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Substituted Benzocarbocycles by Palladium-Catalyzed Cascade Reactions Featuring a C(sp^3)–H Activation Step

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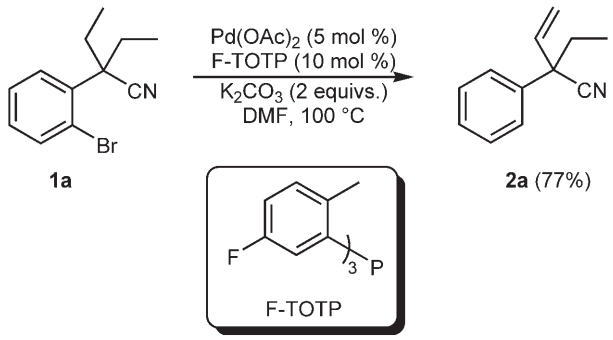
Abstract: Valuable 4- and 5-membered benzocarbocycles were synthesized *via* selective palladium-catalyzed cascade reactions which combined C(sp^3)–H activation, Heck cyclization, Heck arylation or olefin hydrogenation. In all cases, all mechanistically independent steps were catalyzed by a single multi-functional catalyst.

Keywords: benzocarbocycles; cascade reactions; C–H activation; Heck reaction; hydrogenation; palladium

Introduction

In recent years, the transition metal-catalyzed activation of C–H bonds has emerged as a reliable tool[1] to transform otherwise unreactive bonds into carbon-heteroatom or carbon-carbon[2] bonds to access valuable synthetic targets.[3] In this context, we recently reported on the Pd(0)-catalyzed intramolecular functionalization of C(sp^3)–H bonds in benzylic alkane segments, that afforded olefins adjacent to a quaternary benzylic carbon atom.[4] The fluorinated phosphine F-TOTP [tris(5-fluoro-2-methylphenyl)phosphine] proved to be optimal for this transformation (Scheme 1).

On the other hand, cascade processes are now well established methods to access complex molecular scaffolds in a short, economical and ecological fashion.[5] Herein, we describe the design of Pd(0)-catalyzed domino and one-pot sequences[6] which rely on a single catalyst precursor, able to combine an intramolecular C(sp^3)–H activation step with other mechanistically distinct transformations,[7] thereby giving access to high molecular complexity in a concise manner.

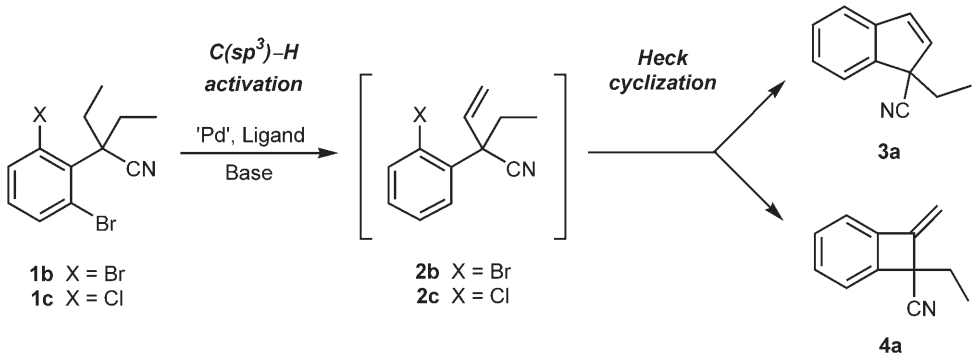


Scheme 1. Palladium-catalyzed dehydrogenation.

Results and Discussion

According to our initial studies,[4] we envisioned that if the dehydrogenation reaction was carried out on 2,6-dihalophenylacetonitrile derivatives, the resulting olefins could react further by intramolecular Heck reaction (Scheme 2). The latter would be initiated by the oxidative addition of the remaining aromatic carbon-halogen bond to Pd(0) and it could afford a functionalized indene by 5-*endo-trig* cyclocarbopalladation[8] or an *exo*-methylenebenzocyclobutene by a much more unusual 4-*exo-trig* cyclocarbopalladation. To the best of our knowledge, only one synthetically useful case of 4-*exo-trig* Heck cyclization has been reported to date.[9]

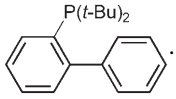
This novel Pd-catalyzed C(sp^3)–H activation/Heck cyclization pseudo-domino process[10] was investigated with the transformation of **1b** into **3a** and **4a** as the model reaction (Scheme 2). Under conditions that we reported previously[4b] [$Pd(OAc)_2$ 5 mol%, F-TOTP 10 mol%, K_2CO_3 2 equivs., DMF, 100 °C] traces of the expected products were indeed detected by ^{1}H NMR. However, the very low conversion (<5%) prompted us to undertake a complete reoptimization of the reaction conditions (Table 1).



Scheme 2. C(sp^3)–H activation/Heck cyclization cascade reaction.

Table 1. Optimization of conditions for the C(sp^3)–H activation/Heck cyclization cascade reaction.[a]

Entry	Compound	Palladium source	Ligand	Base	Solvent	Yield [%][b]	
						3a	**4a**
1	**1b**	$Pd(OAc)_2$	F-TOTP	K_2CO_3	DMF	14	28
2	**1b**	$Pd(OAc)_2$	F-TOTP	K_2CO_3	NMP	20	24
3	**1b**	$Pd(OAc)_2$	F-TOTP	K_2CO_3	DMA	28	29
4	**1b**	$Pd_2(dba)_3$	F-TOTP	K_2CO_3	DMA	12	4
5	**1b**	$PdBr_2$	F-TOTP	K_2CO_3	DMA	46	6
6	**1b**	$Pd(OAc)_2$	F-TOTP	KOAc	DMA	76	<1[c]
7	**1b**	$Pd(OAc)_2$	F-TOTP	Na_2CO_3	DMA	68	<1[c]
8[d]	**1b**	$Pd(OAc)_2$	F-TOTP	K_2CO_3	DMA	8	39
9[e]	**1b**	$Pd_2(dba)_3$	JohnPhos	K_2CO_3	DMF	77	2
10[d]	**1c**	$Pd(OAc)_2$	F-TOTP	K_2CO_3	DMA	5	71
11[e]	**1c**	$Pd_2(dba)_3$	JohnPhos	K_2CO_3	DMF	8	31

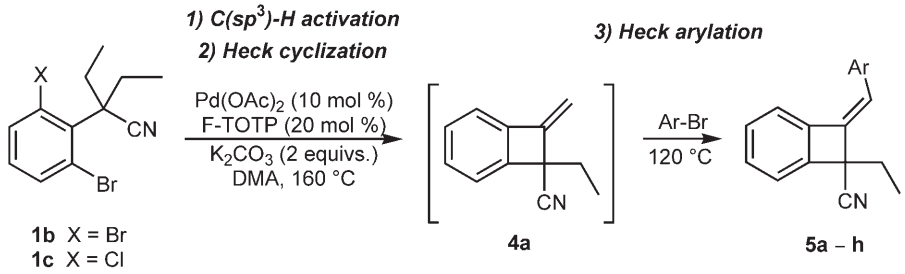
[a] *Reaction conditions:* 10 mol% Pd(0), 20 mol% F-TOTP or 10 mol% JohnPhos, 130 °C.; JohnPhos =  .

[b] Isolated yields.
[c] Undetectable by ^{1}H NMR.
[d] The reaction was carried out at 160 °C.
[e] The reaction was carried out at 150 °C.

First, the effect of the solvent was assessed at 130 °C with a catalyst generated from $Pd(OAc)_2$ and F-TOTP (entries 1–3). DMA gave the best yield albeit with no regioselectivity, **3a** and **4a** being obtained as an inseparable 1:1 mixture. Several other palladium sources were assayed, including $Pd_2(dba)_3$, $PdBr_2$ and $Pd(acac)_2$. With the latter, catalyst deactivation occurred before full conversion whereas the reaction went to completion with the other palladium sources (entries 4 and 5). The nature of the precatalyst had a dramatic influence on both yield and regioselectivity. For example, the replacement of $Pd(OAc)_2$ for $PdBr_2$ favored 5-*endo* cyclization (entries 3 and 5). The reaction outcome was also highly dependent on the choice of the base. Notably, the poor regioselectivity observed with K_2CO_3 (entry 3) contrasted with the exclusive formation of **3a** using KOAc (entry 6) and Na_2CO_3 (entry 7), thus revealing a strong influence of both the cation and anion of these inorganic bases. In addition, with $Pd(OAc)_2$ and K_2CO_3, **4a** was obtained as the major product in 39% yield by increasing the reaction temperature to 160 °C (entry 8). Finally we assessed the use of much more electron-rich phosphines, in combination with $Pd_2(dba)_3$. Interestingly, Buchwald's JohnPhos[11] afforded **3a** in 77% yield with excellent regioselectivity (entry 9) which proved that the ligand was also critical to the product distribution. To summarize these optimization studies, it was not only possible to perform consecutive C(sp^3)–H functionalization and Heck cyclization with a single catalyst but also to control the cyclization mode by a proper choice of each reaction parameter.

We then applied the two optimal complementary sets of conditions, that is, $Pd(OAc)_2$/F-TOTP/K_2CO_3 in DMA at 160 °C (conditions A) or $Pd_2(dba)_3$/JohnPhos/K_2CO_3 in DMF at 150 °C (conditions B), to the 2-bromo-6-chloro analogue **1c**. Much satisfyingly, under conditions A (entry 10), this substrate afforded

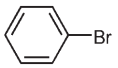
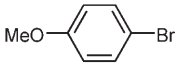
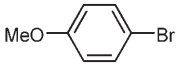
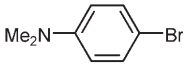
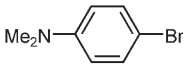
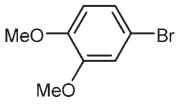
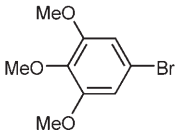
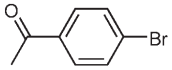
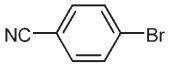
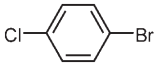
Table 2. Scope of the C(sp^3)-H activation/Heck cyclization/Heck arylation sequence.



1b X = Br
1c X = Cl

4a

5a – h

Entry	Substrate	Aryl bromide[a]	Product	Yield [%][b]
1	**1c**		**5a**	58[c]
2	**1b**		**5b**	24
3	**1c**		**5b**	35
4	**1b**		**5c**	28
5	**1c**		**5c**	47
6	**1c**		**5d**	31
7	**1c**		**5e**	34
8	**1c**		**5f**	32
9	**1c**		**5g**	19
10	**1c**		**5h**	25

[a] 1.5 equivs. of electron-neutral and electron-rich aryl bromides (entries 1–7), 4 equivs. of electron-poor aryl bromides (entries 8–10).
[b] Isolated yields.
[c] GC yield (compound **5a** could not be isolated in pure form).

the **3a**/**4a** mixture in a better yield and regioselectivity (5% **3a**, 71% **4a**) than **1b**. ^{1}H NMR and GC/MS monitoring revealed that starting from **1b**, Heck cyclization was so fast that only traces of the brominated intermediate **2b** could be observed during the course of the reaction. On the contrary, with substrate **1c** the sequence proceeded stepwise: the chlorinated intermediate **2c** cyclized only when conversion of **1c** was almost complete. Given that the overall reaction times are similar for both substrates, the relative difference in the rates of both steps observed with starting material **1c** is better suited to the synthesis of the heat-sensitive *exo*-methylenebenzocyclobutene product. When starting from this substrate, the product may decompose to a lesser extent as it is formed later in the process, and the overall yield is thus improved.[12] Interestingly, the cyclization of intermediate **2c** constitutes a rare example of intramolecular Heck reaction of an unactivated aryl chloride.[13] Unexpectedly, when **1c** was reacted under conditions B (entry 11), the yield was lower and the regioselectivity was reversed compared to substrate **1b**.

In order to functionalize further the unusual *exo*-methylenebenzocyclobutene moiety resulting from the cascade reaction under conditions A, we decided to perform a third sequential transformation in the

same reaction vessel. We envisioned that employing an intermolecular Heck coupling as this third step would lead to a modular C(sp^3)–H activation/Heck cyclization/intermolecular Heck sequence that would not require re-addition of catalyst. To probe this concept, bromobenzene was added directly to the mixture resulting from the reaction of substrate **1c** using the $Pd(OAc)_2$/F-TOTP catalyst. To our delight, when performed at 120 °C the intermolecular Heck reaction smoothly afforded the expected trisubstituted olefin **5a** in 58% GC yield (Table 2, entry 1).

This procedure (conditions C) was employed to evaluate the scope of this sequence starting from substrates **1b** and **1c** and a variety of substituted aryl bromides (Table 2).[14]

In all cases, the products were successfully isolated as single olefin isomers. Electron-donating substituents on the aryl bromide were well tolerated. The reaction product from **1c** and *p*-bromoanisole was isolated as a single stereoisomer in 35% yield (average of 70% yield per step, entry 3). The double bond geometry was evidenced to be *E* by NOE correlations between the protons of the olefin and the ethyl benzylic substituent.[15] The di- and trimethoxy analogues were isolated in 31% and 34% yields, respectively (entries 6 and 7). Similarly, a satisfaying overall yield (47%) was obtained by reaction with 4-bromo-*N*,*N*-dimethylaniline (entry 5). Products **5b** and **5c** could also be formed from dibromo substrate **1b** but, as expected, with lower yields (entries 2 and 4). Electron-poor aryl bromides also participated in the 3-step sequence although the yields were lower, mainly because of prolonged reaction times and incomplete conversion of the intermediate olefin **4a** prior to catalyst deactivation.[16] Thus, starting from **1c** the reaction with 4′-bromoacetophenone and 4-bromobenzonitrile afforded the target coupling products **5f–g** in 32% and 19% yields, respectively (entries 8 and 9). The reaction could also be performed in the presence of an additional halogen atom: with 1-bromo-4-chlorobenzene, the chlorinated benzocyclobutene **5h** was chemoselectively obtained from **1c** in a moderate 25% yield (entry 10).

The products resulting from this versatile methodology displayed an original 4-membered ring-bridged *cis*-stilbene scaffold. Notably, compound **5e** featuring a trimethoxyphenyl moiety can be considered as a conformationally restricted analogue of the antimicrotubule natural product combretastatin A-4 (Figure 1).[17] The antimicrotubule activity of **5e** was evaluated using colchicine as reference. It was found to be 13× less active (IC_{50} = 49 μM) than colchicine (IC_{50} = 3.8 μM). Further structural optimization of **5e** is underway to improve this encouraging activity.

The precipitation of palladium black during the course of the transformations described above suggested the intermediate formation of metal nanoparticles.[18] Considering this observation, we tried to take advantage of the *in situ* modification of our catalyst by performing an additional hydrogenation step.[7a]

Substrate **1a** was chosen for a proof-of-concept experiment (Scheme 3). Dehydrogenation was carried out under conditions that were previously reported for this substrate.[4b] The formation of palladium nanoparticles during the course of this reaction was evidenced by transmission electronic microscopy (TEM) analysis of aliquots of the reaction mixture.[19] After complete conversion of **1a** into olefin **2a**, the reaction mixture was placed under a hydrogen atmosphere. Satisfyingly, the hydrogenation product of **2a** could be isolated in 73% yield after stirring at room temperature for 15 h.

This *in situ* hydrogenation was applied to the bicyclic olefins obtained from the cascade processes described above (Table 3). Conditions A, B and C all allowed the formation of an active hydrogenation catalyst.

Starting from **1c**, the *in situ* hydrogenation of intermediate **4a** obtained under conditions A afforded

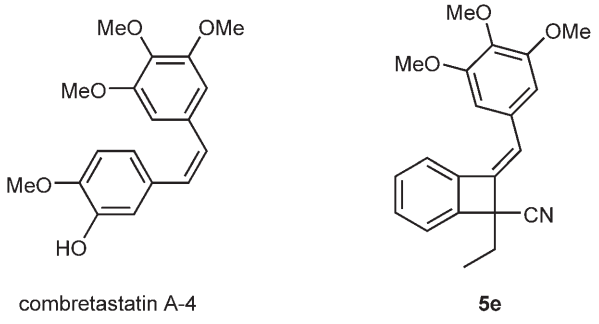
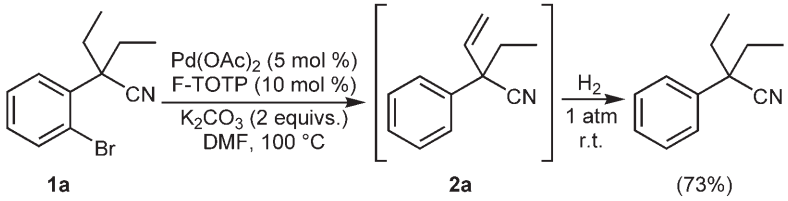
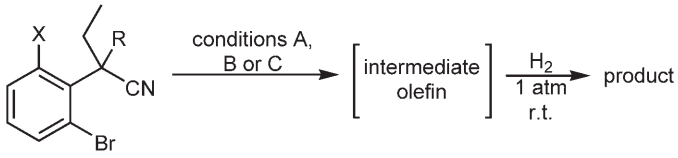


Figure 1. Combretastatin A-4 and the conformationally restricted analogue **5e**.



Scheme 3. C(sp^3)–H activation/hydrogenation one-pot process.

Table 3. Scope of the in situ hydrogenation process.[a]



1b – d

Entry	Substrate	Intermediate olefin (conditions)	Product	Yield [%][b]
1	**1c**	**4a** (A)	**6a**	44
2	**1b**	**4a** (A)	**6a**	28
3	**1b**	**3a** (B)	**6b**	49
4	**1d**	**3b** (B)	**6c**	26
5	**1b**	**5a** (C)	**6d**	47[c]

[a] *Conditions A:* $Pd(OAc)_2$ (10 mol%), F-TOTP (20 mol%), K_2CO_3 (2 equivs.), DMA, 160 °C; *conditions B:* $Pd_2(dba)_3$ (5 mol%), JohnPhos (10 mol%), K_2CO_3 (2 equivs.), DMF, 150 °C; *conditions C:* conditions A, then PhBr (1.5 equivs.), 120 °C.
[b] Isolated yields.
[c] GC yield.

benzocyclobutene **6a** that was isolated in 44% yield (average of 76% yield per step) as a single diastereoisomer, the *cis*-relative stereochemistry of which was assigned from a NOESY experiment (entry 1).[15] Following the same procedure, **6a** was isolated in a lower 28% yield from **1b** (entry 2). Five-membered rings obtained under conditions B were also smoothly hydrogenated, giving indanes **6b** and **6c** in 49% and 26% isolated yields, respectively. Finally, the *in situ* hydrogenation of the trisubstituted olefin **5a** resulting from the 3-step dehydrogenation/Heck cyclization/Heck arylation sequence (Table 2, entry 1; Table 3, entry 5) also occurred and displayed good diastereoselectivity (*dr* 10:1, from ^{1}H NMR of the crude mixture). The major diastereoisomer **6d** was formed in 47% GC yield.

Conclusions

We have disclosed novel approaches to functionalized 4- and 5-membered benzocarbocyclic building blocks by developing versatile, regio- and stereoselective palladium-catalyzed cascade reactions that all feature a C(sp^3)–H activation step, rely on single multi-functional palladium catalysts and proceed with moderate to good overall yields. Notably, original functionalized benzocyclobutenes were obtained,[20] including a conformationally restricted analogue of combretastatin A-4 (**5e**) with promising antimicrotubule activity.

Experimental Section

General Considerations

Reagents were commercially available and used without further purification except 2-bromo-6-chlorotoluene which was filtered through a pad of silica before use. All solvents were distilled from the appropriate drying agents immediately before use. The dihalophenylacetonitrile substrates **1b–d** were prepared from the corresponding 2,6-dihalotoluenes according to standard methods (see Supporting Information). The F-TOTP ligand was synthesized from 2-bromo-4-fluorotoluene according to a reported procedure.[4b] Yields

refer to chromatographically and spectroscopically homogeneous materials. Merck silica gel 60 (particle size 40–63 μm) was used for flash column chromatography, 1 mm and 2 mm SDS silica gel coated glass plates (60 F_{254}) were used for preparative TLC using UV light as visualizing agent. NMR spectra were recorded on Bruker Avance 300 or Avance 500 instruments, at 295 K with tetramethylsilane or residual protiated solvent used as an internal reference. Assignments were made on the basis of 2D experiments (COSY, HMQC, HMBC). 3D structures supporting NOE analyses (see spectra copies) were obtained by molecular mechanics energy minimization (MM2 force field, minimun RMS gradient = 0.050, CambridgeSoft Chem3D 9.0). IR spectra were recorded on a Perkin–Elmer Spectrum BX spectrometer and only the strongest or structurally most important peaks were listed. Products that had been reported previously were isolated in greater than 95% purity, as determined by ^{1}H NMR and capillary gas chromatography (GC). GC analyses were performed with a Shimadzu QP2010 GC/MS apparatus, with a simultaneous double injection on a DB-5 ms column linked with a mass or a FID detection system. GC yields were evaluated using tetradecane as an internal standard.

C(sp^3)–H Activation/Heck Cyclization Domino Process (Scheme 2, Table 1)

Conditions A: Representative procedure for exo-*methylenebenzocyclobutene* **4a**: A dry Schlenk tube containing a magnetic rod was charged with substrate **1c** (100 mg, 0.35 mmol), palladium acetate (7.8 mg, 0.035 mmol), F-TOTP (25.0 mg, 0.07 mmol) and potassium carbonate (96 mg, 0.70 mmol). The Schlenk tube was twice evacuated and backfilled with argon, then capped with a rubber septum. Dry *N*,*N*-dimethylacetamide (1.7 mL) was injected under argon and the mixture was stirred at 160 °C (preheated oil bath) for 1.5 h. After cooling, the mixture was diluted with diethyl ether (15 mL) and filtered through celite. The organic solution was washed with water (15 mL) and the aqueous layer was extracted with diethyl ether (15 mL × 3). The combined organic layers were washed with brine (25 mL), dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography (silica gel, heptanes/diethyl ether, 9:1) to afford a **3a**/**4a** mixture as an oil (**3a**:**4a** = 7:93 by ^{1}H NMR, 45 mg, 5% **3a**, 71% **4a**). This mixture was further purified by another careful flash chromatography (silica gel, heptanes/diethyl ether, 95:5) in order to obtain an analytically pure sample of **4a** for characterization purpose; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19 (dd, *J* = 7.4, 7.4 Hz, 3H), 1.98 (dq, *J* = 14.7, 7.4 Hz, 1H), 2.16 (dq, *J* = 14.8, 7.4 Hz, 1H), 5.22 (d, *J* = 2.1 Hz, 1H), 5.43 (d, *J* = 2.1 Hz, 1H), 7.25–7.39 (m, 4H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 10.4, 29.8, 51.4, 104.4, 120.2, 120.5, 121.9, 129.9, 130.1, 143.3, 144.8, 146.5; GC/MS (EI, DB-5 ms column, 1 min at 90 °C then 90→220 °C at 8 °C min^{-1}): 9.0 min (*m*/*z* = 169 [M$^+$]); IR (film): ν = 1460, 2231, 2970 cm^{-1}.

Conditions B: Representative procedure for indene **3a**: A dry Schlenk tube containing a magnetic rod was charged with substrate **1b** (100 mg, 0.30 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (15.6 mg, 0.015 mmol), JohnPhos (9.0 mg, 0.030 mmol) and potassium carbonate (83 mg, 0.60 mmol). The Schlenk tube was twice evacuated and backfilled with argon, then capped with a rubber septum. Dry *N*,*N*-dimethylformamide (1.5 mL) was injected under argon and the mixture was stirred at 150 °C (preheated oil bath) for 1.5 h. The reaction mixture was treated as described above for the preparation of compound **4a** and the crude product was purified by preparative TLC (2 mm silica gel, heptanes/diethyl ether, 9:1) to afford **3a** as a colourless oil (40 mg, 78%); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (dd, *J* = 7.4, 7.4 Hz, 3H), 1.84 (dq, *J* = 14.5, 7.4 Hz, 1H), 2.15 (dq, *J* = 14.3, 7.4 Hz, 1H), 6.41 (d, *J* = 5.5 Hz, 1H), 6.91 (d, *J* = 5.4 Hz, 1H), 7.26–7.38 (m, 3H), 7.53 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 9.9, 30.4, 50.7, 120.0, 122.2, 122.9, 126.8, 128.8, 134.1, 134.7, 142.6, 143.5; GC/MS (EI, DB-5 ms column, 1 min at 90 °C then 90→220 °C at 8 °C min^{-1}): 9.5 min (*m*/*z* = 169 [M$^+$]); IR (film): ν = 1457, 2232, 2972 cm^{-1}.

C(sp^3)–H Activation/Heck Cyclization/Heck Arylation Process (Table 2)

Conditions C: Representative procedure for amine **5c**: Substrate **1c** (100 mg, 0.35 mmol) was reacted with $Pd(OAc)_2$, F-TOTP and K_2CO_3 in dry DMA at 160 °C as described above for the preparation of **4a**. When the reaction was almost over, the brown reaction medium turned black (after 80 min) and this mixture was transferred to an oil bath at 120 °C. A solution of 4-bromo-*N*,*N*-dimethylaniline (105 mg, 0.52 mmol) in DMA (200 μL) was then added and the mixture was stirred at 120 °C for 1 h. After cooling, the mixture was diluted with diethyl ether (15 mL) and filtered through celite. The filtrate was washed with water (15 mL) and the aqueous layer was extracted with diethyl ether (15 mL × 3). The organic layers were combined, washed with brine (25 mL) and dried over magnesium sulfate. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, heptanes/ethyl acetate, 5:1) to afford **5c** as an orange oil (47 mg, 47%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.22 (dd, *J* = 7.5, 7.5 Hz, 3H), 2.01 (dq, *J* = 14.4, 7.5 Hz, 1H), 2.24 (dq, *J* = 14.3, 7.5 Hz, 1H), 3.02 (s, 6H,), 6.44 (s, 1H), 6.77 (d, *J* = 8.3 Hz, 2H), 7.28–7.40 (m, 3H), 7.47 (d, *J* = 9.0 Hz, 2H), 7.52 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 10.4, 30.1, 40.3, 50.9, 112.1, 121.2, 121.4, 121.6, 122.7, 123.7, 129.0, 129.2, 129.8, 134.6, 143.3, 144.9, 150.2; HR-MS (ESI, MeOH + CH_2Cl_2): m/z = 289.1708, calcd. for $C_{20}H_{21}N_2$ [(M + H)$^+$]: 289.1705; IR (film): ν = 1520, 1605, 2228, 2967 cm^{-1}.

C(sp^3)–H Activation/Heck Reactions/Hydrogenation One-Pot Sequences (Table 3)

Representative procedure for benzocyclobutene **6a**: Substrate **1c** (100 mg, 0.35 mmol) was reacted with $Pd(OAc)_2$, F-TOTP and K_2CO_3 in dry DMA at 160 °C as described above for the preparation of **4a**. After 1.5 h the reaction mixture was cooled to room temperature and the Schlenk tube was purged with dihydrogen. The mixture was stirred under 1 atm of dihydrogen at room temperature for 16 h. It was then diluted with diethyl ether (15 mL) and filtered through celite. The solution was washed with water (15 mL) and the aqueous layer was extracted with diethyl ether (15 mL × 3). The organic layers were combined, washed with brine (25 mL) and dried with magnesium sulfate. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (silica gel, heptanes/

diethyl ether, 95:5) to afford **6a** as a colourless oil (26 mg, 44%); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 1.22$ (dd, $J = 7.4$, 7.4 Hz, 3H), 1.58 (d, $J = 7.2$ Hz, 3H), 1.90–2.02 (m, 2H), 3.49 (q, $J = 7.2$ Hz, 1H), 7.13 (dd, $J = 7.1$, 0.8 Hz, 1H), 7.22 (d, $J = 7.2$ Hz, 1H), 7.27–7.30 (m, 2H); ^{13}C NMR (125.8 MHz, $CDCl_3$): $\delta = 10.7$, 16.9, 30.7, 48.5, 50.6, 120.4, 122.0, 122.6, 128.3, 129.4, 142.2, 146.7; GC/MS (EI, DB-5 ms column, 1 min at 90 °C then 90→220 °C at 8 °C min^{-1}): 8.3 min ($m/z = 171$ [M$^+$]); IR (film): $\nu = 1458$, 2231, 2968 cm^{-1}.

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