JOC The Journal of Organic Chemistry

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An Investigation into the One-Pot Heck Olefination−Hydrogenation Reaction

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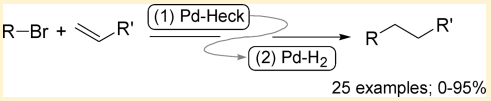
Supporting Information

ABSTRACT: Herein is described an operationally simple process concerning the observation that, following either inter-, or intramolecular Heck olefination, stirring of the so formed substituted alkenyl product under an atmosphere of hydrogen efficiently effects alkene hydrogenation. Overall this two-operation, one-pot "reductive Heck" sequence is notable since direct reductive Heck processes, using additives such as formate salts, are restricted to a limited range of substrates. In total 25 examples are reported (yields ranging from 0 to 95%), which were selected in order to probe the scope and limitations of this method. Finally, the utility of this sequence was demonstrated in a short synthesis of the calcimimetic agent, cinacalcet.



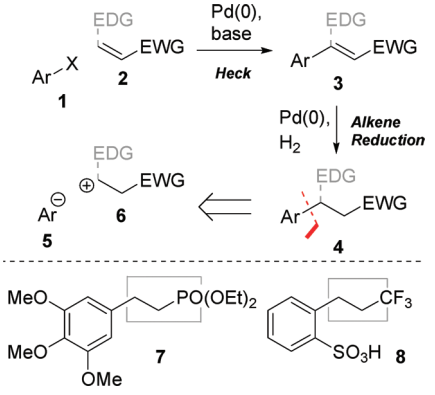
INTRODUCTION

The advantages of one-pot operations over multipot, "stop-go" processes in chemical synthesis have been much discussed in recent times. Savings in time and cost, in addition to positive environmental aspects, mean that new one-pot methods are continually sought.[1] Within this area the reuse of a common catalyst in two or more different but coupled reactions is an attractive concept. The ability of such a species to effect distinct chemical transformations has recently and appropriately been coined "multi-task" catalysis.[2]

The widely reported versatility of palladium catalysis makes it an excellent candidate for use in this type of process, and elegant sequences featuring palladium-mediated steps are frequently cited as seminal examples of reaction cascades.[3] We have recently considered the preparation of cyclic sulfonamides with the ultimate aim of studying the behavior of the *N*-sulfonyl moiety under reductive conditions.[4] The palladium-based Heck olefination[5] reaction (Scheme 1) proved a convenient method for the assembly of such compounds, and in order to facilitate the study, hydrogenation of the resultant Heck-adduct alkene was required (*i.e.*, **3** to **4**). Since the latter conversion is traditionally effected using palladium, we wondered if the sequence might be performed in the same reaction vessel using multitask palladium catalysis. Overall, this type of conversion, **1** to **4**, resembles in a retrosynthetic sense a conjugate addition or a Freidel−Crafts-type process.

This type of Heck−alkene hydrogenation sequence does have some precedence, and intermolecular examples exist using both heterogeneous and homogeneous palladium catalysis. For example, Genêt and co-workers demonstrated in 2000 that a substituted diazonium salt undergoes an intermolecular Matsuda−Heck process with a vinyl phosphonate and that the intermediate alkene could be efficiently reduced in the same reaction vessel, affording **7** in 83% yield.[6] Similarly, the synthesis of **8**, which was used to access the herbicide prosulfuron, was achieved in one pot.[7] Concerning the latter alkene to alkane transformation the

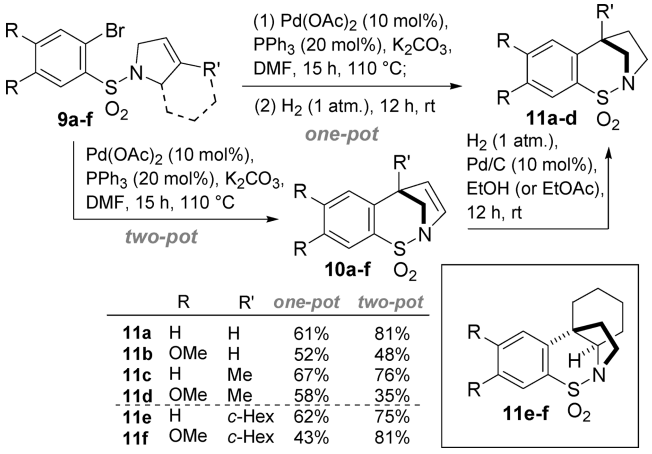
Scheme 1. Heck−Hydrogenation Sequence Including Selected Examples Prepared Using a One-Pot Process



authors advocated the inclusion of charcoal to enhance catalyst turnover in the hydrogenation operation. More recently Felpin et al. described a Heck−reduction−cyclization domino reaction.[8] Their method utilized the palladium catalyst in a Heck reaction, followed by nitro group reduction, and finally the thus formed aniline underwent intramolecular cyclization leading to the preparation of a series of 2-quinolones. A similar domino reaction has also been described in work published by Fagnou et al. where a direct arylation−Heck−hydrogenation reaction was carried out using a single palladium catalyst.[9] In a paper primarily focused with the use of palladium on carbon as a catalyst for domino C−C bond coupling reactions, Djakovitch et al. demonstrated that this type of heterogeneous catalyst was effective in a Heck−hydrogenation reaction sequence.[10] The support of a palladium catalyst on nanocrystalline magnesium oxide has been studied by Kantam et al. and was demonstrated to be

Received: January 5, 2011
Published: March 07, 2011

Scheme 2. One-Pot Intramolecular Heck−Hydrogenation Sequence for the Synthesis of Cyclic Sulfonamides



	R	R'	one-pot	two-pot
11a	H	H	61%	81%
11b	OMe	H	52%	48%
11c	H	Me	67%	76%
11d	OMe	Me	58%	35%
11e	H	*c*-Hex	62%	75%
11f	OMe	*c*-Hex	43%	81%

a viable mediator of Heck−hydrogenation reaction series.[11] The one-pot conversion of an electron-rich aryl iodide into the "raspberry scent" ketone was reported under the influence of a similar heterogeneous palladium catalyst.[12] Broadening the scope of this general type of process, in 2007 Shi and co-workers detailed a palladium-mediated oxidative Heck−hydrogenation sequence (*i.e.*, **1** to **4**, where X = H).[13] Notably, however, while this operation was effected in one pot, additional Pd/C was required to convert the initial Heck derived alkene into the alkane.

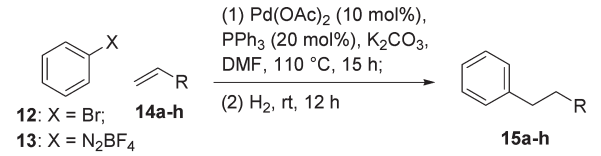
Conceptually, the types of product accessed from the Heck−hydrogenation reaction, *i.e.*, **4**, can also be achieved in one pot by a reductive Heck reaction. However, these processes, which are typically carried out using Pd(0) in the presence of formate, are limited to specific structural examples whereby, following carbopalladation, β-hydride elimination is precluded.[14] Alternatively, in terms of specifically accessing saturated aldehydes or ketones, the use of allylic alcohols as reaction partners are reported, in certain instances, to efficiently generate the carbonyl bearing product following enol tautomerisation.[15]

RESULTS AND DISCUSSION

Preliminary studies aimed at achieving the one-pot, telescoped conversion outlined in Scheme 1 were investigated using cyclic alkenes **9a**, **9b** in order to construct benzo-annulated sulfonamides **11a** and **11b** (Scheme 2).[4d] Standard conditions used to effect Heck olefination generated **10a** and **10b**. While the subsequent conversion into **11a** and **11b** may, unsurprisingly, be effected by Pd/C, encouragingly we have also found that the palladium used for the initial Heck cyclization can subsequently mediate the alkene to alkane transformation by simply cooling and replacing the nitrogen atmosphere with hydrogen. Additional examples performed (**9c**−**f**) indicate that this is a reliable process, and broadly equivalent yields have been obtained for the one-pot method compared to the traditional two-pot process.

Building on these intramolecular examples we were interested to study the scope and generality of this potentially useful Heck−hydrogenation reaction using bromobenzene **12** and a series of alkenes **14** under conditions frequently employed to mediate Heck reactions (Scheme 3). Initial attempts (Entry 1)

Scheme 3. One-Pot Intermolecular Heck−Hydrogenation Sequence Varying the Alkene Component 14



Entry	Alkene **14**	Product **15**	Yield[a]
1	CO$_2$Me **14a**	Ph CO$_2$Me **15a**	X = Br; 73%, 24%,[b] 43%[c] X = N_2BF_4;[d] 92%
2	CO$_2$*n*-Bu **14b**	Ph CO$_2$*n*-Bu **15b**	79%
3	SO$_2$Ph **14c**	Ph SO$_2$Ph **15c**	51%[e]
4	CN **14d**	Ph CN **15d**	43%
5	COMe **14e**	Ph COMe **15e**	15% (62%)[f]
6	Ph **14f**	Ph Ph **15f**	49%
7	*n*-Bu **14g**	Ph *n*-Bu **15g**	24% (84%)[f]
8	O **14h**	Ph O **15h**	55% (77%)[f]

[a] Isolated yield following purification by column chromatography. [b] Yield obtained in the absence of PPh_3. [c] Conditions: $Pd(OAc)_2$ (5 mol %), Et_4NBr (1 equiv), NaOAc (2.5 equiv), DMF, 50 °C. [d] Conditions: (1) $Pd(OAc)_2$ (5 mol %), NaOAc, MeCN, rt; (2) H_2, rt. [e] Alkane:alkene = 4:1. [f] Heck reaction performed under nitrogen atmosphere in a sealed tube.

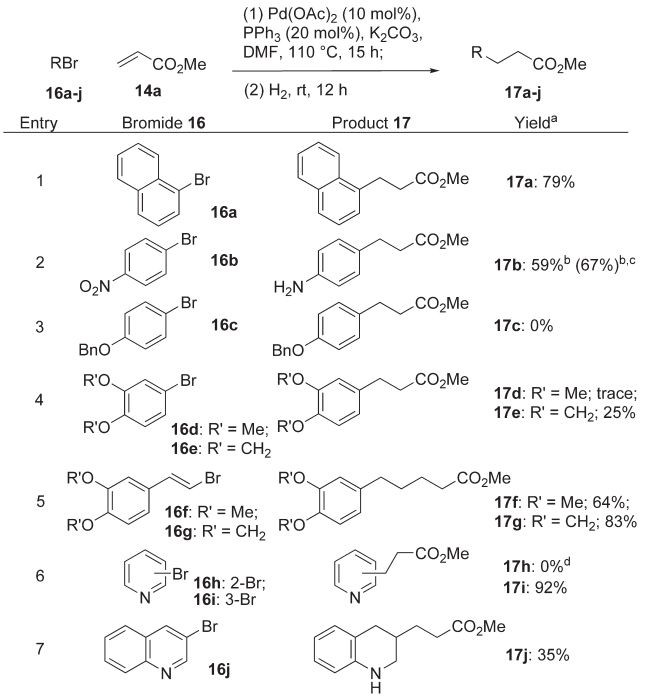
demonstrated that with 1 equiv of **12** and 5 equiv of methyl acrylate **14a** in the presence of 10 mol % palladium acetate as the precatalyst (20 mol % triphenylphosphine, potassium carbonate in dimethylformamide at 110 °C) followed by stirring under a hydrogen atmosphere (1 atm) the corresponding methyl ester **15a** was isolated in good yield (73%). If the Heck process was conducted at 60 °C, lower yields were obtained, similarly, omission of triphenylphosphine[16] had a detrimental effect on the overall yield (24%) as did the use of a tetraalkylammonium salt (Jeffery's conditions)[17] (43%).

Using phenyl diazonium tetrafluoroborate **13** the Heck reaction could be effected at room temperature, and following completion of this process the reaction was stirred under hydrogen to afford **15a** in excellent yield.[18] However, in our hands this process proved less reliable than the corresponding reaction using **12** because occasionally the alkene hydrogenation, for reasons not understood, did not proceed and the intermediate alkene Heck product was isolated.

On the basis of the successes described, the $Pd(OAc)_2$-PPh_3 conditions were subsequently applied to alternative electron-deficient (**14b**−**14f**) and electron-rich (**14g** and **14h**) alkene components. Thus, use of *n*-butyl acrylate **14b** (Entry 2) proceeded smoothly, and **15b** was isolated in 79% yield. Phenyl vinyl sulfone **14c** (Entry 3) underwent the Heck olefination relatively efficiently; however, alkene hydrogenation proved sluggish, and a mixture of the hoped for product **15c** and the α,β-unsaturated vinyl sulfone (4:1) was isolated in approximately 50% yield.[19] Use of increased hydrogen pressure (5 atm), intended to increase the effective dissolved hydrogen concentration, did not alter this ratio. Acrylonitrile **14d** (Entry 4) gave **15d**

dx.doi.org/10.1021/jo200023r |*J. Org. Chem.* 2011, 76, 2187–2194

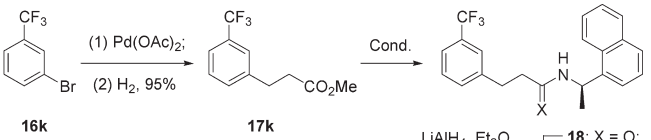
Scheme 4. One-Pot Intermolecular Heck−Hydrogenation Sequence Varying the Bromide Component 16



in moderate (43%) yield; however, unlike **14c** was not contaminated with the Heck product. It is worthwhile to mention that under these mild hydrogenation conditions in the absence of a Brønsted acid no nitrile reduction was encountered.[20] Use of the volatile methyl vinyl ketone **14e**, using the previously used protocol, initially proved problematic, and low yields (15%) of **15e** were encountered even using large excesses of **14e**. However, transferral of the Heck process to a sealed reaction vessel gave **15e** in improved yield (62%). Undistilled styrene **14f** (Entry 6) gave adduct **15f** in reasonable (49%) yield, a figure reflecting somewhat difficulties associated with effective purification of the nonpolar compound by flash column chromatography. The terminal alkene hex-1-ene **14g** (Entry 7) afforded the adduct **15g** in a regioselective (linear:branched, 9:1) fashion, and as for Entry 5, improved yields were observed if the intermolecular Heck reaction was conducted in a sealed system. The heterocyclic alkene dihydrofuran **14h** proved an efficient reaction partner (Entry 8), and optimal yields of **15h** were again achieved in a sealed tube. In this example no benzylic hydrogenolysis was observed under the reaction conditions.[21]

We next aimed to investigate the analogous sequence with a series of alternative bromides and methyl acrylate **14a** (Scheme 4). 1-Bromonaphthalene **16a**[22] (Entry 1) afforded **17a** in good yield; however, use of 1-bromo-4-nitrobenzene **16b** (Entry 2) was not as straightforward. A mixture of the hoped for product **17b** and the intermediate alkene (4:1) was isolated in approximately 60% yield. In both of these compounds the nitro group had been reduced into the corresponding amino moiety.[23] Attempts to improve this ratio by conducting the hydrogenation at elevated pressure (5 atm) delivered the mixture in slightly improved yield but with no benefit in selectivity. Using the electron-rich aromatic bromide **16c** (Entry 3) the initial,

Scheme 5. Synthesis of (*R*)-Cinacalcet 19 Featuring a One-Pot Heck−Hydrogenation Approach



Cond. (*R*)-1-naphthyl-1-ethylamine, 1,2,4-triazole, DBU, 70 °C, 64%; ***or*** (1) $LiOH_{(aq)}$, THF, rt; (2) (*R*)-1-naphthyl-1-ethylamine, EDCI·HCl, Et*i*-Pr_2N, CH_2Cl_2, rt, 83%

intermolecular Heck reaction did not proceed efficiently. On the basis of this failure it was unsurprising that **16d** (Entry 4) did not generate **17d** in synthetically useful amounts. However, the dioxolane **16e** gave the adduct **17e** albeit in low yield (25%). Presumably, this outcome reflects perturbation of mesomeric communication of the 4-oxygen substituent with the *ipso*-bromide carbon atom due to the dioxolane ring structure.

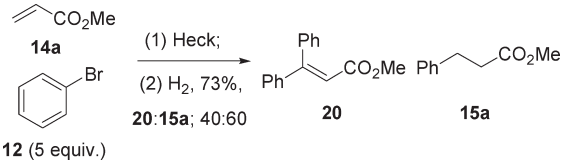
The shortcomings associated with the use of electron-rich aromatic halides in Heck reactions under the Pd-conditions described are well established,[5] and this issue has been partly solved by the introduction of nitrogen gas as a leaving group in the Matsuda−Heck reactions[5h,18] and the use of more stable catalyst/catalyst precursors,[5,24] electron-rich phosphines[5,25] and *N*-heterocyclic carbenes.[5,26] On the basis of the recalcitrance of bromides **16c−e** it was somewhat surprising to observe that bromostyrenes **16f** and **16g**[27] (Entry 5) efficiently participated in the Heck process[28] and the resultant 5-aryl esters **17f** and **17g**, resulting from diene hydrogenation, were isolated in good yield.

At this juncture we were interested to investigate if heteroaromatic compounds with Lewis basic functionality would participate in the process. Therefore, 2-bromopyridine **16h** (Entry 6) was selected, and in this instance the Heck reaction was not successful[29] with only 2,2′-bipyridine being isolated. This observation was in contrast to the outcome observed with the isomeric 3-bromopyridine **16i**,[21,30] which afforded the adduct **17i** in 92% yield with no loss of aromaticity following alkene hydrogenation. On the basis of this success the use of 3-bromoquinoline **16j**[29b] was investigated (Entry 7), and in this case a mixture of products were formed, the major isolable compound (35%) being **17j** in which the heterocycle underwent reduction.

In terms of specifically demonstrating the utility of the method, the synthesis of the calcimimetic agent cinacalcet **23**, which acts on the calcium-sensing receptor of the parathyroid, was considered (Scheme 5).[31] This compound is clinically used (Sensipar, Mimpara) to treat hyperthyroidism in sufferers of chronic kidney disease and for the control of elevated calcium levels in patients with parathyroid carcinoma. Thus, **16k** was converted to **17k** in excellent yield under the standard conditions, and then this methyl ester was converted into **19** by two alternative sequences. First, direct aminolysis, using a recently reported method,[32] gave the amide **18** in 64% yield, and second, a hydrolysis-carbodiimide coupling sequence was investigated, which although one step longer proved more efficient.

Amide **18** underwent smooth reduction to amine **19** with an excess of $LiAlH_4$ in ether at reflux. In relation to this sequence the use of 1 mol % palladium loading was investigated as a means to form **17k**. In this instance the Heck reaction worked smoothly; however, the transfer of hydrogen was inefficient, leading to the

Scheme 6. Trisubstituted Alkenes in the Heck−Hydrogenation Process



isolation of the typical cinnamate Heck adduct (not shown) in 69%.

In summary, on the basis of the well-documented performance of palladium-based species to mediate both coupling reactions and hydrogenation reactions, we have demonstrated that these distinct reactions may be combined using a very commonly used catalyst recipe for effecting inter- and intramolecular Heck reactions. The structural examples selected were chosen to uncover the scope and limitaions of this method. Results demonstrated that electron-rich arenes may only be utilized in certain instances due to inefficient Heck olefination under the conditions used. In some cases we found that the catalyst was unable to effect complete reduction of the intermediate alkene, and it appears that the relatively high level of palladium loading is required for the second hydrogenation step. In terms of additional functional group behavior, aromatic nitro groups undergo reduction, whereas benzyl ethers and nitrile groups are unchanged. In an attempt to form and reduce trisubstituted alkene **20** (Scheme 6) an excess of **12** was used, and although this did facilitate partial formation of **20** (formed along with 3-phenylacrylic acid methyl ester), subsequent introduction of hydrogen gas led to the isolation of a mixture of **20** and **15a** (ratio 42:58), indicating that trisubstituted alkenes of the type in **20** are not readily reduced under the reaction conditions.

The mechanism and identity of the catalytically active species in the Heck reaction has been much discussed in recent times.[5,15,33] One possible scenario is that the colloidal palladium, deposited from heating Pd(II) salts, mediates the olefination process. The consideration of such species as heterogeneous, however, is an oversimplification, and a situation involving a reversible solvation of nanoparticulate palladium has been suggested to account for high activity of some catalyst preparations.[34] In terms of the identity of the catalytic species mediating the hydrogenation event, Fagnou and co-workers[9] observed the formation of Pd-black during their related cascade process, and it seems likely that the colloidal palladium formed over the duration of the Heck process is the active species for the hydrogen addition. Indeed a precedent for such Pd-species effecting hydrogenation (with poor turnover/stability) is available.[35]

EXPERIMENTAL SECTION

General Directions. Reagents were obtained from commercial suppliers and were used without further purification. Anhydrous dimethylformamide (DMF) was used as supplied and stored under inert gas at room temperature. Anhydrous diethyl ether was distilled under nitrogen from the sodium-benzophenone ketyl radical. Ace pressure tubes were used for the reactions involving volatile alkenes. Thin-layer chromatography was performed on silica coated aluminum sheets (60 F_{254}) supplied by Merck. Flash column chromatography was performed under moderate pressure using flash silica 60 Å (230−400 mesh) 9385 supplied by Merck. ^{1}H and ^{13}C NMR spectra were recorded using 300 and 400 MHz instruments as indicated. Deuterochloroform was used as the solvent and chemical shifts are given in ppm relative to the standard reference TMS or residual chloroform. Samples for infrared spectroscopy were recorded as films on NaBr plates using a FT-IR spectrometer. Optical rotation measurements were recorded at 589 nm, 25 °C and are quoted in units of 10^{-1} deg cm^2 g^{-1}. The synthesis and data for compounds **9a**, **9b**, **9c**, **9f**, **10a**, **10b**, **10c**, **10f**, **11a**, **11b**, and **11f** have been reported previously.[4] Compounds **9c**, **9d**, and **9e** were prepared analogously to published procedures.[4]

General Procedures. Under nitrogen, the aryl bromide (1 equiv) and, for intermolecular Heck processes, the alkene (1−10 equiv depending on volatility) were dissolved in anhydrous DMF (*ca.* 0.125 mol dm^{-3}). To this solution were added $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %) and K_2CO_3 (2 equiv). The mixture was degassed under a stream of nitrogen (*ca.* 0.5 h) prior to heating at 110 °C (oil bath temperature) for 15 h. The reaction vessel was cooled to room temperature, and the nitrogen atmosphere exchanged for hydrogen (*ca.* 1 atm). The black mixture was stirred for 15 h before extraction with water and ethyl acetate. The combined organic extracts were dried over $MgSO_4$ and filtered, the solvent was removed under reduced pressure, and the crude residue was purified by flash column chromatography.

For volatile alkenes improved yields were typically observed when the Heck reaction was performed in a sealed reaction vessel. The procedure above was followed apart from conducting the Heck reaction under nitrogen at 110 °C for 15 h within an Ace pressure tube, after which time the reaction vessel was cooled and the contents were stirred under a hydrogen atmosphere (*ca.* 1 atm) for 15 h. Workup and purification was performed as above.

*1-Methyl-8-thia-9-aza-tricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene 8,8-Dioxide (**11c**).* A solution of **9c** (370 mg, 1.23 mmol, 1 equiv) in DMF (8 mL) was treated with $Pd(OAc)_2$ (27 mg, 0.120 mmol, 10 mol %), PPh_3 (64 mg, 0.244 mmol, 20 mol %) and K_2CO_3 (373 mg, 2.70 mmol, 2.2 equiv). The mixture was degassed by passing a steady stream of N_2 through the solution (for 1 h) and then heated at 110 °C (oil bath temperature), where the reaction was monitored by TLC. On cooling the mixture was stirred under an atmosphere of H_2 for 15 h. Water (10 mL) was added and then extracted with EtOAc (4 × 10 mL). The combined organic extracts were dried over $MgSO_4$ before filtration and solvent removal under reduced pressure gave the crude material. Purification by flash column chromatography (*c*-Hex/EtOAc; 3:1) gave **11c** (177 mg, 65%) as a colorless solid. Mp 186−188 °C; R_f = 0.3 (*c*-Hex/EtOAc; 3:1); IR (KBr, dep. from DCM) 3064, 2963, 2881, 1464, 1331, 1166, 1058 cm^{-1}; HRMS (ESI) calcd for [($C_{11}H_{13}NO_2S$ + H^+)] 224.0745, found 224.0744; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82 (d, J = 8.0 Hz, 1H), 7.52 (t, J = 8.0 Hz, 1H), 7.47−7.31 (m, 2H), 4.18 (d, J = 13.0 Hz, 1H), 3.93−3.80 (m, 1H), 3.66−3.55 (m, 1H), 3.09 (d, J = 13.0 Hz, 1H), 2.00−1.94 (m, 2H), 1.58 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 143.6, 135.2, 132.9, 128.3, 126.6, 124.6, 63.1, 48.1, 42.2, 40.4, 16.0.

*4,5-Dimethoxy-1-methyl-8-thia-9-aza-tricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene 8,8-Dioxide (**11d**).* As described above; a solution of **9d** (100 mg, 0.28 mmol, 1 equiv) in DMF (2.3 mL) was treated with $Pd(OAc)_2$ (6 mg, 0.027 mmol, 10 mol %), PPh_3 (15 mg, 0.057 mmol, 20 mol %) and K_2CO_3 (77 mg, 0.56 mmol, 2 equiv). The mixture was degassed before heating (110 °C) for 18 h. On cooling the mixture was stirred under an atmosphere of H_2 for 15 h. Following workup as above and purification by flash column chromatography (pentane/Et_2O; 2:1) **11d** (79 mg, 58%) was isolated as a colorless solid. Mp 192−196 °C; R_f = 0.3 (*c*-Hex/EtOAc; 3:1); IR (KBr, dep. from DCM) 3086, 2939, 1507, 1462, 1326, 1270, 1150, 1041 cm^{-1}; HRMS (ESI) calcd for [($C_{13}H_{17}NO_4S$ + H^+)] 284.0957, found 284.0963; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24 (s, 1H), 6.77 (s, 1H), 4.15 (d, J = 13.5 Hz,

1H), 3.93 (s, 3H), 3.91 (s, 3H), 3.89−3.79 (m, 1H), 3.65−3.54 (m, 1H), 3.06 (d, J = 13.5 Hz, 1H), 1.97−1.92 (m, 2H), 1.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.4, 148.8, 137.1, 126.5, 108.07, 106.9, 63.4, 56.4, 56.3, 48.3, 42.0, 40.3, 20.3.

*(±)-(4aR,10aS)-4a,10-Ethano-2,3,4,4a,10,10a-hexahydro-1H-9-thia-10-azaphenanthrene 9,9-Dioxide (**11e**).* A solution of **9e** (250 mg, 0.73 mmol, 1 equiv) in DMF (6 mL) was treated with $Pd(OAc)_2$ (16 mg, 0.071 mmol, 10 mol %), PPh_3 (40 mg, 0.153 mmol, 20 mol %) and K_2CO_3 (207 mg, 1.50 mmol, 2 equiv). The mixture was degassed by passing a steady stream of N_2 through the solution (for 1 h) and then heated at 110 °C (oil bath temperature) for 15 h. On cooling the mixture was stirred under an atmosphere of H_2 for 15 h. Water (10 mL) was added and then extracted with EtOAc (4 × 10 mL). The combined organic extracts were dried over $MgSO_4$ before filtration and solvent removal under reduced pressure gave the crude material. Purification by flash column chromatography (*c*-Hex/EtOAc; 4:1) gave **11e** (119 mg, 62%) as a colorless solid. Mp 138−140 °C; R_f = 0.3 (*c*-Hex/EtOAc; 3:1); IR (KBr, dep. from DCM) 3086, 2935, 2883, 1840, 1723, 1591, 1463, 1439, 1386, 1329, 1277, 1243, 1207, 1166, 1112, 1053, 1027 cm^{-1}; HRMS (ESI) calcd for $[(C_{14}H_{18}NO_2S + H^+)]$ 264.1058, found 264.1066; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.83 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 8.0 Hz, 1H), 7.43−7.31 (m, 2H), 4.10 (dd, J = 12.0, 6.0 Hz, 1H), 3.89−3.81 (m, 1H), 3.66−3.59 (m, 1H), 2.58−2.27 (m, 2H), 2.03−1.48 (m, 4H), 1.47−1.19 (m, 4H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.3, 135.7, 132.8, 127.9, 126.6, 124.0, 67.4, 45.7, 44.9, 33.4, 29.3, 27.5, 23.8, 21.4.

*3-Phenylpropionic Acid Methyl Ester (**15a**).* Following the general procedure; $Pd(OAc)_2$ (14 mg, 0.063 mmol, 10 mol %), PPh_3 (33 mg, 0.126 mmol, 20 mol %) and K_2CO_3 (177 mg, 1.25 mmol, 2 equiv) were sequentially added to a degassed (bubbled with a N_2 stream *ca*. 30 min) solution of bromobenzene **12** (0.07 mL, 0.64 mmol, 1 equiv) and methyl acrylate **14a** (0.3 mL, 3.19 mmol, 5 equiv) in DMF (5 mL). The mixture was heated at 110 °C for 15 h. On cooling the nitrogen atmosphere was then swapped to hydrogen (balloon *ca*. 1 atm) and stirring was continued for 15 h at room temperature. Water (15 mL) and EtOAc (25 mL) were added, the resultant aqueous layer was further extracted with EtOAc (3 × 25 mL), and the combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent removal *in vacuo* yielded the crude product. Purification by flash column chromatography (*c*-Hex/EtOAc, 6:1) afforded **15a** (76 mg, 73%) as a yellow oil.[36] R_f = 0.3 (*c*-Hex/EtOAc, 6:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.23 (m, 3H), 7.23−7.16 (m, 2H), 3.67 (s, 3H), 2.96 (t, J = 8.0 Hz, 2H), 2.63 (t, J = 8.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 140.7, 128.7, 128.5, 126.5, 51.7, 35.9, 31.2.

Phosphine-Free Procedure. A mixture of bromobenzene **12** (0.07 mL, 0.64 mmol, 1 equiv), methyl acrylate **14a** (58 μL, 0.64 mmol, 1 equiv), $Pd(OAc)_2$ (14 mg, 0.063 mmol, 10 mol %), and K_2CO_3 (177 mg, 1.28 mmol, 2 equiv) in DMF (5 mL) afforded **15a** (25 mg, 24%) following standard workup and purification by flash column chromatography with data as above.

Jeffery's Conditions. $Pd(OAc)_2$ (7 mg, 0.031 mmol, 5 mol %), *n*-Bu_4NBr (205 mg, 0.64 mmol, 1 equiv) and NaOAc (131 mg, 1.60 mmol, 2.5 equiv) were sequentially added to a degassed (bubbled with a N_2 stream *ca*. 30 min) solution of bromobenzene **12** (0.07 mL, 0.64 mmol, 1 equiv) and methyl acrylate **14a** (0.058 μL, 0.64 mmol, 1 equiv) in DMF (0.6 mL). The mixture was then heated at 50 °C for 15 h. On cooling the nitrogen atmosphere was exchanged for hydrogen (balloon *ca*. 1 atm), and stirring was continued for 15 h at room temperature. Water (10 mL) and EtOAc (15 mL) were added, and the resultant aqueous layer was further extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent removal *in vacuo* yielded the crude product, which was purified by flash column chromatography (*c*-Hex/EtOAc, 6:1) affording **15a** (45 mg, 43%) with data as above.

Matsuda−Heck Reaction. NaOAc (270 mg, 3.30 mmol, 1.7 equiv) and benzenediazonium tetrafluoroborate[37] **13** (380 mg, 1.98 mmol, 1 equiv) were added sequentially to a degassed (bubbled with a N_2 stream *ca*. 10 min) solution of methyl acrylate **14a** (0.62 mL, 6.93 mmol, 3.5 equiv) in acetonitrile (HPLC grade without further drying or distillation, 7.5 mL). At room temperature $Pd(OAc)_2$ (20 mg, 0.089 mmol, 5 mol %) was added to the mixture, and stirring was maintained for 15 h (after approximately 30 min gas evolution was observed and the orange solution became black). The nitrogen atmosphere was then swapped with hydrogen (balloon *ca*. 1 atm), and stirring was continued for 15 h at room temperature. Water (15 mL) and ether (15 mL) were added, and the resultant aqueous layer was further extracted with ether (2 × 15 mL). The combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent removal *in vacuo* afforded **15a** (298 mg, 92%) with data as above.

*n-Butyl 3-Phenylpropanoate (**15b**).* According to the general procedure above; a mixture of bromobenzene **12** (0.07 mL, 0.64 mmol, 1 equiv), *n*-butyl acrylate **14b** (0.09 mL, 0.64 mmol, 1 equiv), $Pd(OAc)_2$ (14 mg, 0.063 mmol, 10 mol %), PPh_3 (33 mg, 0.126 mmol, 20 mol %) and K_2CO_3 (177 mg, 1.28 mmol, 2 equiv) in DMF (5 mL) afforded **15b** (104 mg, 79%) as a white solid following purification by flash column chromatography (*c*-Hex).[36] R_f = 0.7 (*c*-Hex/EtOAc, 9:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32−7.22 (m, 2H), 7.23−7.14 (m, 3H), 4.07 (t, J = 7.0 Hz, 2H), 2.95 (t, J = 8.0 Hz, 2H), 2.61 (t, J = 8.0 Hz, 2H), 1.67−1.49 (m, 2H), 1.40−1.24 (m, 2H), 0.91 (t, J = 7.5 Hz, 3H).

*1-Phenylsulfonyl-2-phenylethane (**15c**).* According to the general procedure described above; a mixture of bromobenzene **12** (0.07 mL, 0.64 mmol, 1 equiv), phenyl vinyl sulfone **14c** (107 mg, 0.64 mmol, 1 equiv), $Pd(OAc)_2$ (14 mg, 0.063 mmol, 10 mol %), PPh_3 (33 mg, 0.126 mmol, 20 mol %) and K_2CO_3 (177 mg, 1.28 mmol, 2 equiv) in DMF (5 mL) afforded an inseparable mixture (4:1) of **15c** and the alkene Heck adduct, (*E*)-1-phenylsulfonyl-2-phenylethene (80 mg, 51%) following purification by flash column chromatography (*c*-Hex/EtOAc, 4:1).[38] R_f = 0.2 (*c*-Hex/EtOAc, 4:1); HRMS (ESI) calcd for $[(C_{14}H_{14}O_2S + Na^+)]$ 269.0612, found 269.0602; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97−7.90 (m, 2H), 7.66 (m,1H), 7.56 (m, 2H), 7.26 (m, 2H), 7.22−7.16 (m, 1H), 7.10 (d, J = 7.0 Hz, 2H), 3.39−3.32 (m, 2H), 3.08−3.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 139.3, 137.6, 133.8, 129.5, 128.9, 128.4, 128.2, 127.0, 57.7, 28.9.

*3-Phenylpropanenitrile (**15d**).* According to the general procedure a mixture of bromobenzene **12** (0.07 mL, 0.64 mmol, 1 equiv), acrylonitrile **14d** (46 mg, 0.87 mmol, 1.4 equiv), $Pd(OAc)_2$ (14 mg, 0.063 mmol, 10 mol %), PPh_3 (33 mg, 0.126 mmol, 20 mol %) and K_2CO_3 (177 mg, 1.28 mmol, 2 equiv) in DMF (5 mL) gave **15d** (36 mg, 43%) as a colorless oil following purification by flash column chromatography (*c*-Hex/EtOAc, 4:1).[39] R_f = 0.3 (*c*-Hex/EtOAc, 4:1); HRMS (EI) calcd for $[C_9H_9N]^+$ 131.0735, found 131.0735; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (t, J = 7.0 Hz, 2H), 7.30−7.21 (m, 3H), 2.96 (t, J = 7.0 Hz, 2H), 2.62 (t, J = 7.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 129.0, 128.4, 127.4, 119.2, 31.8, 19.5.

*4-Phenylbutan-2-one (**15e**).* Due to alkene volatility this reaction was performed in a sealed tube. A mixture of bromobenzene **12** (0.07 mL, 0.64 mmol, 1 equiv), 3-buten-2-one **14e** (0.5 mL, 6.37 mmol, 10 equiv), $Pd(OAc)_2$ (14 mg, 0.063 mmol, 10 mol %), PPh_3 (33 mg, 0.126 mmol, 20 mol %) and K_2CO_3 (177 mg, 1.28 mmol, 2 equiv) in DMF (5 mL) was mixed and sealed in a screw capped thick walled glass reaction vessel. The tube was immersed in an oil bath (110 °C) for 15 h. Upon cooling hydrogen was introduced (balloon, *ca.* 1 atm), and stirring was continued for 15 h. Following standard workup (as above) purification flash column chromatography (*c*-Hex/EtOAc, 4:1) afforded **15e** (59 mg, 62%) as a pale orange oil.[40] R_f = 0.4 (*c*-Hex/EtOAc, 4:1); HRMS (EI) calcd for $[C_{10}H_{12}O]^+$ 148.0888, found 148.0887; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.23 (m, 2H), 7.11−7.08 (m, 3H), 2.88

(t, J = 8.0 Hz, 2H), 2.74 (t, J = 8.0 Hz, 2H), 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.9, 141.1, 128.5, 128.3, 126.1, 45.2, 30.1, 29.8.

*1,2-Diphenylethane (**15f**).* According to the general procedure; a mixture of bromobenzene **12** (0.07 mL, 0.64 mmol, 1 equiv), styrene **14f** (used as supplied, *i.e.*, not distilled, 0.07 mL, 0.64 mmol, 1 equiv), $Pd(OAc)_2$ (14 mg, 0.063 mmol, 10 mol %), PPh_3 (33 mg, 0.126 mmol, 20 mol %) and K_2CO_3 (177 mg, 1.28 mmol, 2 equiv) in DMF (5 mL) followed by purification flash column chromatography (*c*-Hex) afforded **15f** (57 mg, 49%) as a white solid.[41] Mp 45−47 °C (45−49 °C);[42] R_f = 0.4 (*c*-Hex); HRMS (EI) calcd for $[C_{14}H_{20}O_4]^+$ 182.1096, found 182.1098; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.15 (m, 10H), 2.92 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 128.6, 128.5, 126.1, 38.1.

*1-Hexylbenzene (**15g**).* Due to alkene volatility this reaction was performed in a sealed tube using a mixture of bromobenzene **12** (0.07 mL, 0.64 mmol, 1 equiv), hex-1-ene **14g** (0.40 mL, 3.20 mmol, 5 equiv), $Pd(OAc)_2$ (14 mg, 0.063 mmol, 10 mol %), PPh_3 (33 mg, 0.126 mmol, 20 mol %) and K_2CO_3 (177 mg, 1.28 mmol, 2 equiv) in DMF (5 mL). Purification flash column chromatography (*c*-Hex) afforded **15g** (87 mg, 84%) as a colorless oil.[43] R_f = 0.6 (*c*-Hex); HRMS (EI) calcd for $[C_{12}H_{18}]^+$ 162.1409, found 162.1408; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.11 (m, 5H), 2.72−2.50 (m, 2H); 1.68−1.49 (m, 2H), 1.35−1.23 (m, 4H), 0.89 (t, J = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 128.5, 128.4, 125.7, 36.2, 31.9, 31.7, 29.2, 22.8, 14.2.

*2-Phenyltetrahydrofuran (**15h**).* Due to alkene volatility this reaction was performed in a sealed tube. A mixture of bromobenzene **12** (0.07 mL, 0.64 mmol, 1 equiv), 2,3-dihydrofuran **14h** (0.24 mL, 3.20 mmol, 5 equiv), $Pd(OAc)_2$ (14 mg, 0.063 mmol, 10 mol %), PPh_3 (33 mg, 0.126 mmol, 20 mol %) and K_2CO_3 (177 mg, 1.28 mmol, 2 equiv) in DMF (5 mL) followed by purification flash column chromatography (*c*-Hex/EtOAc, 6:1) afforded **15h** (52 mg, 55%) as a light brown oil and NMR spectroscopic analysis indicated purity and compound identity.[44] R_f = 0.6 (*c*-Hex/EtOAc, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.19 (m, 5H), 4.88 (t, J = 7.0 Hz, 1H), 4.09 (dd, J = 15.0, 7.0 Hz, 1H), 3.93 (dd, J = 15.0, 7.0 Hz, 1H), 2.31 (td, J = 13.0, 7.0 Hz, 1H), 2.04−1.93 (m, 2H), 1.80 (ddd, J = 16.0, 12.0, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6, 128.7, 127.2, 125.7, 80.8, 68.8, 34.7, 26.1.

*Methyl 3-(1-Naphthyl)propanoate (**17a**).* According to the general procedure a mixture of 1-bromonaphthalene **16a** (100 mg, 0.48 mmol, 1 equiv), methyl acrylate **14a** (0.22 mL, 2.40 mmol, 5 equiv), $Pd(OAc)_2$ (10 mg, 0.046 mmol, 10 mol %), PPh_3 (25 mg, 0.095 mmol, 20 mol %) and K_2CO_3 (133 mg, 0.96 mmol, 2 equiv) in DMF (4 mL) afforded **17a** (81 mg, 79%) as a yellow oil. R_f = 0.4 (*c*-Hex/EtOAc, 9:1); IR (KBr, dep. from DCM) 3047, 2950, 1737, 1435, 1167, 777 cm^{-1}; HRMS (ESI) calcd for $[(C_{14}H_{14}O_2 + Na^+)]$ 237.0891, found 237.0900; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.55−7.43 (m, 2H), 7.41−7.30 (m, 2H), 3.68 (s, 3H), 3.45−3.37 (m, 2H), 2.79−2.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 136.6, 133.9, 131.7, 128.9, 127.3, 126.2, 126.0, 125.7, 125.7, 123.5, 51.8, 35.1, 28.3.

*Methyl 3-(4-Aminophenyl)propanoate (**17b**).* According to the general procedure above; a mixture of 1-bromo-4-nitrobenzene **16b** (100 mg, 0.49 mmol, 1 equiv), methyl acrylate **14a** (0.22 mL, 2.45 mmol, 5 equiv), $Pd(OAc)_2$ (11 mg, 0.049 mmol, 10 mol %), PPh_3 (25 mg, 0.095 mmol, 20 mol %) and K_2CO_3 (135 mg, 0.98 mmol, 2 equiv) in DMF (4 mL) afforded a mixture (4:1) of **17b** and the alkene Heck product 3-(4-aminophenyl)-acrylic acid methyl ester (52 mg, 59%) as a brown solid.[45] R_f = 0.2 (*c*-Hex/EtOAc, 5:1); HRMS (ESI) calcd for $[(C_{10}H_{14}O_2N + H^+)]$ 180.1025, found 180.1023; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00−6.94 (m, 2H), 6.63−6.58 (m, 2H), 3.65 (s, 3H), 2.83 (t, J = 8.0 Hz, 2H), 2.56 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 144.8, 130.0, 129.2, 115.4, 51.63, 36.3, 30.3.

*Methyl 3-(3,4-Methylenedioxyphenyl)propanoate (**17e**).* According to the general procedure; a mixture of 1-bromo-3,4-(methylenedioxy)-benzene **16e** (60 μL, 0.50 mmol, 1 equiv), methyl acrylate **14a** (0.22 mL, 2.50 mmol, 5 equiv), $Pd(OAc)_2$ (11 mg, 0.049 mmol, 10 mol %), PPh_3 (26 mg, 0.099 mmol, 20 mol %) and K_2CO_3 (135 mg, 0.98 mmol, 2 equiv) in DMF (4 mL) afforded **17e** (25 mg, 25%) as a yellow oil.[46] R_f = 0.4 (*c*-Hex/EtOAc 9:1); HRMS (EI) calcd for $[C_{11}H_{12}O_4]^+$ 208.0736, found 208.0741; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76−6.60 (m, 3H), 5.92 (s, 2H), 3.67 (s, 3H), 2.87 (t, J = 8.0 Hz, 2H), 2.58 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 147.8, 145.1, 134.4, 121.2, 108.9, 108.4, 100.9, 51.8, 36.2, 30.8.

*Methyl 5-(3,4-Dimethoxyphenyl)pentanoate (**17f**).* According to the general procedure; a mixture of (*E*)-4-(2-bromovinyl)-1,2-di-methoxybenzene **16f** (40 mg, 0.165 mmol, 1 equiv), methyl acrylate **14a** (74 μL, 0.825 mmol, 5 equiv), $Pd(OAc)_2$ (4 mg, 0.018 mmol, 11 mol %), PPh_3 (9 mg, 0.034 mmol, 21 mol %) and K_2CO_3 (46 mg, 0.33 mmol, 2 equiv) in DMF (1.4 mL) afforded **17f** (35 mg, 83%) as a yellow oil. R_f = 0.25 (*c*-Hex/EtOAc, 4:1); IR (KBr, dep. from DCM) 3051, 2929, 1734, 1515, 1439, 1260, 1155, 1027, 801 cm^{-1}; HRMS (ESI) calcd for $[(C_{14}H_{20}O_4 + Na^+)]$ 275.1259, found 275.1259; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.70 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.66 (s, 3H), 2.58 (t, J = 7.0 Hz, 2H), 2.34 (t, J = 7.0 Hz, 2H), 1.73−1.57 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.2, 148.9, 147.3, 134.9, 120.3, 111.9, 111.4, 56.1, 55.9, 51.6, 35.3, 34.1, 31.2, 24.7.

*Methyl 5-(3,4-(Methylenedioxy)phenyl)pentanoate (**17g**).* According to the general procedure described a mixture of (*E*)-5-(2-bromovinyl)benzo[*d*][1,3]dioxole **16g** (100 mg, 0.44 mmol, 1 equiv), methyl acrylate **14a** (0.20 mL, 2.20 mmol, 5 equiv), $Pd(OAc)_2$ (9 mg, 0.040 mmol, 10 mol %), PPh_3 (23 mg, 0.088 mmol, 20 mol %) and K_2CO_3 (121 mg, 0.88 mmol, 2 equiv) in DMF (4 mL) afforded **17g** (86 mg, 83%) as a yellow oil.[47] R_f = 0.4 (*c*-Hex/EtOAc, 9:1); HRMS (ESI) calcd for $[(C_{13}H_{16}O_4 + Na^+)]$ 259.0946, found 259.0956; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74−6.57 (m, 3H), 5.91 (s, 2H), 3.66 (s, 3H), 2.54 (t, J = 7.0 Hz, 2H), 2.32 (t, J = 7.0 Hz, 2H), 1.79−1.44 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 147.7, 145.7, 136.1, 121.2, 108.9, 108.2, 100.9, 51.6, 35.4, 34.1, 31.3, 24.6.

Bipyridyl. This reaction was performed in a sealed tube as follows; a mixture of 2-bromopyridine **16h** (50 μL, 0.53 mmol, 1 equiv), methyl acrylate **14a** (0.24 mL, 2.65 mmol, 5 equiv), $Pd(OAc)_2$ (12 mg, 0.053 mmol, 10 mol %), PPh_3 (27 mg, 0.103 mmol, 20 mol %) and K_2CO_3 (146 mg, 1.06 mmol, 2 equiv) in DMF (5 mL) after standard workup and purification by flash column chromatography (*c*-Hex/EtOAc, 1:2) afforded the *title compound* (21 mg, 61%) as a colorless oil.[48] R_f = 0.2 (*c*-Hex/EtOAc, 1:2); HRMS (ESI) calcd for $[(C_{10}H_8N_2 + H^+)]$ 157.0766, found 157.0763; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (s, 2H), 8.41 (d, J = 8.0 Hz, 2H), 7.81 (td, J = 8.0, 1.0 Hz, 2H), 7.36−7.22 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 149.3, 137.0, 123.9, 121.3.

*Methyl 3-(Pyridin-3-yl)propanoate (**17i**).* This reaction was performed in a sealed tube as follows; a mixture of 3-bromopyridine **16i** (50 μL, 0.53 mmol, 1 equiv), methyl acrylate **14a** (0.24 mL, 2.65 mmol, 5 equiv), $Pd(OAc)_2$ (12 mg, 0.053 mmol, 10 mol %), PPh_3 (27 mg, 0.103 mmol, 20 mol %) and K_2CO_3 (146 mg, 1.06 mmol, 2 equiv) in DMF (5 mL) afforded **17i** (73 mg, 84%) as a colorless oil following purification by flash column chromatography (*c*-Hex to *c*-Hex/EtOAc 1:3).[49] R_f = 0.35 (*c*-Hex/EtOAc, 1:2); HRMS (ESI) calcd for $[(C_9H_{11}NO_2 + H^+)]$ 166.0868, found 166.0866; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 2H), 7.53 (d, J = 8.0 Hz, 1H), 7.22 (dd, J = 7.0, 5.0 Hz, 1H), 3.67 (s, 3H), 2.96 (t, J = 8.0 Hz, 2H), 2.65 (t, J = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 149.8, 147.8, 135.9, 135.8, 123.4, 51.7, 35.2, 28.1.

*Methyl 3-(1,2,3,4-Tetrahydroquinolin-3-yl)propanoate (**17j**).* This reaction was performed in a sealed tube as follows; according to the

general procedure above a mixture of 3-bromoquinoline **16j** (65 μL, 0.48 mmol, 1 equiv), methyl acrylate **14a** (0.22 mL, 2.40 mmol, 5 equiv), $Pd(OAc)_2$ (11 mg, 0.049 mmol, 10 mol %), PPh_3 (26 mg, 0.099 mmol, 20 mol %) and K_2CO_3 (138 mg, 1.00 mmol, 2 equiv) in DMF (4.0 mL) afforded **17j** (37 mg, 35%) as a colorless oil. R_f = 0.5 (c-Hex); IR (KBr, dep. from DCM) 3028, 2924, 1735, 1430, 1179, 712 cm^{-1}; HRMS (ESI) calcd for $[(C_{13}H_{17}NO_2 + H^+)]$ 220.1338, found 220.1335; ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (m, 2H), 6.60 (t, *J* = 7.0 Hz, 1H), 6.47 (d, *J* = 8.0 Hz, 1H), 3.67 (s, 3H), 3.32 (m, 1H), 2.96 (dd, *J* = 11.0, 9.0 Hz, 1H), 2.90−2.78 (m, 1H), 2.45 (m, 4H), 1.95 (bs, 1H), 1.81−1.59 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 144.4, 129.8, 127.0, 120.6, 117.4, 114.1, 51.7, 46.9, 33.4, 31.9, 31.9, 28.8.

*Methyl 3-(3-(Trifluoromethyl)phenyl)propanoate (**17k**).* This reaction was performed in a sealed tube as follows; according to the general procedure above a mixture of 3-bromobenzotrifluoride **16k** (0.12 mL, 0.89 mmol, 1 equiv), methyl acrylate **14a** (0.40 mL, 4.45 mmol, 5 equiv), $Pd(OAc)_2$ (20 mg, 0.09 mmol, 10 mol %), PPh_3 (47 mg, 0.18 mmol, 20 mol %) and K_2CO_3 (248 mg, 1.80 mmol, 2 equiv) in DMF (7 mL) afforded **17k** (198 mg, 95%) as a yellow colorless oil. R_f = 0.3 (*c*-Hex/EtOAc; 2:1); IR (KBr, dep. from DCM) 3053, 2955, 2849, 1740, 1430, 1331, 1164, 1124, 702 cm^{-1}; HRMS (EI) calcd $[(C_{11}H_{11}O_2F_3)]^+$ 232.0711, found 232.0700. ^1H NMR (400 MHz, $CDCl_3$) δ 7.48−7.42 (m, 2H), 7.41−7.33 (m, 2H), 3.65 (s, 3H), 3.00 (t, *J* = 8.0 Hz, 2H), 2.63 (t, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 141.6, 131.9 (C, d, *J* = 1.0 Hz), 131.0 (C, q, *J* = 34.0 Hz), 129.1, 125.2 (C, q, *J* = 4.0 Hz), 124.3 (C, q, *J* = 270.0 Hz), 123.3 (C, q, *J* = 4.0 Hz), 51.7, 35.4, 30.8; ^{19}F NMR (282 MHz, $CDCl_3$) δ −62.79.

*(R)-N-(1-(Naphthalen-1-yl)ethyl)-3-(3-(trifluoromethyl)phenyl)propanamide (**18**).* A solution **17k** (625 mg, 2.71 mmol, 1 equiv) dissolved in $CDCl_3$ (1 mL) (*R*)-1-(1-naphthyl)ethylamine (0.48 mL, 3.00 mmol, 1.1 equiv), 1,2,4-triazole (69 mg, 1.00 mmol, 37 mol %) and DBU (80 μL, 0.54 mmol, 20 mol %) was heated to reflux for 24 h. On cooling the crude material was flushed through a plug of silica and recrystallization (*c*-Hex) afforded **18** (645 mg, 64%) as a white solid. Mp 90−92 °C (*c*-Hex); R_f = 0.3 (*c*-Hex/EtOAc, 3:1); $[\alpha]_D$ = +9.5 (*c* 0.1, $CHCl_3$); IR (KBr, dep. from DCM) 3292, 3065, 2973, 2929, 1638, 1329, 1163, 1122, cm^{-1}; HRMS (ESI) calcd for $[(C_{22}H_{20}NOF_3 + H^+)]$ 372.1575, found 372.1587; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07−8.00 (m, 1H), 7.85 (dd, *J* = 6.0, 4.0 Hz, 1H), 7.78 (dd, *J* = 6.0, 4.0 Hz, 1H), 7.50 (p, *J* = 6.0 Hz, 2H), 7.47−7.38 (m, 4H), 7.33 (q, *J* = 8.0 Hz, 2H), 5.96−5.86 (m, 1H), 5.61−5.51 (m, 1H), 3.12−2.95 (m, 2H), 2.46 (td, *J* = 7.0, 3.0 Hz, 2H), 1.60 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 141.9, 138.3, 134.1, 132.0 (q, *J* = 1.0 Hz), 131.2, 130.9 (q, *J* = 32.0 Hz) 128.9 (q, *J* = 6.5 Hz), 128.5, 126.7, 124.2 (q, *J* = 270.0 Hz), 125.9, 125.3, 125.1 (q, *J* = 4.0 Hz), 123.4, 123.2 (q, *J* = 4.0 Hz), 122.6, 44.8, 38.0, 31.4, 20.7; ^{19}F NMR (282 MHz, $CDCl_3$) δ −62.64.

Hydrolysis−Amide Coupling. At room temperature a solution of methyl ester **17k** (40 mg, 0.17 mmol, 1 equiv) in THF (3 mL) was treated with a solution of $LiOH \cdot H_2O$ (22 mg, 0.52 mmol, 3 equiv) in water (2 mL). Stirring was continued for 48 h before Et_2O (5 mL) and 1 M HCl (5 mL) were added. The resultant aqueous layer was further extracted with Et_2O (2 × 5 mL), and the combined organic extracts were dried over $MgSO_4$. Filtration and solvent removal under reduced pressure afforded the crude carboxylic acid. The crude material was dissolved in dry DCM (2 mL) and treated with EDCI·HCl (36 mg, 0.19 mmol, 1.1 equiv), (*R*)-(+)-1-(1-naphthyl)ethylamine (30 μL, 0.19 mmol, 1.1 equiv) and DIPEA (34 μL, 0.19 mmol, 1.1 equiv) at rt under N_2. Stirring was continued for 15 h before DCM (10 mL) and water (10 mL) were added. The organic layer was dried over $MgSO_4$ to afford the crude material. Recrystallation (*c*-Hex) gave **18** (52 mg, 83%) as a white solid with data consistent with above.

*(R)-N-(1-(Naphthalen-1-yl)ethyl)-3-(3-(trifluoromethyl)phenyl)propan-1-amine (**19**).* A slurry of lithium aluminum hydride (106 mg, 2.79 mmol, 10 equiv) in Et_2O (10 mL) was treated with a solution of **18** (100 mg, 0.27 mmol, 1 equiv) in Et_2O (10 mL). The reaction mixture was heated to reflux for 5 h. On cooling the reaction mixture was added to ice and extracted with Et_2O (3 × 50 mL), and the combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent removal *in vacuo* yielded the crude product, which was purified by flash column chromatography (*c*-Hex/EtOAc, 1:2) affording **19** (77 mg, 80%) as a yellow oil. R_f = 0.2 (*c*-Hex/EtOAc, 1:2); $[\alpha]_D$ = +10 (*c* 0.1, $CHCl_3$); IR (KBr, dep. from DCM) 3339, 3049, 2958, 2927, 2856, 1450, 1330, 1163, 1124, 1073 cm^{-1}; HRMS (ESI) calcd for $[(C_{22}H_{22}NF_3 + H^+)]$ 358.1783, found 358.1795; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 7.0 Hz, 1H), 7.53−7.38 (m, 5H), 7.36−7.25 (m, 2H), 4.61 (q, *J* = 7.0 Hz, 1H), 2.77−2.53 (m, 4H), 1.82 (p, *J* = 7.0 Hz, 2H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 141.3, 134.0, 131.8 (q, *J* = 1.0 Hz), 131.3, 130.6 (q, *J* = 32.0 Hz), 129.0, 128.6, 127.2, 125.7, 125.6, 125.3, 125.0 (q, *J* = 4.0 Hz), 124.3 (q, *J* = 270.0 Hz, CF_3), 122.9, 122.7, 122.6 (q, *J* = 3.0 Hz), 53.8, 47.2, 33.4, 31.9, 23.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ −62.55.

*Methyl 3,3-Diphenylacrylate (**20**).* This reaction was performed in a sealed tube according to the general procedure above, using a mixture of bromobenzene **12** (0.6 mL, 5.80 mmol, 5 equiv), methyl acrylate **14a** (0.10 mL, 1.16 mmol, 1 equiv), $Pd(OAc)_2$ (29 mg, 0.13 mmol, 10 mol %), PPh_3 (63 mg, 0.24 mmol, 20 mol %) and K_2CO_3 (331 mg, 2.40 mmol, 2 equiv) in DMF (9 mL). On cooling the mixture was stirred under a H_2 atmosphere for 15 h, which afforded, following standard workup and column chromatography (*c*-Hex/EtOAc, 6:1), an inseparable mixture of **20** and **15a** (161 mg, 73%; **20**:**15a**; 40:60) as a pale yellow oil. NMR spectroscopic analysis indicated identity of **20**.[50] R_f = 0.3 (*c*-Hex/EtOAc, 6:1); HRMS (ESI) calcd for $C_{16}H_{14}O_2$ 238.0994, found 238.0993; ^1H NMR (400 MHz, $CDCl_3$) δ 7.31−7.24 (m, 5H), 7.22−7.13 (m, 5H), 6.36 (s, 1H), 3.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 157.1, 140.7, 138.9, 129.5, 129.3, 128.6, 128.4, 128.3, 128.0, 126.4, 117.0, 51.3.

■ ASSOCIATED CONTENT

Supporting Information. Copies of proton, carbon NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

The authors thank University College Dublin for financial support and the National University of Ireland for an NUI Travelling Studentship (K.G.).

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