves were added to the purchased solvents and the solvents stored in the glovebox. ICH_2BF_3K (>98.0%) was acquired from TCI, further purified by washing several times with Et_2O, dried under high vacuum, and then stored in the glovebox. NMR data were recorded at 300, 400, or 600 MHz (Bruker AV300, AV400, and AV600 spectrometers) with $CDCl_3$, CD_3OD, THF-d_8, or DMF-d_7 as solvent. Chemical shifts (δ) are reported in ppm with the residual solvent signal as internal standard (chloroform at 7.26 and 77.00 ppm for ^1H and ^{13}C spectroscopy, respectively; methanol at 3.31 and 49.00 ppm for ^1H and ^{13}C spectroscopy, respectively; tetrahydrofuran at 3.58 and 67.57 ppm for ^1H and ^{13}C spectroscopy, respectively; dimethylformamide at 2.75, 2.92, and 8.03 ppm for ^1H spectroscopy). ^{13}C NMR spectra were recorded with complete ^1H decoupling. Service measurements were performed by the NMR service team of the Laboratorium für Organische Chemie, ETH Zürich, by Mr. Rainer Frankenstein, Mr. René Arnold, and Mr. Stephan Burkhardt under the supervision of Dr. Marc-Oliver Ebert. X-ray structural analysis was performed by the X-ray crystallography group of the Laboratorium für Organische Chemie, ETH Zürich. High-resolution mass spectra were recorded by the mass spectrometry service of the ETH Zürich Laboratorium für Organische Chemie with a Micromass (Waters) AutoSpec Ultima (EI) or a Bruker solariX (MALDI-FTICR) instrument. GC-FID analysis was performed on a Finnigan Focus GC instrument with a Zebron ZB-5MS 30 m × 0.25 mm column or a Restek Rtx-Wax 30 m × 0.25 mm column using a flame ionization detector. Qualitative gas-phase studies were performed on a Thermo Finnigan TSQ Quantum ESI-MS/MS instrument. Charged species were generated by electrospray ionization (ESI) from dilute ($\sim 10^{-5}$ mol/L) solutions freshly prepared in the glovebox, taken into a Hamilton gastight syringe, and used immediately. All samples were electrosprayed with a flow rate of 5 mL/min.

Representative Methylenation Procedure in DMA/EG or THF/EG. An oven-dried Schlenk (2.5 or 5 mL) equipped with a Teflon J. Young valve and an oven-dried magnetic stir bar was charged in a N_2-filled glovebox with powdered K_2CO_3 (80.9 mg, 5.0 equiv) and anhydrous ethylene glycol (EG, 0.1 mL). The mixture was vigorously stirred for 10 min before and during the addition of a solution of anhydrous dimethylacetamide (DMA, 0.6 mL) containing the Pd catalyst $[(o\text{-tolyl})_3P]_2PdCl_2$ (4.6 mg, 5 mol %), ICH_2BF_3K (34.8 mg, 1.2 equiv), and cyclooctene (COE, 15.2 μL, 0.117 mmol). The rest of the anhydrous DMA (2 × 0.5 mL) was utilized to rinse the vial containing the previous solution and then added to the reaction mixture. The tube was sealed, removed from the glovebox, and heated to 75 °C for 22 h. The reaction mixture was then rapidly cooled to 0 °C in an ice bath for 15 min, and a workup was conducted.

Representative Methylenation Procedure in DMA/MeOH. A 5 mL oven-dried Schlenk (2.5 or 5 mL) equipped with a Teflon J. Young valve and an oven-dried magnetic stir bar was charged in a N_2-filled glovebox with powdered K_2CO_3 (80.9 mg, 5.0 equiv) and anhydrous MeOH (0.5 mL). The mixture was vigorously stirred for 10 min before, and during, the addition of a solution of anhydrous DMA (0.6 mL) containing the Pd catalyst $[(o\text{-tolyl})_3P]_2PdCl_2$ (4.6 mg, 5 mol %), ICH_2BF_3K (34.8 mg, 1.2 equiv) and COE (15.2 μL, 0.117 mmol). The rest of the anhydrous DMA (2 × 0.5 mL) and anhydrous MeOH (0.3 mL) was utilized to rinse the vial containing the previous solution and then added to the reaction mixture. The tube was sealed, removed from the glovebox, and heated to 75 °C for 22 h. The reaction mixture was then rapidly cooled to 0 °C in an ice bath for 15 min, and a workup was conducted.

Representative Kinetic Experiment. Each time point in a kinetic run was acquired with the following procedure. An oven-dried Schlenk (2.5 or 5 mL) equipped with a Teflon Young valve and an oven-dried magnetic stir bar was charged in a N_2-filled glovebox with powdered K_2CO_3 (80.9 mg, 5.0 equiv) and anhydrous EG (0.1 mL). The mixture was vigorously stirred for 10 min before, and during, the addition of a solution of anhydrous DMA (0.6 mL) containing either the Pd catalyst $[(o\text{-tolyl})_3P]_2PdCl_2$ (4.6 mg, 5 mol %) or a mixture of $(o\text{-tolyl})_3P$ (1.78 mg, 5 mol %) and the Pd catalyst $[COD]PdCl_2$ (1.67 mg, 5 mol %), ICH_2BF_3K (34.8 mg, 1.2 equiv), and COE (15.2 μL, 0.117 mmol). The rest of the anhydrous DMA (2 × 0.5 mL) was utilized to rinse the vial containing the previous solution and then added to the reaction mixture. The tube was sealed, removed from the glovebox, and heated to 75 °C for the indicated reaction time. Then the reaction mixture was rapidly cooled to 0 °C in an ice bath for 15 min and a workup was conducted. The resulting solution was analyzed by GC-FID.

Procedure for Small-Scale Workup. The internal standard, undecane (10 μL, around 0.40 equiv for 0.117 mmol scale of olefin), was added to the tube with the reaction mixture, followed by Et_2O (2 × 35 mL/mmol substrate). The solution was transferred to a 15 mL glass vial. The Schlenk tube was rinsed with H_2O (45 mL/mmol substrate) or saturated NH_4Cl (for the allylic alcohols). The aqueous layer was transferred to the 15 mL glass vial, and the layers were separated. The organic phase was transferred to another 15 mL glass vial, washed with H_2O (45 mL/mmol substrate) and brine (45 mL/mmol substrate), dried over $MgSO_4$, and then filtered through Celite. The resulting solution was analyzed by GC-FID.

Representative Procedure for the Scale-Up of the Methylenation Reaction of Olefins to Millimole (Gram-Scale) Amounts. A 250 mL oven-dried round-bottom flask equipped with an oven-dried magnetic stir bar was charged in a N_2-filled glovebox with powdered K_2CO_3 (4.04 g, 5.0 equiv), anhydrous EG (5 mL), and anhydrous DMA (20 mL). The resulting mixture was stirred vigorously. $[(o\text{-tolyl})_3P]_2PdCl_2$ (230 mg, 5 mol %), $(o\text{-tolyl})_3P$ (89 mg, 5 mol %), ICH_2BF_3K (2.18 g, 1.5 equiv), and cyclooctene (645 mg, 5.85 mmol) were added to the mixture with stirring. A 60 mL portion of DMA was used to rinse the vials utilized to weigh all the reagents and was subsequently added to the reaction mixture. The round-bottom flask was then closed and removed from the glovebox, and the contents were stirred at 75 °C for the indicated time. At the end of the reaction, which was monitored by GC/MS, the flask was cooled to 0 °C and its contents were poured over Celite. The filter cake was washed with Et_2O (3 × 50 mL). The filtrate was transferred to a separatory funnel, and H_2O (200 mL) was added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 100 mL). The fractions were combined, dried over $MgSO_4$, and filtered, and the ether solution was removed by a rotary evaporator. The resulting oil residue

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was purified by flash column chromatography over silica gel using pentane as eluent. Slow evaporation of the solvent yielded 654 mg (90%) of a mixture of bicyclo[6.1.0]nonane (**2a**) and methylenecyclooctane (**3a**) (50:1 ratio of products in favor of the cyclopropane) as a colorless oil. MS (EI): 124 (32, $[M]^+$), 96 (94), 81 (77), 67 (100), 54 (73), 41 (27). HRMS (EI, ($[M]^+$)): *m/z* calcd for C_9H_{16}, 124.1247; found, 124.1247. See the Supporting Information for further details related to each isolated cyclopropane.

Sample Preparation for NMR Methylenation Reaction Monitoring. An oven-dried NMR tube equipped with a Teflon screw cap was transferred into a N_2-filled glovebox and charged with powdered K_2CO_3 (0.195 mmol, 5.0 equiv). A 1.5 mL oven-dried vial was charged with $[(o\text{-tolyl})_3P]_2PdCl_2$ (1.53 mg, 5 mol %), ICH_2BF_3K (9.67 mg, 1.2 equiv), COE (5.1 μL, 0.039 mmol), anhydrous EG-d_6 (0.33 mL), and anhydrous DMA-d_9 (2.33 mL). The solution was then transferred to the NMR tube and the vial rinsed with anhydrous DMA-d_9 (2 × 1.5 mL). The rinse solution was placed in the NMR tube. The NMR tube was sealed, shaken, and maintained at 75 °C for 16 h.

Oxidative Addition of ICH_2Bpin in THF. An oven-dried NMR tube was brought into a N_2-filled glovebox and charged with $Pd(dba)_2$ (30 mg, 0.052 mmol, 1.05 equiv), $(o\text{-tolyl})_3P$ (15 mg, 0.049 mmol, 1.0 equiv), and anhydrous THF-d_8 (0.4 mL). The tube was then closed and agitated for ∼5 min. A 1.5 mL oven-dried vial was charged with ICH_2Bpin (33 mg, 0.123 mmol, 2.5 equiv) and anhydrous THF-d_8 (0.2 mL). The solution was then transferred to the NMR tube. The tube was closed with a cap and agitated for 15 min, and the NMR spectrum was taken at room temperature. The dark red solution turned yellow with deposition of a greenish solid.

Oxidative Addition of ICH_2Bpin in the Presence of NBE in THF. An oven-dried NMR tube was transferred into a N_2-filled glovebox and charged with $Pd(dba)_2$ (30 mg, 0.052 mmol, 1.05 equiv), $(o\text{-tolyl})_3P$ (15 mg, 0.049 mmol, 1.0 equiv), and anhydrous THF-d_8 (0.4 mL). The tube was closed and agitated for ∼5 min. NBE (23.07 mg, 0.245 mmol, 5 equiv) in anhydrous THF (0.2 mL) was added, and an NMR of the resulting orange solution was taken 30 min later. The tube was then transferred back to the glovebox and charged with ICH_2Bpin (33 mg, 0.123 mmol, 2.5 equiv). Another NMR spectrum was taken, and the mixture was heated to 60 °C for 10 min and then cooled to room temperature, diluted, and used immediately for gas-phase studies.

Oxidative Addition of ICH_2BF_3K in DMF. An oven-dried NMR tube was brought into a N_2-filled glovebox and charged with the Pd complex *t*-BuXPhos Pd G3 (4.8 mg, 6.0 μmol, 1.0 equiv), ICH_2BF_3K (3.0 mg, 1.2 μmol, 2.0 equiv), and powdered K_2CO_3 (1.7 mg, 1.2 μmol, 2.0 equiv), successively dissolved in anhydrous DMF-d_7 (0.6 mL). The tube was then closed and agitated for ∼5 min, and the NMR spectrum was taken at room temperature. The mixture was diluted and immediately used for gas-phase studies.

Preparation of the Pd Complex 8. A 25 mL oven-dried round-bottom flask was brought into a N_2-filled glovebox and charged with K_2CO_3 (136 mg, 4.0 equiv), ICH_2BF_3K (183.4 mg, 3.0 equiv), and DMF (1 mL). The Buchwald palladium precatalyst tBuXPhos Pd G3 (196 mg, 0.246 mmol, 1.0 equiv) in DMF (1 mL) was added to this mixture with stirring at ambient temperature, and the vial containing the precatalyst was rinsed with another 1 mL of DMF that was then transferred to the reaction mixture. Stirring was continued for 10 min before removal of the solvent by rotary evaporation. A DCM/pentane (5 mL/10 mL) mixture was added to the resulting residue, and this mixture was filtered over Celite. The Celite filter cake was washed with pentane (5 mL). The solvents were slowly evaporated on a rotary evaporator under moderate vacuum (no water bath) until a great deal of clear green microcrystals appeared in the flask. Evaporation was stopped, and the crystals were isolated by filtration, washed with a small volume of cold pentane, and dried under high vacuum. These crystals were suitable for X-ray analysis. A 126 mg amount of product was obtained (NMR reveals the presence of 9*H*-carbazole). ^{1}H NMR (400 MHz, CH_2Cl_2-d_2): δ 7.99 (tq, $^3J_{HH}$ = 6.5 Hz and $^4J_{HP}$ = 2.2 Hz, 1H, aryl C*H*), 7.57−7.51 (m, 2H, aryl C*H*), 7.28−7.27 (m, 2H, aryl C*H*), 7.19−7.11 (m, 1H, aryl C*H*), 3.02 (hept, $^3J_{HH}$ = 6.9 Hz, 1H, iPr C*H*), 2.45 (hept, $^3J_{HH}$ = 6.7 Hz, 2H, iPr C*H*), 1.56 (d, $^3J_{HH}$ = 6.8 Hz, 6H, iPr CH_3), 1.48 (d, $^3J_{HP}$ = 15.1 Hz, 18H, tBu), 1.36 (d, $^3J_{HH}$ = 6.9 Hz, 6H, iPr CH_3), 1.19 (qd, $^3J_{HF}$ = 8.0 Hz and $^3J_{HP}$ = 1.6 Hz, 2H, PdCH_2BF$_3$), 0.95 (d, $^3J_{HH}$ = 6.6 Hz, 6H, iPr CH_3). ^{31}P NMR (162 MHz, CH_2Cl_2-d_2): δ 75.42 (q, $^4J_{PF}$ = 32.6 Hz). ^{19}F NMR (376 MHz, CH_2Cl_2-d_2): δ −140.53 (s, PdCH$_2$B*F*$_3$). ^{11}B NMR (160 MHz, CH_2Cl_2-d_2): δ 5.38 (s, PdCH$_2$*B*F$_3$). HRMS (MALDI-FTICR/DCTB, ($[M\text{-}BF_3]^+$)): *m/z* calcd for $C_{30}H_{47}PPd$, 544.2456; found, 544.2456. All spectra are available in the Supporting Information.

Control Experiments. The methylenation procedures were followed, and only the reagents needed for each experiment were charged in the oven-dried Schlenk tube. The tube was sealed, removed from the glovebox, and heated to 75 °C for 16 h. At the end of the indicated time, the Schlenk tube was cooled to 0 °C for 15 min, dried, and transferred to the glovebox. A 0.6 mL portion of the solution was filtered and transferred into an oven-dried NMR tube placed in an external NMR tube containing the reference solvent DMF-d_7. The tubes were closed, and NMR was taken at room temperature.

Gas-Phase Studies. In the glovebox, 0.1 mL of the reaction mixture was diluted to ∼10^{-5} M in dry MeCN or dry THF and used immediately for gas-phase studies. Conditions: spray voltage 5 kV, collision offset 35 V, tube lens offset 100 V, and capillary temperature 50 or 170 °C. Collision-induced dissociation (CID) experiments were done with an argon pressure of 0.5 mTorr in the collision cell.

RESULTS

As will be detailed in the Discussion, the expansion of the substrate scope and improvement of product selectivity were based on mechanistic and kinetic studies, proceeding in tandem with the preparative work. The preparative results are shown first, though, to indicate the degree to which the optimization succeeded. The experimental results pertinent to the reaction mechanism follow in the text, although the two processes actually ran concurrently.

Reaction Optimization. Cyclooctene (COE) was chosen as a model substrate for the development of a generalized procedure for the methylenation of electron-rich alkenes because, as we had shown in the previously published work (Scheme 2), COE gave only modest yields of both cyclopropanation and side products. Accordingly, as a test substrate, there was ample room for improvement in yield and selectivity. Table 1 summarizes the results of the optimization of the cyclopropanation of COE. $[(o\text{-tolyl})_3P]_2PdCl_2$ (**Cat1**) proved to be the most active catalyst in the conversion of COE among the catalysts we tested. At 75 °C, it outperformed the previously utilized Herrmann−Beller catalyst (**Cat2**) when used in the presence of 1.2 equiv of the methylenating agent ICH_2BF_3K and 3.0 equiv of the base K_2CO_3 in (DMA/MeOH, 2/1) and without an additional free phosphine ligand (entries 1 and 2). Under these conditions, the expected bicyclo[6.1.0]-nonane (**2a**) product was prepared in 74% yield, a satisfactory mass balance being obtained, with the balance of the material being accounted for by the side product methylenecyclooctane (**3a**) and recovered starting material. Increasing the amount of the base to 5 equiv significantly improved the selectivity (entry 3). Interestingly, substituting CH_3OH with CD_3OD appeared to give even better results (entry 4), although it is not clear if the putative isotope effect exceeds the range of variation in the experiment.

The yield of **2a** was further improved to 94% by replacing the former solvent mixture with DMA/EG in a ratio of 16/1 (entry 5). Lowering (8/1) or increasing (32/1) this ratio led to decreased product yields of 84% and 87%, respectively (entries 6 and 7). No products were observed when pinacol was used instead of EG (entry 8). The use of glycerol gave 71% of **2a** (entry 9). Substituting THF for DMA led to a reduced

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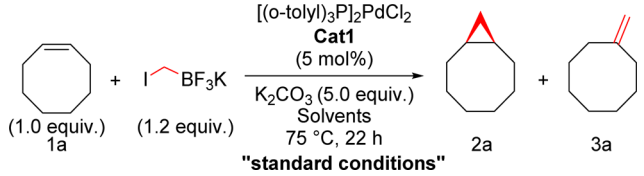
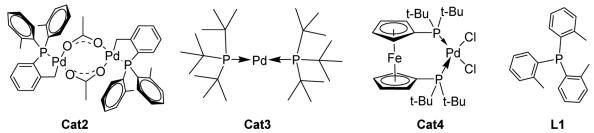
Table 1. Optimization Experiments for the Pd-Catalyzed Methylenation Reaction of COE (1)[a]



no.	variation from "standard conditions"	solvent (ratio)	2 (%)[b]	3 (%)[b]
1[c,d]	**Cat2** (5 mol %)	DMA/MeOH (2/1)	63.6	0.8
2	3 equiv of K_2CO_3	DMA/MeOH (2/1)	74.0	1.1
3	none	DMA/MeOH (2/1)	76.5	0.5
4	none	DMA/CD_3OD (2/1)	82.9	0.6
5[c]	none	DMA/EG (16/1)	93.6	2.3
6[c]	none	DMA/EG (8/1)	83.8	3.2
7[c]	none	DMA/EG (32/1)	86.5	2.3
8	pinacol (15 equiv)	DMA	0.3	0.9
9	glycerol (10 equiv)	DMA	71.9	5.3
10	none	THF/EG (16/1)	12.9	0.4
11	ICH_2BF_3K (1.0 equiv)	DMA/EG (16/1)	81.7	1.7
12	$BrCH_2BF_3K$	DMA/EG (16/1)	0	0
13	in situ made catalyst[e]	DMA/EG (16/1)	85.5	2.1
14	**Cat1** (1 mol %)	DMA/EG (16/1)	71.2	1.7
15[f]	**Cat1** (1 mol %)	DMA/EG (16/1)	86.1	2.1
16	**Cat3**	DMA/EG (16/1)	53.7	1.2
17	**Cat4**	DMA/EG (16/1)	70.1	2.0
18	65 °C	DMA/EG (16/1)	90.4	2.5
19	65 °C for 36 h	DMA/EG (16/1)	96.2	2.6

[a]Standard conditions: 0.117 mmol (15.2 μL, 1.0 equiv) of alkene **1a**, ICH_2BF_3K (34.8 mg, 1.2 equiv), K_2CO_3 (80.9 mg, 5.0 equiv), **Cat1** (4.6 mg, 5 mol %), 75 °C, 22 h.



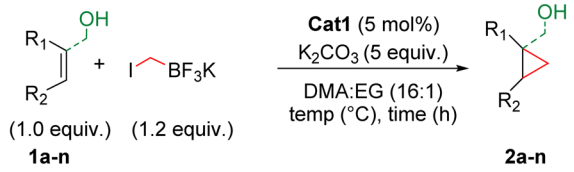
[b]Yields were evaluated by GC-FID. [c]~0.069 M solution. [d]In the presence of extra **L1** (15 mol %). [e]Mixture of **L1** (10 mol %) and [COD]$PdCl_2$ (5 mol %). [f]In the presence of extra **L1** (1 mol %).

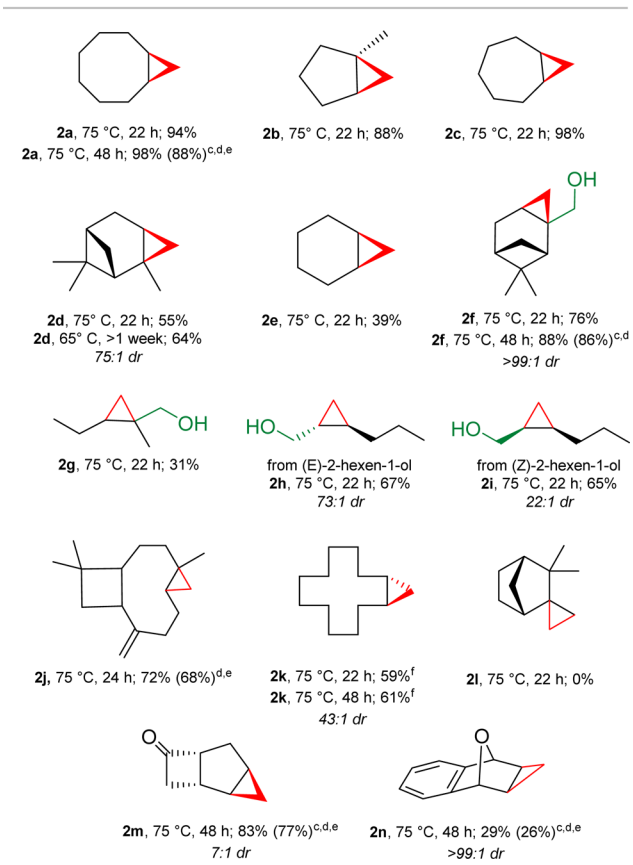
conversion of COE (entry 10). The yield also dropped to 81% when exactly 1.0 equiv of ICH_2BF_3K was utilized (entry 11). Use of $BrCH_2BF_3K$ as the methylenating agent resulted in a full recovery of the starting material (entry 12).

In accordance with previous reports, the in situ generated catalyst gave a lower yield (entry 13). Reducing the amount of catalyst to 1 mol % decreased the yield of the cyclopropane to 71% (entry 14). The addition of 1 mol % extra ligand to the latter improved the catalytic coupling (entry 15). The use of the bulky and electron-rich **Cat3** resulted in only a moderate yield (entry 16), which was slightly improved with its bidentate ferrocenyl analogue **Cat4** (entry 17). Interestingly, lowering the temperature to 65 °C for an extended reaction time (36 h) slightly increased the yield of formation of the product **2a** to 96% (entry 19).

Substrate Scope and Limitations. Having optimized the reaction conditions, the scope of this transformation was explored with various unactivated olefins and allylic alcohols, leading to the main products which were determined to have the same stereochemical configuration as those produced by a control Simmons–Smith-type cyclopropanation. The products were obtained in moderate to excellent yields, an exception being camphene (**1l**), for which only the starting material was recovered at the end of the reaction (Scheme 3). In general, the

Scheme 3. Pd-Catalyzed Methylenation Reaction: Scope of the Alkenes and Allylic Alcohols[a,b]





[a]Conditions: 0.117 mmol (1.0 equiv) of alkene **1**, ICH_2BF_3K (34.8 mg, 1.2 equiv), K_2CO_3 (80.9 mg, 5.0 equiv), **Cat1** (4.6 mg, 5 mol %), solvents DMA/EG (1.6 mL/0.1 mL, 16/1). [b]Yields were evaluated by GC-FID. [c]1.5 equiv of ICH_2BF_3K used. [d]Isolated yields are given in parentheses (5.85 mmol of alkene **1** used). [e]In the presence of extra **L1** (5 mol %). [f]Commercial mixture of cis and trans (2:1 trans:cis).

mass balance in these cyclopropanations was good, with the material not accounted for as cyclopropane consisting of the starting materials and/or β-hydride elimination products. GC-FID yields with detector calibration using independently synthesized reference compounds (see the Supporting Information) are given; selected substrates were cyclopropanated on the millimole, i.e. gram, scale, the isolated yields for which are given in parentheses in Scheme 3. Under the given reaction conditions, α-pinene, isolated in only 12% yield following the Simmons–Smith procedure,[15] gave up to 64%

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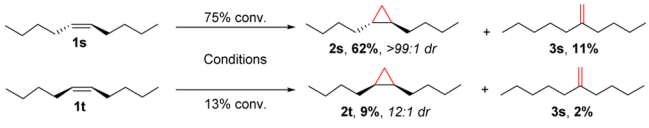
GC yield of the cyclopropane **2d**. It is noteworthy that only one stereoisomer was obtained in this case, which was confirmed to be the diastereomer **2d** through nuclear Overhauser effect spectroscopy (NOESY) experiments (Figure SI-20 in the Supporting Information). Although the reaction is stereospecific, a significant difference in selectivity and reactivity is observed between (*E*)- and (*Z*)-2-hexenol (73:1 dr and 22:1 dr, respectively). *trans*-Cyclododecene (**1k**; 2:1 trans:cis in the commercial mixture used) is mostly converted into the cyclopropane **2k**. The tricyclic ketone **2m** was prepared in good yield as a 7:1 mixture of its two isomers. The less abundant isomer corresponds to that having its cyclopropyl protons close to the carbonyl, leading to a downfield shift of δ 0.62 ppm. The cyclopropanation reaction of oxabenzonorbornadiene (**1n**), which does not cyclopropanate under Simmons–Smith conditions at all,[16] led specifically to the exoisomer **2n** in only 29% GC yield despite the complete consumption of the starting alkene.

Methylenation Reaction of 5-Decene. A discrimination in the methylenation reaction of the isomers of 5-decene is observed (Scheme 4). Under the same reaction conditions,

Scheme 4. Methylenation Reaction of 5-Decene[a]



[a]Conditions: 0.117 mmol (1.0 equiv) of alkene, ICH_2BF_3K (1.2 equiv), K_2CO_3 (5.0 equiv), **Cat1** (5 mol %), **L1** (5 mol %), solvents: DMA/EG (16/1), 75 °C, 24 h.

trans-5-decene (**1s**) and *cis*-5-decene (**1t**) were converted into the corresponding cyclopropanes in 75% and 13% yields, respectively. Furthermore, the cyclopropane **2s** was formed in 62% yield and >99:1 dr with an observed deposit of metallic black palladium, while **2t** was obtained in 9% yield and 12:1 dr with no similar catalyst aggregation and deposition observed.

Methylenation Reaction of a Linear Terminal Alkene. The cyclopropanation reaction of 1-octene (**1o**) presented in Table SI-9 in the Supporting Information highlights the strong influence of the β-hydride elimination on the catalytic outcome, as multiple consecutive methylene-inserted products, both branched and linear, are observed alongside the corresponding cyclopropanes.

Limitation on Yields. Control experiments were performed to ascertain the cause of lower cyclopropanation yield for some of the substrates. The low yield obtained with α-pinene, cyclohexene, and *cis*-5-decene, particularly, arises because the reaction is simply slow with these substrates. No deposition of palladium black was present after 22 h at 75 °C. With α-pinene, an additional 1 equiv of ICH_2BF_3K added to the reaction after 18 h at 75 °C resulted in an increase of cyclopropanation yield to 74% 24 h later (against 55% after 22 h at the same temperature; see Table SI-5 in the Supporting Information, entry 3), indicating that the catalyst remained active. Second, a control reaction under otherwise "standard conditions", but with no olefinic substrate (D-3 in the Supporting Information), gave no palladium black after 16 h at 75 °C. Subsequent addition of 1 equiv of cyclooctene into that flask gave a 53% yield of the cyclopropane after 24 h (against 94% yield at the same temperature and time when cyclooctene is added from the beginning). This experiment shows that (1) the dimeric reservoir (vide infra) has to be cleaved by an olefin and only then can the catalyst decompose and (2) the methylenating agent ICH_2BF_3K *slowly* decomposes, or converts into a less reactive reagent, under the reaction conditions when no olefin is available into which insertion can occur. This should represent a limitation of the present reaction for less reactive olefins. Finally, more reactive olefins, for which the cleavage of the dimeric reservoir species is more efficient, e.g. *trans*-5-decene, do show formation of palladium black, which signals that the reaction has ended with catalyst decomposition. For the unprotected allyl alcohols, an aldehydic oxidation (side) product was identified in the case of myrtenol (**1f**; see the Supporting Information).

Spectroscopic Studies. For a better understanding of the reaction, relevant reaction intermediates and/or products needed to be identified or isolated. Therefore, the reaction of COE with 1.2 equiv of ICH_2BF_3K in the presence of 5 equiv of K_2CO_3 catalyzed by 5 mol % of **Cat1** in DMA-d_9/EG-d_6 was conducted in an NMR tube and was monitored by ^1H and ^{11}B spectroscopy at 75 °C for 16 h (Figures SI-27 and SI-28 in the Supporting Information and Figure 1). It has to be noted that

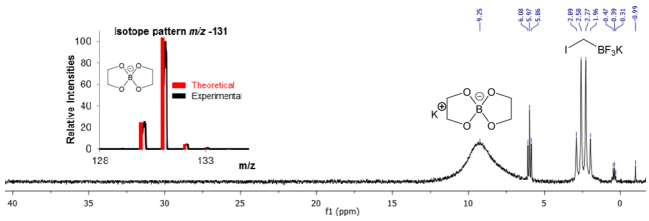


Figure 1. ^{11}B NMR spectrum of the methylenation reaction of COE recorded at 75 °C and isotope pattern of the bis(ethylene glycolato)borate anion in the ESI-MS.

this NMR study was hampered by the poor solubility of K_2CO_3 due to the lack of stirring in the tube. Consequently, the cyclopropane was produced in only 60% yield. ^{31}P NMR spectra were also taken at the beginning and the end of the reaction. No phosphorus signal was observed at the onset of the reaction because of the low solubility of the catalyst. At the end of the reaction, the ^{31}P NMR spectrum contained only one singlet at δ −30.4 ppm corresponding to the free tri-*o*-tolylphosphine ligand **L1**. Similarly, the ^{11}B NMR spectrum contained only two major peaks, one quartet at δ 2.6 ppm and one broad singlet at δ 9.3 ppm. The quartet signal corresponds to the starting ICH_2BF_3K. The broad singlet is assigned to the potassium bis(ethylene glycolato)borate having bound EG exchanging in solution with free EG and/or fluoride. Of note is the absence of a signal in the region of the spectrum where signals of trivalent boron should be present (δ 20–40 ppm;[17] Figure 1). The species observed in NMR were confirmed by ESI-MS experiments showing a peak in the spectrum at m/z −131 (Figure 1). Identical observations were made when an independently prepared synthetic standard was used.

Similar peaks were observed in the ^{11}B NMR spectrum of a control reaction consisting of a mixture of 10 mol % of **Cat1**, 1.2 equiv of ICH_2BF_3K and 5 equiv of K_2CO_3 in DMA/EG (2/1) at 75 °C for 16 h in the fume hood (Figure SI-43 in the Supporting Information). No traces of palladium black were observed in the final reaction mixture under those conditions. The ^{31}P NMR spectrum in Figure SI-42 in the Supporting Information shows the signal of the free **L1** ligand (δ −30.4 ppm) and two small broad peaks at δ 35.6 and 40.4 ppm which

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may correspond to cis and trans isomers of a bridged, dinuclear Pd(II) species (vide infra).

ESI-MS analysis of a reaction mixture, prepared analogously to the NMR samples, allowed the detection, in the positive mode, of a peak at m/z 595 that is assigned as the cationic palladium intermediate **IM1**, whose collision-induced dissociation (CID) is shown in Figure 2.

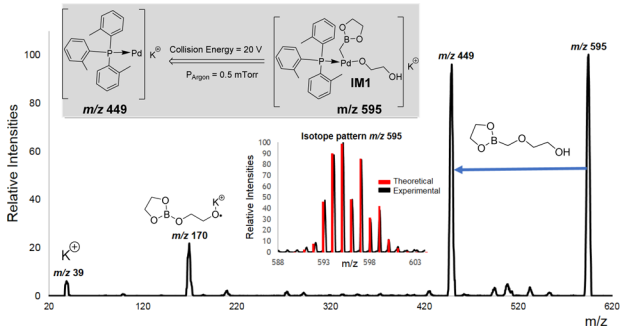

Figure 2. CID on the cation at m/z 595. Collision gas pressure: 0.5 mTorr, Collision energy: 20 V (center-of-mass reference frame). The structure in the inset represents the composition and makes no claim about whether the EG is bound monodentate or bidentate. The otherwise neutral Pd species are observed by MS as their K^+ adducts.

Direct Oxidative Addition to Pd(0). Oxidative addition of ICH_2Bpin occurs at room temperature in THF-d_8 to the Pd(0) species, formed in situ from 1.05 equiv of $Pd(dba)_2$ and 1 equiv of **L1**, to generate two major phosphine-containing species, observed in the ^{31}P NMR spectrum shown in Figure SI-29 in the Supporting Information. The two broad singlets appeared at δ 32.2 and 31.2 ppm. These peaks are most likely signals of phosphine ligands in the cis and trans isomers of bridged, dinuclear Pd species which would be formed after oxidative addition of Pd(0) to the C−I bond of ICH_2Bpin. Analysis of the NMR tube content using ESI-MS, sprayed after dilution with acetonitrile, permitted the observation of undesired products (m/z 319 and 431) as well as intermediate **IM2** (m/z 592; Figure 3) as the main palladium-containing species in the positive mode. Acetonitrile cleaves the presumed bridged, dinuclear Pd species to generate the observed mononuclear cationic palladium species. When the reaction was repeated in the presence of excess NBE, a new peak corresponding predominantly to the NBE-coordinated palladium species **IM3** was observed at m/z 645 after 10 min (Figure 4). Nevertheless, a small peak was observed in the CID spectrum at m/z 537, which most likely corresponds to the release of tricyclo(3.2.1.$0^{2,4}$)octane from **IM4**, a β-hydride elimination being disfavored for NBE.

The direct oxidative addition of ICH_2BF_3K to a "$(o\text{-tolyl})_3PPd^0$" intermediate at ambient temperature was not observed by NMR or ESI-MS, the reaction evidently requiring the higher temperatures specified in the preparative runs. In contrast, spectroscopic observations (NMR and ESI-MS) clearly show that a direct oxidative addition of ICH_2BF_3K to an in situ generated Pd(0) complex stabilized by the ligand *t*-BuXPhos in DMF-d_7 does occur at room temperature. A quartet with a coupling constant of 32.1 Hz at δ 75.5 ppm was observed in the proton-decoupled ^{31}P NMR spectrum. The observed quartet should arise from the fluorine−phosphorus coupling. The resulting palladium complex **8** was stable enough to be isolated and characterized by X-ray single-crystal

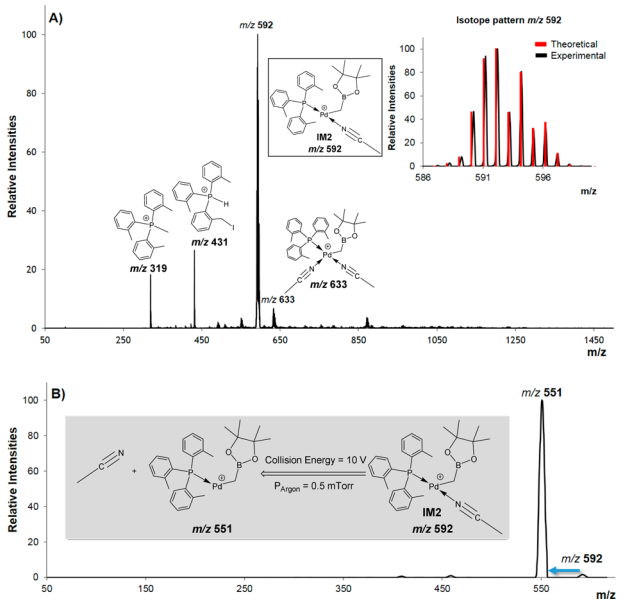

Figure 3. (A) Full scan in the positive mode showing products of oxidative addition and substitution by MeCN. (B) CID on the cation at m/z 592. Collision gas pressure: 0.5 mTorr, Collision energy: 10 V (center-of-mass reference frame).

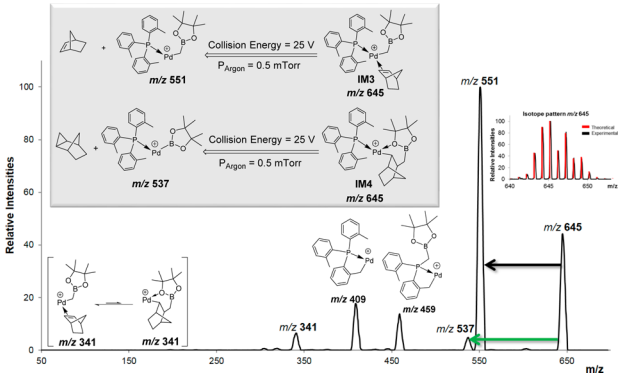

Figure 4. CID on the cation at m/z 645. Collision gas pressure: 0.5 mTorr, Collision energy: 25 V (center-of-mass reference frame).

diffraction. The X-ray structure of **8** depicted in Figure 5, the first-formed intermediate in the proposed catalytic cycle, confirms the presence of a coordination to the Pd metal of one of the fluorides (2.1833 Å) attached to boron. A markedly small B1−C1−Pd1 angle (93.17°) is therefore observed. Furthermore, the additional C2−Pd (2.400 Å) interaction leads to a Pd1−F1 bond sitting on top of the triisopropylbenzene group participating in the stabilization of the whole structure.

Kinetic Studies. To assess the rate law of the reaction, kinetic investigations were conducted. Using the "different excess" protocol of reaction progress kinetic analysis (RPKA) developed by Blackmond,[18] the data obtained from the given methylenation reaction conditions and for two different known concentrations of the reagent of interest were analyzed. The consumption of COE was followed over time, and yields were obtained by GC-FID. The results are reported in the Supporting Information. The overall reaction displayed zero-order kinetics with respect to ICH_2BF_3K and COE. Reaction orders of 0.5 and −0.5 with respect to Pd and EG, respectively, were also observed (see Figure 6 and the Supporting

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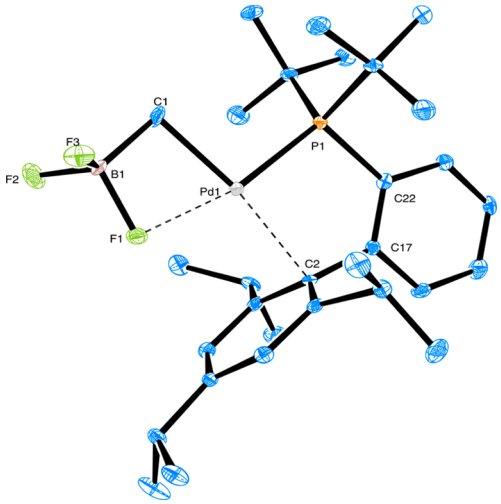


Figure 5. ORTEP diagram of $C_{30}H_{47}BF_3PPd$ (**8**) with 50% probability thermal ellipsoids. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and angles (deg) of **8**: Pd1−P1 = 2.2302(8); Pd1−C1 = 2.045(3); Pd1−F1 = 2.1833(17); Pd1−C2 = 2.400(3); B1−C1−Pd1 = 93.17(19); F1−Pd1−P1 = 167.56(5).

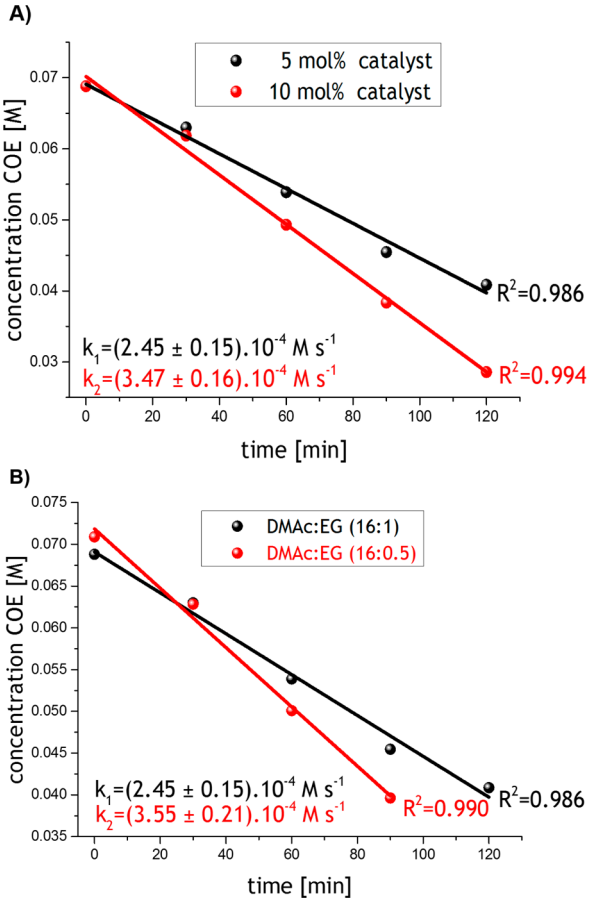


Figure 6. (A) Initial reaction rates for the conversion of COE over time in the presence of 5 mol % of **Cat1** (●) and 10 mol % of **Cat1** (red ●). (B) Initial reaction rates for the conversion of COE over time in the presence of EG (0.1 mL, 0.69 M, black ●) and EG (0.05 mL, 0.71 M, red ●).

Information). The influence of the phosphine ligand on the initial reaction rate was found to be negligible. These results suggest a turnover-limiting cleavage of a dinuclear Pd(II) species, the resting state in the catalytic cycle, to a kinetically competent monomeric species.

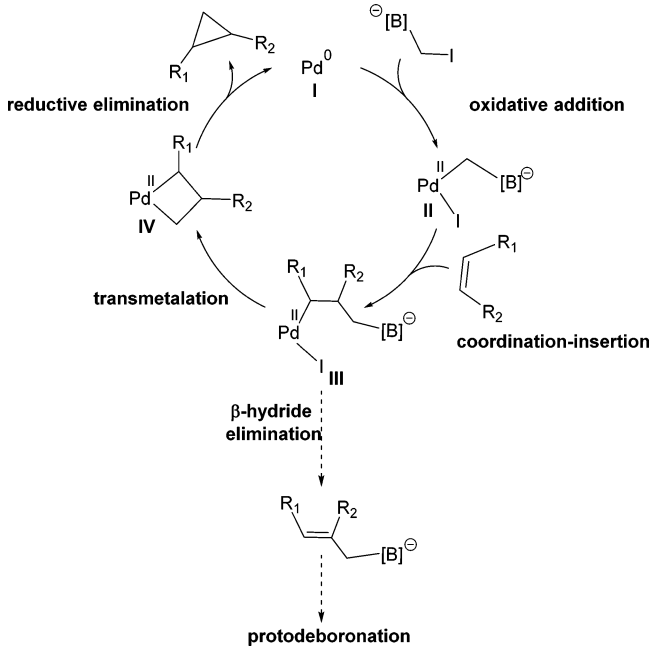
DISCUSSION

The nucleophilic cyclopropanation of electron-deficient or polar olefins is widely documented in the literature.[4] Among the reported approaches, the most important preparative method reported is the MIRC, in which α,β-unsaturated carbonyl, sulfonium, or nitrogen ylides react with styrenes,[19] stilbenes, or a Michael acceptor. For the electrophilic cyclopropanation of electron-rich olefins, the options are decidedly more limited,[20] the leading methods being zinc carbenoid mediated cyclopropanations and metal-catalyzed cyclopropanation with diazo compounds. We had originally reported the Pd-catalyzed cyclopropanation of norbornene with ICH_2BF_3K. We had further presented a heuristic classification of possible mechanisms for the catalytic electrophilic cyclopropanation and proposed that a "diverted Heck" (Scheme 5, mechanism V in the heuristic[13]) was most probable, on the basis of the observation of terminal methylene side products for other substrates. Our original work, while mechanistically novel, suffered from the practical disadvantage of a limited substrate scope. Having a working hypothesis for the mechanism of cyclopropanation, the immediate goals of the study were

- confirmation of the proposed mechanism by observation of putative intermediates
- determination of the kinetic order of the reaction with respect to the different components
- mechanism-based expansion of the substrate scope to preparatively useful levels

The originally proposed "diverted Heck" mechanism, in a simplified form (without possible side equilibria and without hydrolysis or alcoholysis of the borate), is depicted in Scheme 5.

Scheme 5. Proposed "Diverted Heck" Mechanism for the Cyclopropanation of Olefins



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An expectation that two aspects of the reaction, its overall rate and the selectivity for the cyclopropanation over terminal methylene formation, could be separately optimized was given by the observation that the rate-determining step and the product-determining step are necessarily distinct. The kinetic studies indicated that the former involved a cleavage of a dinuclear Pd species. The latter, on the other hand, is determined by the branching between transmetalation and β-hydride elimination in a Pd alkyl species. The tuning of the two different chemical events, however, requires some indications of the reactive intermediates in the reaction.

In principle, spectroscopic studies should seek one or more of the intermediates: the product of oxidative addition, the olefin complex, the product of migratory insertion, and/or the product of intramolecular transmetalation. While THF turned out to be inferior to DMA as a solvent for the cyclopropanation, THF was sufficiently dipolar aprotic and/or sufficiently coordinating that the cyclopropanation did, in fact, run in that solvent, albeit with a reduced yield. It was the NMR solvent of choice, though, and the NMR experiments gave some evidence for intermediates, especially in the case of oxidative addition to ICH_2Bpin. While the ^{31}P and ^{11}B spectra had limited utility in confirming specific structures, they did indicate that the number of species formed in the reaction of the methylenation agent with Pd(0), with or without olefin, was small. Having only one, or a few, species formed in solution suggested that ESI-MS studies could be informative.

ESI-MS studies were done for both ICH_2BF_3K and ICH_2Bpin as methylenation agents. The former reagent is likely to be the reagent of choice in preparative applications on the laboratory scale because it is an easily handled, air-stable, nonhygroscopic solid, but the putative Pd(II) intermediates in solution would be natively uncharged, meaning that electrospray ionization would require coordination of a proton or alkali-metal cation, with potentially increased complexity in the spectrum and likely reduced intensity. The alternative methylenation agent, ICH_2Bpin, had been shown to be comparably effective in the cyclopropanation of norbornene, but it is obtained as a moisture-sensitive oil and is therefore less attractive as a synthetic reagent; the presumed Pd(II) intermediates would be monocationic, though, and therefore ideal for ESI-MS. Comparing the two, we find that the electrospray of solutions prepared with Pd(0) and either ICH_2BF_3K or ICH_2Bpin yields ions assignable to the product of the proposed initial oxidative addition step, the latter methylenation agent unsurprisingly giving much better spectra. In any case, the direct observation of **IM1** (Figure 2) and **IM2** (Figure 3) strongly supports a mechanism with the oxidative addition preceding transmetalation. We should mention that the special case of the very sterically demanding ligand *t*-BuXPhos (Figure 5) gives an intermediate which does not proceed to turn over, at least under the conditions of its formation. The NMR indicated that it is formed as the predominant species in solution. Presumably, the pendant 2,4,6-triisopropylphenyl ring of the ligand occupies the last available coordination site on the Pd(II) center, chelation making substitution by an incoming olefinic substrate kinetically unfavorable. The spin−spin couplings in the ^{1}H and ^{31}P spectra (Figure SI-36 in the Supporting Information) are fully consistent with the proposed structure, which is also supported independently by the ESI-MS spectrum in Figure SI-37 in the Supporting Information and the single-crystal X-ray diffraction result in Figure 5. While the conditions for the formation of **8** are different from those during a preparative reaction, the observation and isolation of **8** mean that there is a good probability that the oxidative addition reaction of Pd(0) and the primary alkyl iodide does indeed constitute the first step in the catalytic cycle, as proposed.

ESI-MS of reactive solutions prepared with ICH_2Bpin as methylenation agent and norbornene as substrate display ions which are assignable to either the olefin π complex or the product of migratory insertion. CID of the ion produces primarily loss of the olefin, which suggests that the ions are most likely the π complexes of norbornene on Pd(II), although collision-induced β-hydrocarbyl elimination from the insertion product would have been possible, in principle. We had observed β-methyl elimination from cationic Pd(II) neopentyl complexes in the gas phase,[21] but this reaction, the microscopic reverse of a migratory insertion, was competitive only in the case that a β-hydride elimination is strongly disfavored or impossible. The loss of norbornene in CID (Figure 4) is most consistent with the parent ion being the simple π complex. Of note is the qualitative order of reactivity for the different olefins (norbornene > cycloheptene > cyclooctene > cyclohexene) in the preparative reactions, which seems to follow their propensity to form π complexes. This suggests, of course, that ESI-MS observation of the adducts with olefins less coordinating than norbornene might be difficult, which corresponds in fact with our experience. Nevertheless, the ESI-MS experiment, this time with ICH_2Bpin and an olefin, provides strong evidence supporting yet another step in the proposed "diverted Heck" mechanism. Moreover, the slower rate of cyclopropanation observed in the case of *cis*-5-decene with respect to that of *trans*-5-decene seems to arise from the steric hindrance induced by the concerted migratory syn insertion of coordinated *cis*-5-decene into the palladium−alkylboron bond in the transition state. Similar observations were reported by James et al.[22] in the carbomethoxypalladation reaction of *trans*- and *cis*-2-butene.

Finally, the CID of the norbornene adduct with the oxidative addition product, m/z 645 in Figure 4, gives a small product peak at m/z 537, which would be consistent with intramolecular transmetalation, followed by reductive elimination of the cyclopropane product. Intramolecular transmetalation in solution is presumably much accelerated by nucleophilic addition to the boronic ester, converting it to an "ate" complex,[23] but one may interpret the CID experiment to mean that, even without nucleophilic assistance, the proposed intramolecular transmetalation and subsequent reductive elimination of the cyclopropane product is a plausible reaction when nothing more facile intervenes. In solution, cyclopropane formation via reductive elimination from proposed in situ generated or isolated palladacyclobutane[24] intermediates, generally upon coordination of π-acceptor ligands, has already been reported in the literature. The intermediates observed by ESI-MS, e.g. **IM1** in Figure 2, clearly indicate that alcoholysis of the trifluoroborate is important. Some assisted version of this reaction may proceed in solution in the final step in the catalytic cycle. The tetracoordinate borate ester in Figure 1 is the expected product.

While the NMR and ESI-MS investigations of the intermediates in the catalytic cycle support the proposed "diverted Heck" mechanism, the kinetics of cyclopropanation, as determined by the RPKA, present a challenge to that hypothesis, as noted at the beginning of the Discussion. In the most likely interpretation, the overall kinetics of the reaction

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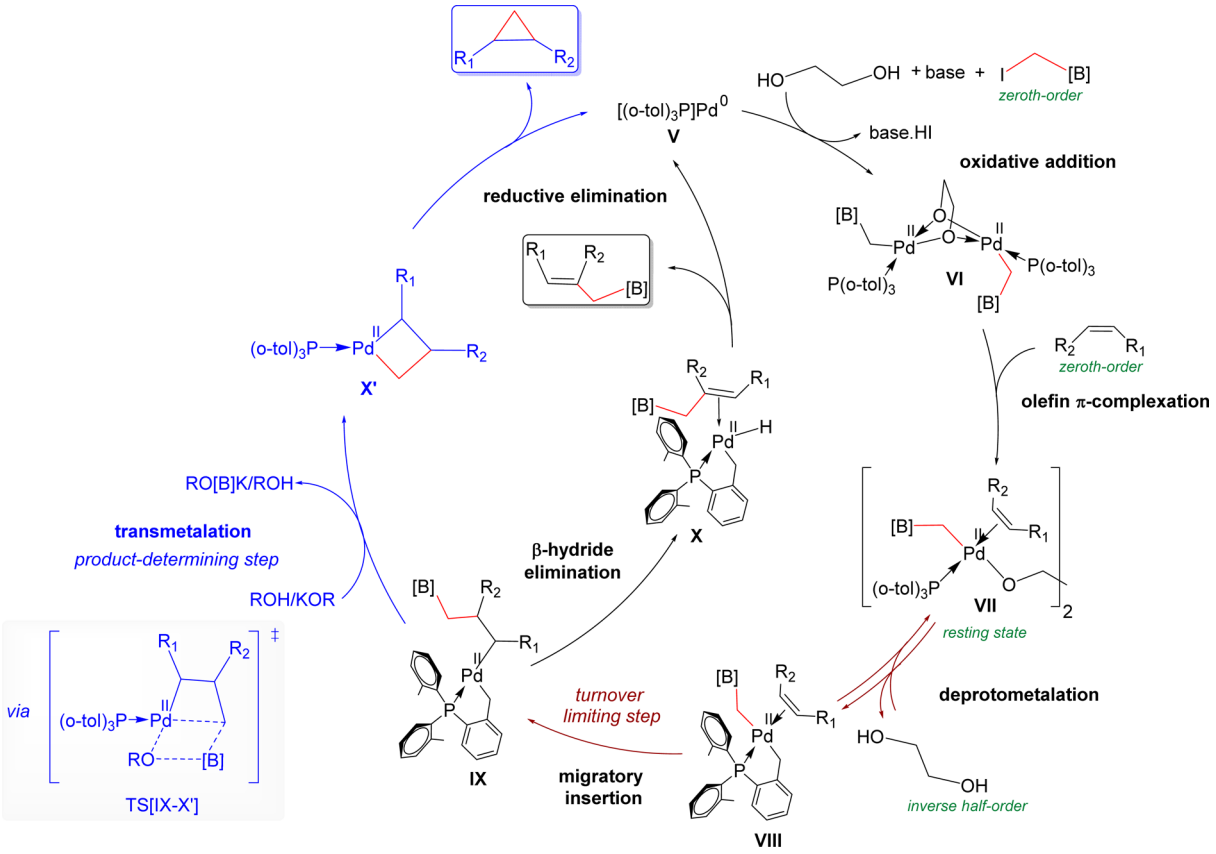
Scheme 6. Proposed Detailed Mechanism for the Pd-Catalyzed Cyclopropanation of Alkenes on the Basos of the Kinetics and the Observed or Isolated Intermediates (R = CH_2CH_2OH)



are determined by the rate of transformation of a dinuclear Pd species bearing at least one molecule of EG into a monomeric, active Pd complex, with release of one molecule of EG. This transformation would be unsurprisingly dependent on ligand and solvent, which offers an opportunity for the engineering of a catalytic reaction with broader substrate scope and preparatively useful yields. Targets for a mechanism-based reaction engineering were 2-fold: suppression of the identified side reaction in which a terminal methylene group, rather than cyclopropanation, is formed and an increase in the rate of reaction so that it can handle substrates less reactive than norbornene.

The branching between the cyclopropane, the "diverted Heck" product, and the terminal methylene, the product of protodeboronation after a normal Heck reaction, would be determined by the relative rates of intramolecular transmetalation versus β-hydride elimination for the intermediate formed by migratory insertion of the olefinic substrate. In the original report, norbornene already gave excellent yields of cyclopropanation, but β-hydride elimination would have had to re-form the strained double bond and can be expected to be disfavored. For other olefins, in our case cyclooctene, or acyclic α-olefins, the β-hydride elimination is less disfavored, leading to significant formation of the terminal methylene product after protodeboronation. β-hydride elimination and the deactivation of the Pd-based catalysts are often more strongly temperature dependent[14,25] than other elementary steps in the catalytic cycle: in particular, migratory insertion or catalyst activation. Systematic reduction in the temperature for the Pd-catalyzed cyclopropanation slowed the overall reaction, but, at least for the initial experiments with H_2O or CH_3OH as hydroxylic additive, it also selectively suppressed the terminal methylene side product, improving the ratio of "diverted Heck" to normal Heck (Table SI-3 in the Supporting Information, entries 1 and 2, in comparison to ref 13).

Alternatively, the branching between intramolecular transmetalation and β-hydride elimination could be shifted by selectively accelerating the transmetalation. Transmetalation of the trifluoroborates has been reported to require prior hydrolysis or alcoholysis, and an acceleration by nucleophilic assistance is well-documented.[23] The nucleophilic solvents DMF and DMA, the hydroxylic additives ranging from water to methanol to ethylene glycol, and the base, either fluoride or carbonate, are all already components in the successful cyclopropanation. A reported nucleophilicity order of $^-OH \ll MeO^- < EtO^- < n\text{-}PrO^- < i\text{-}PrO^-$ in ROH–MeCN mixtures[26] is consistent with our observation that alcohols, as additives, provide higher selectivity for cyclopropanation than does water. Moreover, EG presumably affords a faster alcoholysis than a comparable monobasic alcohol with the same nucleophilicity because of chelate effects. The latter effect is further consistent with the decreased advantage offered by lower temperature in the DMA/EG solvent system, a presumably chelate promoted alcoholysis accelerating transmetalation sufficiently that it outcompetes β-hydride elimination even at higher temperatures.

Engineering a broader substrate scope for olefins less reactive than norbornene is made more difficult by the temperature reduction used to improve selectivity for cyclopropanation. The kinetic studies, however, find that the overall rate appears to be

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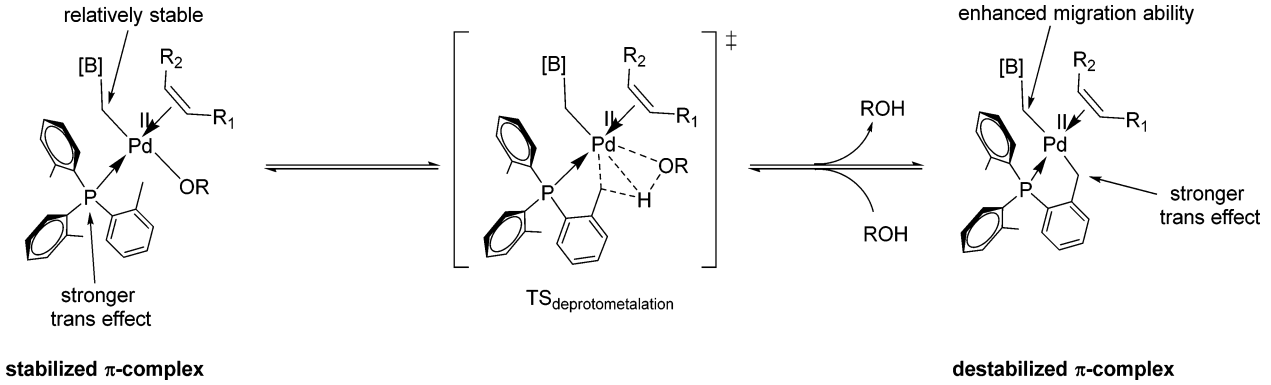
Scheme 7. Proposed Concerted Metalation−Deprotonation Mechanism and Comparison of the π-Complexes Involved



controlled by the cleavage of a presumed dinuclear Pd complex into an active monomeric species. An analogous interpretation had been given for the observations by van Leeuwen, as well as Pfaltz and Blackmond, of 0.5 kinetic order in Pd for Heck reactions.[27] The zeroth order found for the olefin, COE, and the methylene transfer agent, as well as the inverse half-order in EG, together with the intermediates observed in our investigations, can be rationalized by the detailed proposed mechanism shown in Scheme 6, which we present as a mechanism consistent with our experimental observations, but not necessarily exclusively. After the oxidative addition of iodomethylboron species to the Pd(0) complex and substitution of the halide to **VI**, the dinuclear structure **VI** would inhibit the occurrence of an undesired, and catalytically unproductive, β-hydride elimination that one would ordinarily expect from a Pd(II) complex with a primary alkoxide ligand under the reaction conditions.[28] An associative displacement of one of the two oxygens of EG on **VI** by the olefin generates the postulated dinuclear Pd(II) resting state **VII**. The bridging electron-withdrawing alkoxide facilitates the olefin coordination by increasing the electrophilicity of the metal center. Electron-rich alkenes that are not sterically hindered such as COE should thus bind favorably to Pd(II) under the reaction conditions. Mechanistic investigations on the opening of halo-bridged palladacycles by pyridine have shown the reaction to follow a fast and bimolecular associative pathway.[29] The cleavage of the dinuclear Pd resting state should operate through a reversible and concerted alkoxide-assisted deprotometalation[30] mechanism on the *o*-methyl C(sp^3)−H bond of the ligand **L1**, leading to the release of the bridging alkoxide and formation of the palladacycle intermediate **VIII**. The release of one molecule of EG would produce the −0.5 kinetic order in EG observed experimentally. A strong base such as *t*-BuONa had already been used to mediate the C(sp^3)−H functionalization at a benzylic sp^3 position.[30c,d] Additionally, the close proximity between the Pd metal and the *o*-methyl C(sp^3)−H bond of the ligand **L1** (Tolman cone angle[31] of 194°) supports the occurrence of the concerted deprotometalation process. This could explain why catalysts able to form alkyl-phosphapalladacycles work so well in this reaction. A similar cyclometalation to a palladacycle is known from Pd(II) polymerization catalysts.[32] The palladacycle intermediate **VIII** formed after the deprotonation step is destabilized by the new C(sp^3)−Pd bond trans to the alkylboron moiety (Scheme 7).

Such a primary alkyl anion possesses a stronger trans effect in comparison to the phosphine in the palladacycle,[33] which should accelerate the migratory insertion.[34] On the basis of the zero-order dependence observed for both COE and ICH_2BF_3K, this migratory insertion must be the turnover-limiting step. Similar zero-order dependence on the olefin had been reported by Brookhart for Pd(II)-catalyzed olefin polymerization, for which the resting state had been identified to be the olefin π complex and the turnover-limiting step was the migratory insertion.[32] The resulting palladacycle product **IX** could either undergo an intramolecular transmetalation via the transition state **TS[IX-X′]** depicted in Scheme 6 to give the palladacyclobutane **X′** or proceed with a β-hydride elimination to generate the intermediate **X**. Reductive elimination from these two intermediates will regenerate the Pd(0) complex **V**.

The solvents utilized in this reaction are good coordinating nucleophiles, and their coordination to the organometallic reagents helps stabilize the metal catalyst and thus extend its lifetime. Another major role played by DMA or DMF is to ensure the solubility of the metal catalyst, the methylene transfer agent, as well as the inorganic base during the methylenation reaction.

The nucleophilicity is not the sole relevant performance metric for a given additive. For example, although we observe a general trend in which the reaction is improved as the conjugate base of the hydroxylic component (H_2O, MeOH, other aliphatic alcohols) becomes more nucleophilic in reference reactions,[26] we observed only traces of products when EG was replaced by pinacol, even in the presence of 2.0 equiv of methanol (used to ensure the reduction of Pd(II) to Pd(0)). We attribute this result to the steric hindrance of pinacol, which makes the alcoholysis of the trifluoroborate extremely slow (Figure 7), counteracting the favorable effect of what would have been an otherwise more nucleophilic, chelating alkoxide.

Similarly, while EG helps to improve the selectivity for transmetalation over β-hydride elimination, the observed −0.5 kinetic order with respect to EG means that increasing the EG concentration slows the overall turnover frequency. Accordingly, we find a nonmonotonic dependence of the cyclopropane yield on the EG content in the reaction mixture. These examples serve to illustrate the complicated interplay of factors which make reaction optimization less transparent than one would have wished.

CONCLUSION

We report reagents and conditions for a catalytic, electrophilic cyclopropanation reaction without diazo compounds that works efficiently from di- and trisubstituted, electron-rich olefins and allylic alcohols. We further report NMR and ESI-

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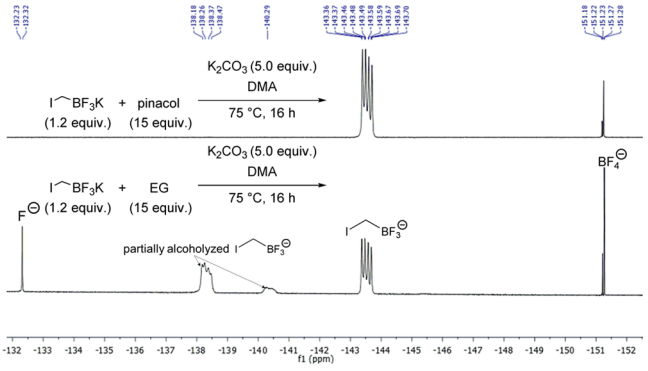

Figure 7. ^{19}F NMR spectra of the alcoholysis of ICH_2BF_3K in DMA, in the presence of pinacol (A) and EG (B).

MS observation of intermediates in the reaction, isolation, and crystallographic characterization of a key model intermediate, as well as kinetics of the cyclopropanation, which support the "diverted Heck" mechanism, on which basis we broadened the substrate scope of the new reaction to preparatively useful levels.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.6b00531.

Synthesis details, characterization results, additional screening tables, GC-FID, kinetic studies, gas-phase observations of intermediates and/or products, and ORTEP representation and crystallographic data of complex **8** (PDF)

X-ray crystallographic data (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail for P.C.: peter.chen@org.chem.ethz.ch.

Notes

The authors declare no competing financial interest.

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