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Palladium-Catalyzed Regioselective C-H Alkenylation of Arylacetamides *via* Distal Weakly Coordinating Primary Amide as Directing Group

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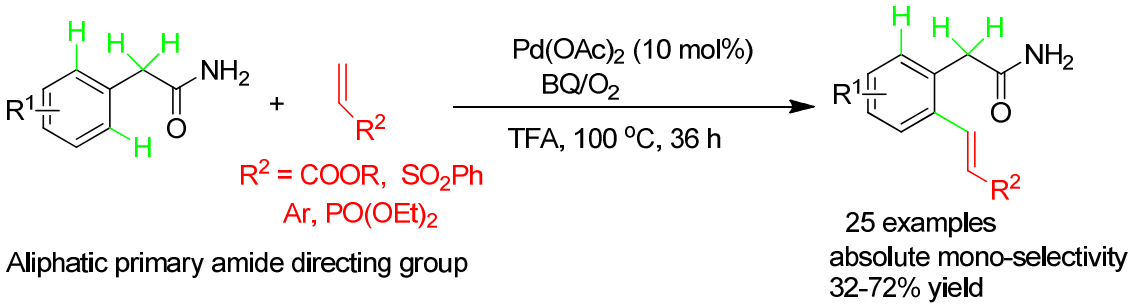
Graphical Abstract



Abstract

Herein, we disclose the Pd(II)-catalyzed efficient and *regio*-selective *ortho* C-H alkenylation of arylacetamide derivatives *viz* weakly coordinating aliphatic primary amide. This protocol utilizes ubiquitous free primary amide as the directing group and circumventing two troublesome steps of installation and removal of an external auxiliary. This strategy directly enables the incorporation of a synthetically versatile olefin in the products in moderate to good yields with *regio* and distereo-selective fashion. The alkenylated acetamides can be easily manipulated and further transformed into a variety of useful derivatives.

Introduction

Amide bonds are the key structural unit that is present in many physiologically active compounds (Figure 1) beside their ubiquitous presence in biopolymers, for instance, proteins and

glycoproteins.[1] The amide functionality also serves as an important building block in organic synthesis and in recent year extensively utilized as a directing group for direct C-H bond activation *viz* cyclopalladation.[2] In this context, pioneer work has been done by Yu, Miura, Daugulis, Glorius, Ackermann, and Dong *et al.* where *N*-substituted secondary[3] and tertiary amides[4] have been used as a directing group for *chemo* and *regio*-selective C-H bond functionalization. In spite of these significant progresses, free form of amide, in particularly, aliphatic primary amide group (-CH_2CONH_2) has been rarely utilized as directing group for C-H bond transformation.[5] Moreover, the primary amide group is more venerable for further functional group inter-conversion after the desired installation. Therefore, an important challenge in the area of direct C-H bond functionalization is to find out a simple and ubiquitous functional group, which can be used as directing group for distal C-H bond activation reaction, without the need of pre-installation, which eventually increases the atom and step economy.

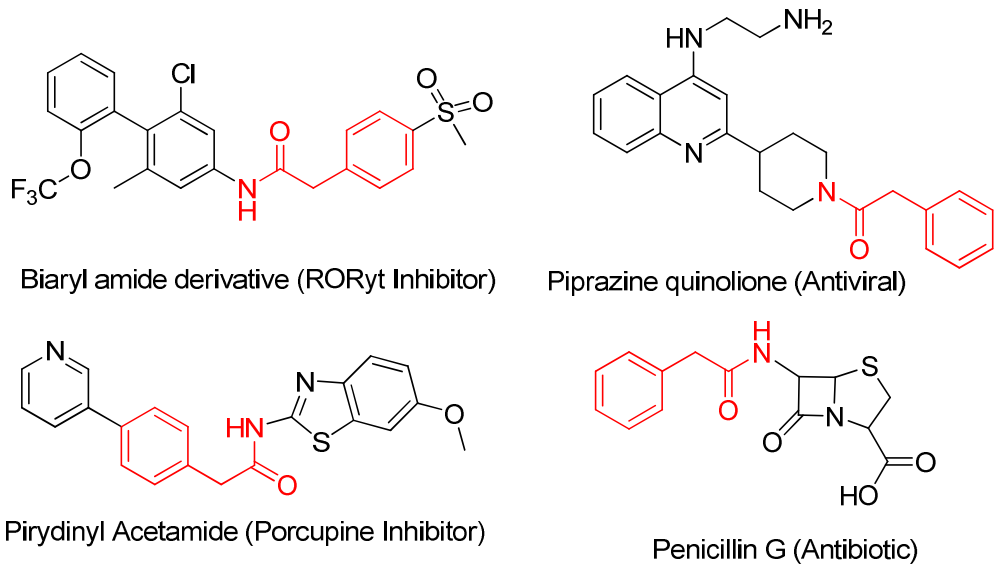
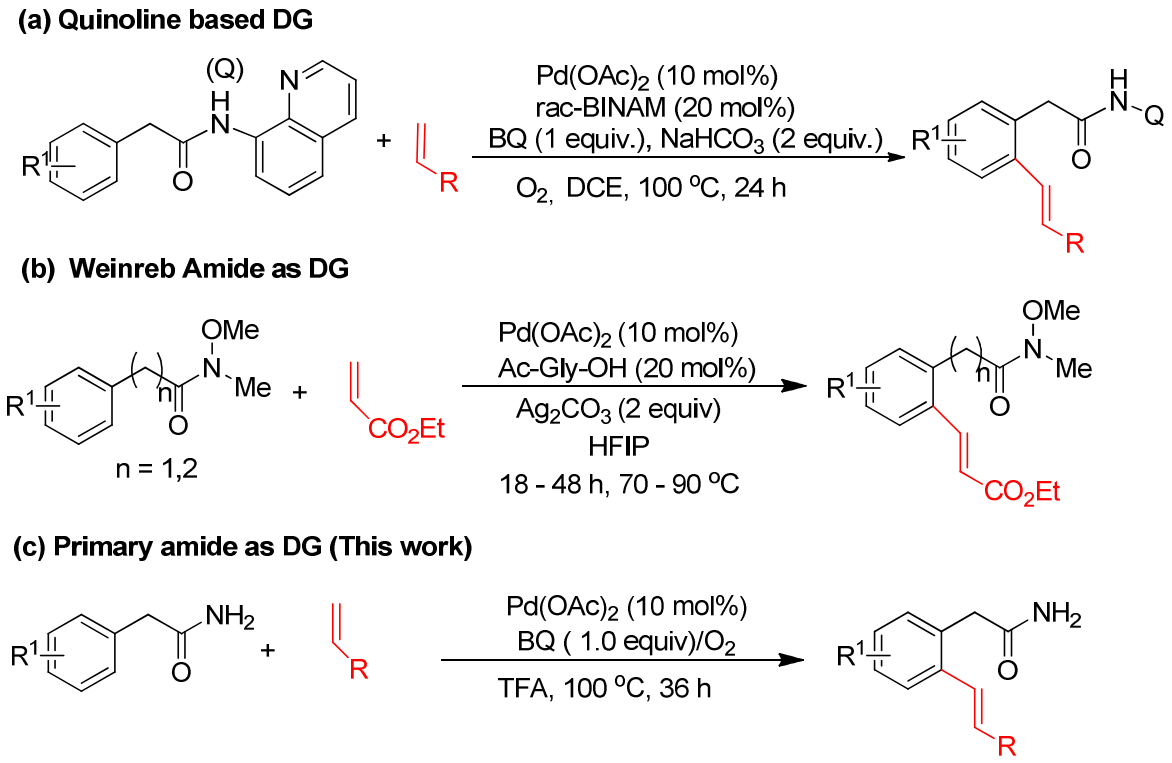


Figure 1: Biologically active molecules containing phenylacetamide motif.

Carbon-carbon bond formation *viz* transition metal catalyzed two-fold C-H activation (Fujiwara-Moritani reaction), in particular, the directing group assisted σ-chelation control reactions have emerged as economical and handful tools in organic synthesis.[6] A range of the directing groups has been introduced on aryl motifs, which control the *regio*-selectivity. However, a major limitation of these strategies lies in requirements of pre-installation of directing groups followed by their uninstallation after the desired operation.[7] Recently Yu *et al*.[8a] (Scheme 1a) and Maity and coworkers[8b] (Scheme 1b) elegantly demonstrated the application of *N*-substituted secondary and tertiary acetamide as an effective distal directing group for *ortho*-C-H olefination of phenylacetamide derivatives. While these σ-chelation-assisted reactions were quite effective for C-C bond formation, Pd-catalyzed oxidative alkenylation with the prevalent functional group, such as aliphatic primary acetamide as a weak coordinating group has never been reported. Recently, our group introduced the use of aliphatic primary acetamide as a versatile directing group for *regio*-selective *ortho*-C-H arylation of phenylacetamides derivatives.[9] Substantial advantage of this distal and weakly coordinating directing group is due to the presence of free amide moiety, which can be easily manipulated by the different functional groups. In our continued efforts to synthesize multifunctionalized arenes,[10] herein we disclose, an efficient Pd(II)-catalyzed mono-*ortho*-olefination of phenylacetamides derivatives *via* distal C-H bond activation (Scheme 1c). The generality of this protocol is demonstrated by preparing a commendable set of E-alkenylated compounds.



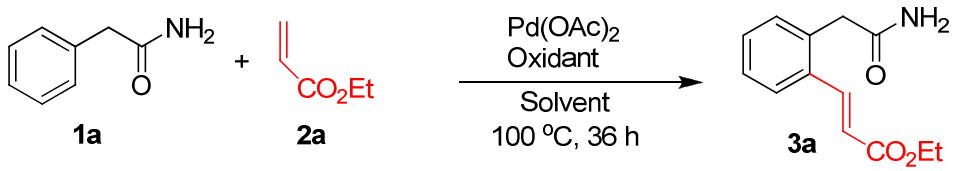
Scheme 1. Weakly coordinating directing group assisted alkenylation of arylacetamides.

Result and Disscussion

Excited form our recent finding, we were further interested to explore the distal directing ability for two-fold C-H activation (Fujiwara-Moritani reaction) on arylacetamides without installing any additional auxiliary. However, to utilize the aliphatic primary amide as a directing group for distal C-H bond activation is by no means routine transformation and not comparable to primary benzamide as a directing group. The presence of free rotating methylene group (-CH_2) between amide group and aryl ring of phenylacetamides increases the challenges in the manifold. Considering this fact, we commenced our studies by selecting phenylacetamide **1a** as model substrate and electron deficient ethyl acrylate **2a** as a coupling partner and palladium (II) salt as a choice of metal catalyst. Other reaction parameters such as solvent, oxidant and reaction temperature (for detailed information see Supporting Information) were optimized for *regio-*

selective *ortho*-alkenylation of phenylacetamides and results are tabulated in Table 1. To our delight, 43% of desired product **3a** was obtained using 10 mol% $Pd(OAc)_2$ in presence of Ag_2CO_3 in AcOH solvent at 100 ^oC for 36 h (Table 1, entry1). Among a broad range of solvents surveyed TFA, AcOH, HIFA, ACN, DMF, and TFE, TFA provided the desired product in superior yield (Table 1, entry 6). Next, the effects of various oxidants were also investigated and it was found the efficiency of the desired transformation increased when benzoquinone (BQ) (entry 12) was used as oxidant under a molecular oxygen atmosphere. Interestingly, we observed that loading of benzoquinone (BQ) plays a significant effect on the efficiency of the overall process (see SI). For example, when the reaction was carried out with 1.0 equiv. of benzoquinone (BQ) under standard conditions, afforded the olefinated product **3a** in 72% yield (entry 13). The yield of the transformation was almost unaffected by increasing the reaction temperature (100 ^0C to 120 ^oC) and time (see SI). Similarly, the use of excess amount of ethyl acrylate (3.0 equiv.) does not affect the product yield considerably. It must be noted that throughout this optimization there was no evidence of *N*-alkenylated product formation, which was a primary concern as primary amide is vulnerable precursor to undergo intermolecular *N*-alkenylation.[11] Finally, the reaction conditions described in entry 13, Table-1 were selected as the standard reaction conditions for further exploration.

Table 1. Optimization of Reaction Conditions[a]



1a **2a** **3a**

Entry	Solvent	Oxidant	Yield [b] (%)
1	AcOH	Ag_2CO_3	43

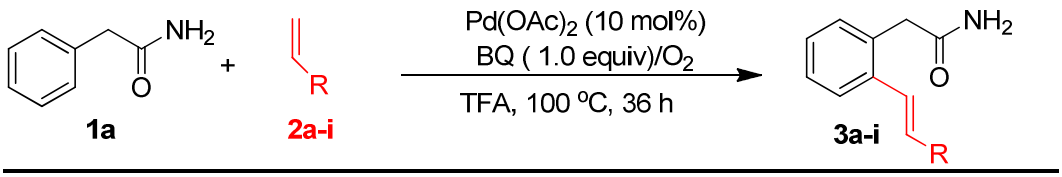
2	HFIP	Ag_2CO_3	36
3	TFE	Ag_2CO_3	40
4	ACN	Ag_2CO_3	12
5	DMF	Ag_2CO_3	18
6	TFA	Ag_2CO_3	50
7	TFA	Ag_2O	45
8	TFA	CH_3CO_2Ag	50
9	TFA	$AgBF_4$	0
10	TFA	CF_3CO_2Ag	53
11	TFA	$AgNO_3$	40
12	TFA	BQ/O_2	63
13	TFA	BQ/O_2	72[c]
14	TFA	$Cu(OAc)_2/O_2$	55

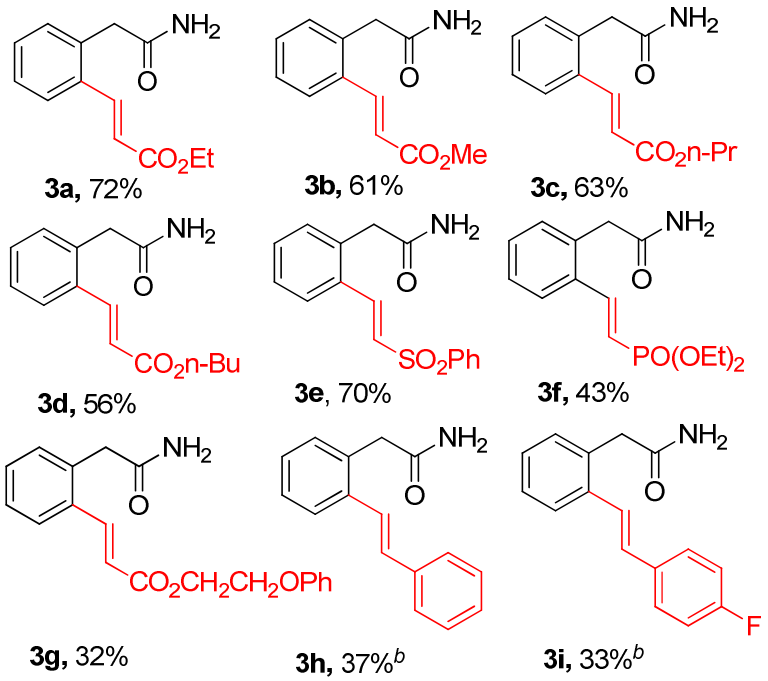
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (10 mol%), oxidant (2.0 equiv.) solvent (2.0 mL), at 100 °C for 36 h. [b]Isolated yield after column chromatography. [c]Oxidant (1.0 equiv.). BQ = Benzoquinone

With these optimized reaction conditions in hand, we explored the reaction scope with a variety of substituted alkenes and results are summarized in Table 2. With the parent system **1** an array of acrylates were examined to furnish E-alkenylated products. For example, differentially substituted acrylic esters such as methyl to *n*-butyl all afforded the corresponding *ortho*-olefinated products (**3a-3d**) and yields were in the range of 56-72% with excellent *regio*-selectivity. Fortunately, when the reaction was carried out with other electron deficient alkenes, for instance, phenyl vinyl sulfone (**2e**), diethyl vinylphosphonate (**2f**) and phenoxyethyl acrylate (**2g**) as a coupling partner, desired products (**3e-3g**) were isolated in good to moderate yields (70%-32%). However, we observed that when the reactions were carried out with unactivated alkenes such as styrene (**2h**) and 4-fluoro styrene (**2i**) under optimized reaction conditions, the desired products were isolated in trace amount along with the formation of polymerized products and some starting material was also recovered. Surprisingly, by changing the solvent from

trifluoroacetic acid to acetic acid afforded the corresponding products (**3h** and **3i**) albeit in low yields 37% and 33% respectively.

Table 2. Scope of Alkene Derivatives[a]



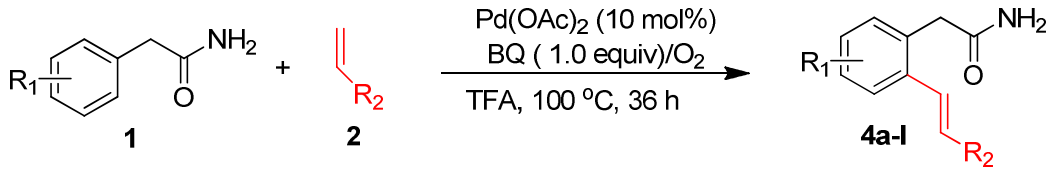


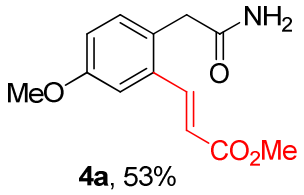
[a]Reaction conditions: see entry 13, Table 1. [b]AcOH was used as a solvent.

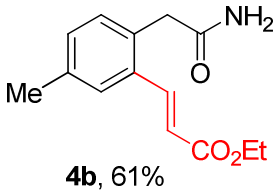
Next, we extended the scope of the alkenylation reaction using a range of substituted arylacetamides with various alkenes (Table 3). Electron donating group such as methoxy, methyl and 3,4-dioxy at *meta* and *para* positions of aryl ring underwent smooth alkenylation reaction with activated acrylates to give *regio*-selective mono alkenylated products in good yields (53-62%, **4a-4d**). Furthermore, when moderate electron withdrawing group such as fluorine was introduced at *meta*-position of an aryl ring, desired product **4e** was procured in lower yield (34%). It is worth to mention that, *meta*-substituted substrates such as **1c**, **1d** and **1e** containing

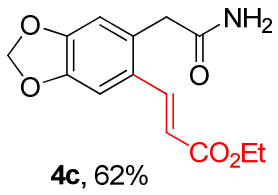
two possible sites for C-H bond alkenylation proceeded selectively at the least sterically hindered position to afford **4c**, **4d** and **4e** as the sole products. When 4-methyl phenylacetamide was employed to couple with diethyl vinyl phosphonate desired olefinated product (**4f**) was obtained in moderate yield (42%). Reaction of phenyl vinyl sulfone with *para*-methyl and *para*-methoxy substituted arylacetamide underwent smooth conversion to give alkenylated products in good yield 68% and 65% respectively (**4g-4h**). Pleasingly, halogen substituted arylacetamide were also compatible with phenyl vinyl sulfone to give *ortho*-alkenylated products in acceptable yields (33%-38%, **4i** and **4j**), which could provide a handle for further synthetic elaboration. Delightfully, styrene was successfully coupled with *para*-methyl and methoxy substituted phenylacetamides (**4k** and **4l**).

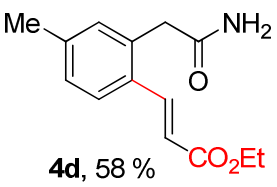
Table 3. Scope with regard to the arylacetamides and alkenes[a]

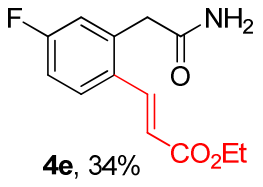


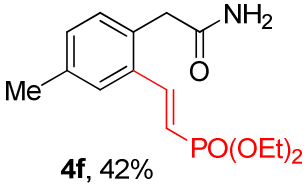


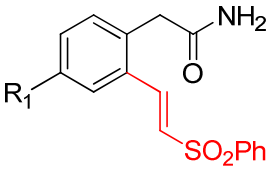




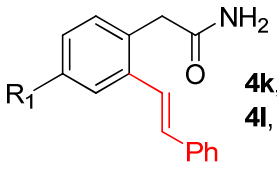








4g, R_1 = Me, 68%
4h, R_1 = OMe, 65%
4i, R_1 = Br, 38%
4j, R_1 = Cl, 33%

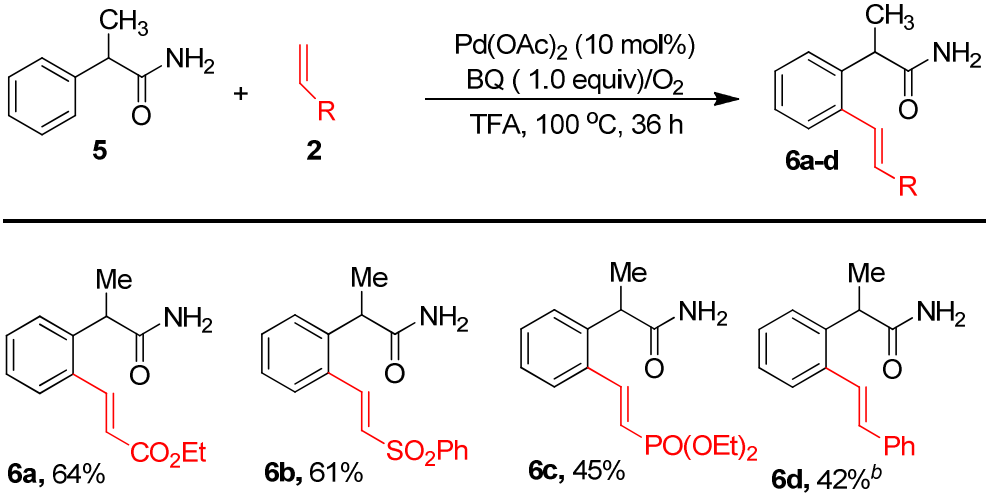


4k, R_1 = Me, 35%[b]
4l, R_1 = OMe, 36%[b]

[a]Reaction conditions: see entry 13, Table 1.[b]AcOH was used as a solvent.

Further, we became interested to check the scope of α-methyl phenylacetamide as directing group for *ortho*-olefination reaction under the optimized reaction conditions (Table 4). Interestingly, ethyl acrylate and phenyl vinyl sulfone reacted well to afford the corresponding *mono*-olefinated products in good yields (61-64%, **6a** and **6b**). Similarly, other alkenes such as diethyl vinylphosphonate and styrene were also coupled to give the corresponding products in moderate yields (42-45%, **6c** and **6d**).

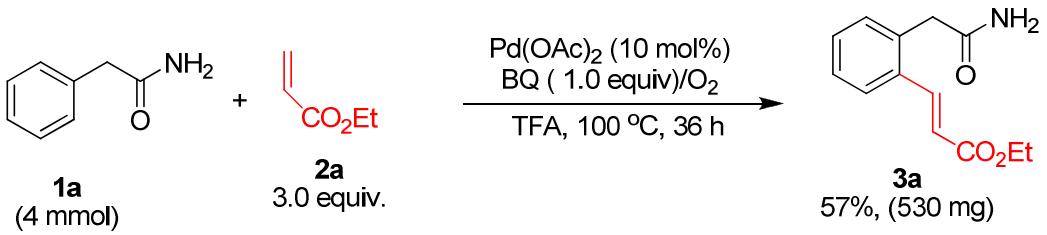
Table 4. Scope of olefins withα-methyl phenylacetamide[a]



[a]Reaction conditions: see entry 13, Table 1.[b]AcOH was used as a solvent.

To demonstrate the synthetic utility, we performed scale-up experiment with 4.0 mmole of phenylacetamide **1a** with ethyl acrylate **2a** under standard conditions. The olefinated product **3a** was isolated in 57% yield and there was a slight drop in the yield in scale-up reaction (Scheme 2).

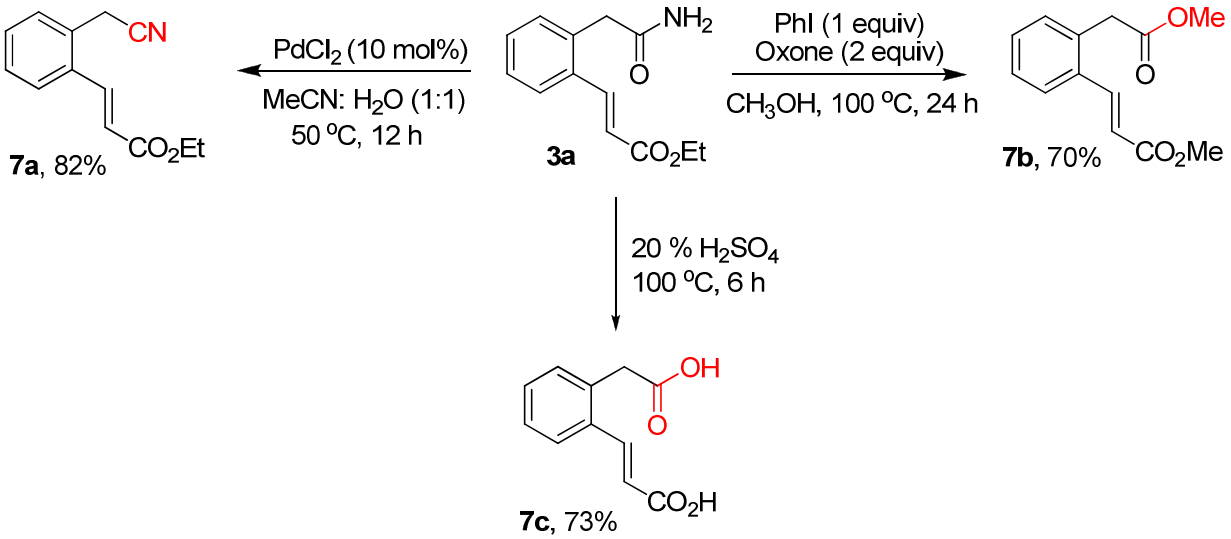
Scheme 2. Preparative Scale Experiment



1a (4 mmol) **2a** 3.0 equiv. **3a** 57%, (530 mg)

After this primary acetamide directed *ortho*-alkenyaltion strategy was established, the further synthetic transformation of alkenylated phenylacetamide product **3a** was explored. Amide group can be easily manipulated to different functional groups as per requirements under given conditions. Treatment of **3a** with a catalytic amount of $PdCl_2$ in the mixture of CH_3CN and water led to dehydration to afford **7a** in 82% yield without affecting ester group. Similarly, when **3a** was treated with iodobenzene and oxone in presence of methanol, amide group was converted to ester via *trans* esterification to give **7b** in 70% yield. Furthermore, the functionalizable primary amide and ester groups can be easily hydrolyzed to the corresponding dicarboxylic acid **7c** by treating with 20% H_2SO_4 at 100 °C for 6h (Scheme 3).

Scheme 3. Functional Group Transformation of 3a

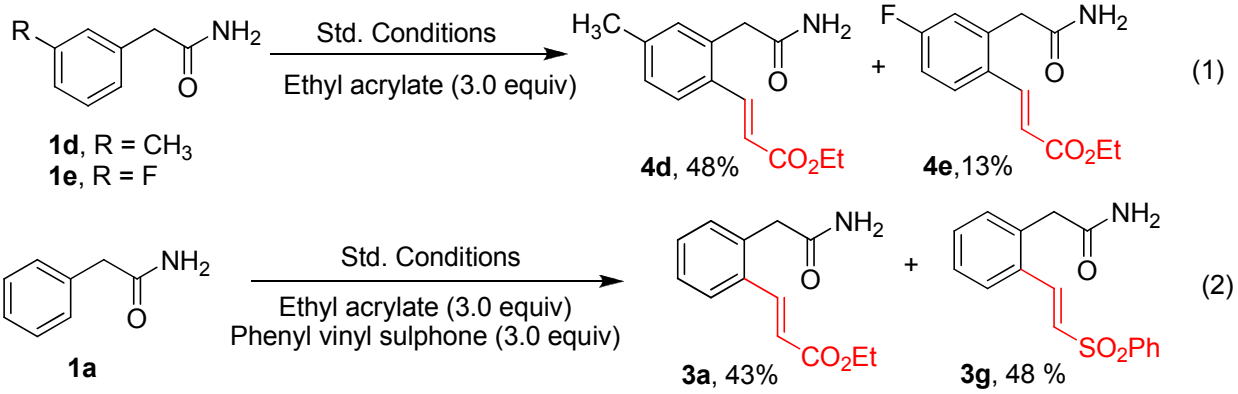


7a, 82% **3a** **7b**, 70% **7c**, 73%

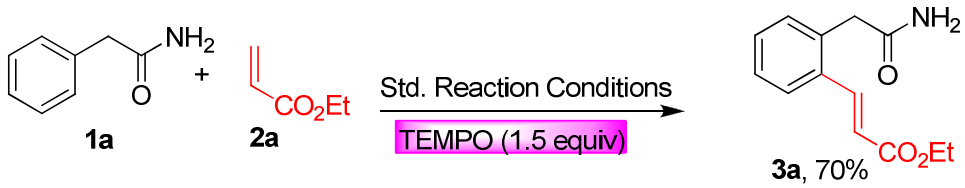
In order to obtain desired information about the electronic preference of reaction, the intermolecular competition experiments were performed. When an equimolar amount of *meta* substituted electron rich **1d** and electron deficient **1e** were allowed to compete under standard conditions in coupling with ethyl acrylate, result highlighted that electron donating **1d** shows higher reactivity with conversion ratio 3.6:1 over **1e** (Scheme 4a, eq. 1). Similarly, when phenylacetamide **1a** reacted with an equimolar amount of ethyl acrylate and phenyl vinyl sulfone under standard conditions, approximately equal amount of product was isolated (1:1) (Scheme 4a, eq. 2). This result demonstrates that both types of alkene have similar reactivity toward the acetamide derivatives. Next, we performed a control experiment in the presence of radical scavenger 2,2,6,6-tetramethylpiperidine N-oxide (TEMPO) (Scheme 4b). There was no significant drop in yield of product formation, the observed results implied that the reaction is likely not to involve a single electron pathway. To gain further insight into the reaction mechanism, intermolecular isotope kinetic experiment was performed between **1a** and **1a-d_5**. An isotope kinetic effect (KIE) of 4.0 was disclosed, thus suggesting that the palladium mediated C-H bond cleavage could potentially be involved in the rate-limiting step (RLS) in the catalytic cycle (Scheme 4c).[12] Notably, when *N*-substituted phenylacetamide **8** was subjected under optimal reaction conditions for *ortho*-alkenylation, the desired product **9** was obtained, albeit in low yield (25%, yield was not optimized at this stage with *N*-substituted phenylacetamides, Scheme 4d).

Scheme 4. Mechanistic Study

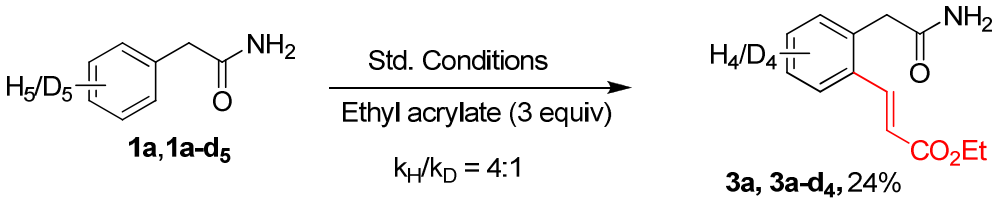
(a) **Intermolecular competition experiment**



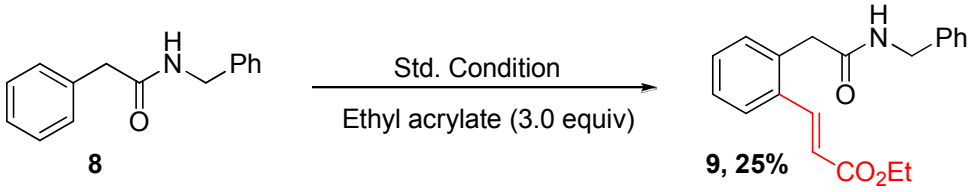
(b) **Radical trapping experiment**



(c) **Competition experiment between 1a and 1a-d_5**



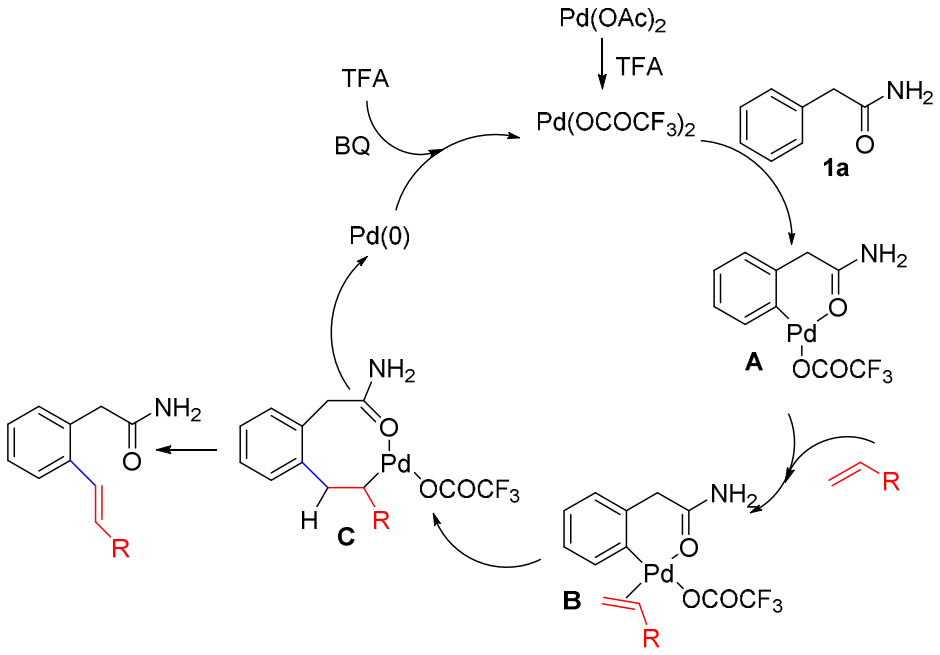
d) **Reaction with N-benzyl phenylacetamide**



On the basis of earlier literature reports[13] and aforementioned results, we propose the plausible reaction mechanism for the *ortho*-alkenylation reaction *via* weakly coordinating directing group

(Scheme 5). The initial step is likely to be an *ortho* C−H bond activation directed by the carbonyl oxygen[9, 14] of phenylacetamide, thus affording six-membered cyclometalated intermediate **A** by the elimination of trifluoroacetic acid. Next, alkene coordinates and insert into Pd-C bond to form eight-membered palladacycle **C**. Finally, β-hydrogen elimination of **C** leads to the desired product and Pd(0) species, which is oxidized to Pd(II) by benzoquinone and completing the catalytic cycle.

Scheme 5. Proposed Mechanism



In summary, we have demonstrated that aliphatic primary acetamides (-CH_2CONH_2) are effective distal directing groups in transition metal catalyzed C-H activation. A variety of alkenyl groups have been remotely incorporated at *ortho*-positions of aryacetamide derivatives selectively *via* weakly coordinating primary amide as directing groups. Furthermore, this strategy avoids troublesome two extra steps of installation and removal of external directing

groups, which eventually decrease the overall cost in terms of time, waste and economy and evade the formation of *N*-alkenylated acetamide derivatives. We anticipate that wide availability of starting materials and high importance of primary aliphatic amides in the field of medicines, this developed strategy will find a broad applications in organic synthesis.

EXPERIMENTAL SECTION

General Consideration:

Unless otherwise noted, all reagents were purchased from a commercial supplier and used without further purification. All the starting material, aryl acetamides were prepared by following known literature procedure.[15] All the reactions were run under oxygen and indicated temperature was that of an oil bath. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C{^{1}H} NMR spectra were recorded at 100 MHz, $CDCl_3$ and DMSO-d_6 were used as a solvent. Chemical shifts are reported in δ ppm referenced to $CDCl_3$ (δ 7.26), DMSO-d_6 (δ 2.50) for ^{1}H NMR and $CDCl_3$ (δ 77.0), DMSO-d_6 (δ 39.5) for ^{13}C NMR. The following abbreviations were used to explain multiplicities: (s, singlet; d, doublet; t, triplet; q, quartet; m, multiple, brs, broad singlet), coupling constant (Hertz). Infrared spectra were recorded by FT-IR apparatus. High-resolution mass spectra (HRMS) spectra were obtained on ESI-TOF (electron spray ionization-time of flight) spectrometer and methanol was used to dissolve the sample. Column chromatography was performed on silica gel (100-200) mesh using ethyl acetate and hexanes or ethyl acetate/DCM as eluent in different ratio.

General procedure for olefination rection (GP-A): To a clean oven-dried 25 mL round bottom flask equipped with magnetic stir bar was sequentially added aryl acetamide (0.4 mmol), $Pd(OAc)_2$ (10 mol %, 8.9 mg), benzoquinone (0.4 mmol, 1.0 equiv, 43.2 mg). Then ethyl

acrylate (1.2 mmol, 3.0 equiv, 127.8 µL) followed by trifluoroacetic acid (4.0 mL) was added to the reaction mixture. The reaction mixture was purged with oxygen thrice. The flask was connected to oxygen ballon through condenser. The reaction mixture was placed in pre heated oil bath of 100 ^{o}C and vigorously stirred for 36 h. After completion, the reaction mixture was cooled to room temperature and solvent was evaporated under reduced pressure and diluted with ethyl acetate followed by neutralization with saturated solution of sodium bicarbonate. After extraction with ethyl acetate (15 mL x 3) organic layer was washed with brine solution and passed through short pad of celite and dried over sodium sulphate. After evaporation of solvent, the crude mixture was purified by column chromatograophy silica gel and ethyl acetate/hexanes or ethyl acetate/DCM as eluent.

(E)-Ethyl 3-(2-(2-amino-2-oxoethyl)phenyl)acrylate (3a): Following **GP-A** the title compound was isolated as white solid (67 mg, 72% yield); R_f (6:4 Hexanes/EtOAc) = 0.35; Mp 110-112 ^{o}C; IR(ATR) 3389, 3188, 2927, 1711, 1659, 1626, 1398 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 16.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.39-7.29 (m, 3H), 6.37 (d, *J* = 16.0 Hz, 1H), 5.87 (brs, 1H), 5.61 (brs, 1H), 4.25 (q, *J* = 8.0 Hz, 2H), 3.72 (s, 2H), 1.32 (t, *J* = 8.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.6, 166.6, 141.0, 134.2, 134.0, 131.4, 130.5, 128.2, 127.2, 121.0, 60.7, 40.6, 14.3; HRMS (ESI-TOF) m/z Calcd for $C_{13}H_{16}NO_3$ $[M + H]^+$ 234.1125, found 234.1141.

(E)-Methyl 3-(2-(2-amino-2-oxoethyl)phenyl)acrylate (3b): Following **GP-A** the title compound was isolated as white solid (53 mg, 61% yield); R_f (6:4 Hexanes/EtOAc) = 0.3; Mp 152-154 ^{o}C; IR (ATR) 3392, 3181, 2923, 1705, 1658, 1393, 763 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 16.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.38-7.29 (m, 3H), 7.38 (d, *J* = 16.0 Hz, 1H), 5.88 (brs, 1H), 5.55 (brs, 1H), 3.79 (s, 3H), 3.72 (s, 2H); ^{13}C{^{1}H} NMR (100

MHz, $CDCl_3$) δ 172.6, 167.0, 141.3, 134.2, 134.0, 131.3, 130.5, 128.2, 127.2, 120.6, 51.8, 40.5; HRMS (ESI-TOF) m/z Calcd for $C_{12}H_{14}NO_3$ $[M + H]^+$ 220.0981, found 220.0968.

(E)-Propyl 3-(2-(2-amino-2-oxoethyl)phenyl)acrylate (3c): Following **GP-A** the title compound was isolated as white solid (62 mg, 63% yield); R_f (6:4 Hexanes/Acetone) = 0.35; Mp 111-113 ^oC; IR (ATR), 3351, 3185, 1701, 1654, 1631, 1408, 1183, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 16.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.38-7.30 (m, 3H), 6.40 (d, *J*= 16.0 Hz, 1H), 5.60 (brs, 1H), 5.45 (brs, 1H), 4.16 (t, *J* = 8.0 Hz, 2H), 3.73 (s, 2H), 1.75-1.70 (m, 2H), 0.99 (t, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.6, 166.7, 141.0, 134.10, 134.08, 131.3, 130.5, 128.2, 127.2, 121.1, 66.3, 40.5, 22.0, 10.4; HRMS (ESI-TOF) m/z Calcd for $C_{14}H_{18}NO_3$ $[M + H]^+$ 248.1281, found 248.1294.

(E)-Butyl 3-(2-(2-amino-2-oxoethyl)phenyl)acrylate (3d): Following **GP-A** the title compound was isolated as white solid (58 mg, 56 % yield); R_f (6:4 Hexanes/Acetone) = 0.4; Mp 112-114 ^oC; IR (ATR) 3352, 3180, 1708, 1657, 1630, 1413, 1172, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 16.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.40-7.29 (m, 3H), 6.39 (d, *J* = 16.0 Hz, 1H), 5.67 (brs, 1H), 5.54 (brs, 1H), 4.20 (t, *J* = 6.8 Hz, 1H), 3.73 (s, 2H), 1.72-1.65 (m, 2H), 1.47-1.38 (m, 2H), 0.96 (t, *J* = 8.0 Hz, 3H),$^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.4, 166.7, 140.9, 134.1, 131.3, 130.5, 128.2, 127.3, 121.2, 66.7, 40.5, 30.7, 19.2, 13.7; HRMS (ESI-TOF) m/z Calcd for $C_{15}H_{19}NNaO_3$ $[M + Na]^+$ 284.1275, found 284.1285.

(E)-2-[2-(2-Benzenesulfonyl-vinyl)-phenyl]-acetamide (3e): Following **GP-A** the title compound was isolated as brownish solid (76 mg, 70% yield); R_f (6:4 Hexanes/EtOAc) = 0.25; Mp 147-149 ^oC; IR (ATR) 3395, 3207, 2924, 1711, 1623, 1306, 1142 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + $CDCl_3$) δ 7.94-7.89 (m, 3H), 7.76-7.70 (m, 2H), 7.67-7.61 (m, 3H), 7.48 (d, *J* =

16.0 Hz), 7.38-7.26 (m, 3H), 3.64 (s, 2H); ^{13}C NMR (400 MHz, DMSO + $CDCl_3$) δ 171.4, 140.7, 140.0, 136.6, 133.1, 131.6, 131.2, 130.5, 129.2, 128.3, 127.1, 127.0, 126.9, 39.4; HRMS (ESI-TOF) m/z Calcd for $C_{16}H_{16}NO_3S[M + H]^+$302.0845, found 302.0860.

(E)-2-{2-[2-(Diethyl-phosphinoyl)-vinyl]-phenyl}-acetamide (3f): Following **GP-A** the title compound was isolated as brownish sticky solid (51 mg, 43 % yield); R_f (EtOAc) = 0.2; IR(ATR) 3343, 3194, 2987, 1671, 1391, 1219, 1018, 958; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 16.0 Hz, 8.0 Hz, 1H), 7.57 (d, *J* = 7.2 Hz, 1H), 7.36-7.33 (m, 3H), 6.26-6.16 (m, 2H), 5.81 (brs, 1H), 4.13-4.10 (m, 4H), 3.69 (s, 2H), 1.34 (t, *J* = 6.8 Hz, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.7, 145.8, 134.5 and 134.3 (d, J_{C-P} = 22.0 Hz), 134.1, 131.5, 130.5, 128.0, 126.7, 117.6 and 115.7 (d, J_{C-P} = 189.0 Hz), 62.13, 62.08,40.2, 16.39, 16.33; HRMS (ESI-TOF) m/z Calcd for $C_{14}H_{20}NNaO_4P$ $[M + Na]^+$ 320.1022, found 320.1029.

(E)-2-Phenoxyethyl 3-(2-(2-amino-2-oxoethyl)phenyl)acrylate (3g): Following **GP-A** the title compound was isolated as white solid (43 mg, 32% yield); R_f (6:4 Hexanes/EtOAc) = 0.3; Mp 136-138 ^{o}C; IR(ATR) 3395, 3199, 2925, 1712, 1651, 1395, 1217, 1045, 745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 16 Hz, 1H), 7.62 (d, *J* = 4.0 Hz, 1H), 7.41-7.23 (m, 5H), 7.0-6.93 (m, 3H), 6.44 (d, *J* = 16 Hz, 1H), 5.47 (brs, 1H), 5.39 (brs, 1H), 4.57 (t, *J* = 4.8 Hz, 2H), 4.25 (t, *J* = 4.8 Hz, 2H), 3.72 (s, 2H), ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.8, 166.5, 158.5, 141.8, 143.1, 133.9, 131.4, 130.7, 129.6, 128.3, 127.3, 121.2, 120.4, 114.7, 65.9, 63.1, 40.4; HRMS (ESI-TOF) m/z Calcd for $C_{19}H_{19}NNaO_4$ $[M + Na]^+$ 348.1206, found 348.1202.

(E)-2-(2-styrylphenyl)acetamide (3h): Following **GP-A** the title compound was isolated as white solid (35 mg, 37% yield); R_f (6:4 Hexanes/EtOAc) = 0.5; Mp 147-149 ^{o}C; IR (ATR) 3397, 3205, 1657, 1404, 964, 762 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 1H), 7.51

(d, J = 8.0 Hz, 2H), 7.38-7.26 (m, 7H), 7.04 (d, J = 16.0 Hz, 1H), 5.53 (brs, 1H), 5.35 (brs, 1H), 3.74 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.4, 137.1, 137.0, 132.5, 131.9, 131.0, 128.8, 128.3, 128.2, 128.0. 126.8, 126.4, 124.9, 41.4; HRMS (ESI-TOF) m/z Calcd for $C_{16}H_{15}NaNO$ $[M + Na]^+$ 260.1046, found 260.1046.

(E)-2-(2-(4-Fluorostyryl)phenyl)acetamide (3i): Following **GP-A** the title compound was isolated as white solid (34 mg, 33% yield); R_f (6:4 Hexanes/EtOAc) = 0.3; Mp 161-163 ^oC; IR (ATR) 3386, 3194, 2921, 1653, 1505, 1398, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 5.4 Hz, 2H), 7.43-7.30 (m, 4H), 7.14-7.05 (m, 3H), 5.61 (brs, 1H), 5.44 (brs, 1H), 3.81 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.2, 163.83 and 161.37 (d, J_{C-F} = 246.0 Hz), 137.0, 133.22 and 133.19 (d, J_{C-F} = 3.0 Hz), 132.5, 131.1, 130.6, 128.36 and 128.31 (d, J_{C-F} = 5.0 Hz), 128.3, 126.3, 124.8, 115.85 and 115.63 (d, J = 22.0 Hz), 41.5; HRMS (ESI-TOF) m/z Calcd for $C_{16}H_{15}FNO[M + H]^+$ 256.1132, found 256.1138.

(E)-3-(2-Carbamoylmethyl-5-methoxy-phenyl)-acrylic acid methyl ester (4a): Following **GP-A** the title compound was isolated as white solid (53 mg, 53% yield); R_f (6:4 Hexanes/EtOAc) = 0.25; Mp 153-155^oC; IR (ATR) 3385, 3199, 2916, 1710, 1651, 1428, 1177 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 16.0 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.10 (s, 1H), 6.93 (d, J = 8.0 Hz, 1H), 6.36 (d, J = 16.0 Hz, 1H)5.87 (brs, 1H), 5.53 (brs, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.65 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.6, 167.0, 159.3, 141.3, 135.0, 132.5, 126.2, 120.8, 116.5, 112.1, 55.4, 51.9, 39.5; HRMS (ESI-TOF) m/z Calcd for $C_{13}H_{16}NO_4$ $[M + H]^+$ 250.1074, found 250.1084.

(E)-Ethyl 3-(2-(2-amino-2-oxoethyl)-5-methylphenyl)acrylate (4b): Following **GP-A** the title compound was isolated as white solid (60 mg, 61% yield); R_f (6:4 Hexanes/EtOAc) = 0.3;

Mp130-132 ^{o}C; IR (ATR) 3377, 3187, 2922, 1712, 1655, 1404, 1177, 1040, 653 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 12.0 Hz, 1H), 7.53 (s, 1H), 7.29 (s, 2H), 6.48 (d, *J* = 12 Hz, 1H), 6.06 (brs, 1H), 5.64 (brs, 1H), 4.35 (q, *J* = 7.2 Hz, 2H), 3.78 (s, 2H), 2.46 (s, 3H), 1.43 (t, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.0, 166.7, 141.1, 137.9, 133.8, 131.33, 131.26, 131.24, 129.7, 129.3, 127.7, 120.7, 60.6, 40.1, 21.0, 14.3; HRMS (ESI-TOF) m/z Calcd for $C_{14}H_{17}NNaO_3$ $[M + Na]^+$ 270.1101, found 270.1104.

(E)-3-(6-Carbamoylmethyl-benzo[1,3]dioxol-5-yl)-acrylic acid ethyl ester (4c): Following **GP-A** the title compound was isolated as white solid (68 mg, 62% yield); R_f (6:4 Hexanes/EtOAc) = 0.3; Mp 167-169 ^{o}C; IR (ATR) 3391, 3190, 2921, 1693, 1655, 1448, 1255, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 16.0 Hz, 1H), 6.82-6.76 (m, 3H), 6.08 (s, 2H), 5.43 (brs, 1H), 5.39 (brs, 1H), 4.26 (q, *J* = 8.0 Hz, 2H), 3.67 (s, 2H), 1.33 (t, *J* = 8.0 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.8, 167.2, 147.50, 147.47, 135.5, 127.8, 124.4, 123.7, 116.8, 109.5, 101.7, 60.7, 40.3, 14.3; HRMS (ESI-TOF) m/z Calcd for $C_{14}H_{15}NNaO_5$ $[M + Na]^+$ 300.0842, found 300.0833.

(E)-Ethyl 3-(2-(2-amino-2-oxoethyl)-4-methylphenyl)acrylate (4d): Following **GP-A** the title compound was isolated as white solid (57 mg, 58% yield); R_f (6:4 Hexanes/EtOAc) = 0.3; Mp 142-144 ^{o}C; IR (ATR) 3386, 3194, 2976, 1711, 1651, 1312, 1175 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 16.0 Hz, 1H), 7.53 (d, *J* = 7.2 Hz, 1H), 7.15-7.11 (m, 2H), 6.35 (d, *J* = 16.0 Hz, 1H), 5.49 (brs, 1H), 5.42 (brs, 1H), 4.25 (d, *J* = 6.8 Hz, 2H), 3.70 (s, 2H), 2.36 (s, 3H), 1.33 (t, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.7, 166.9, 140.95, 140.87, 134.1, 132.1, 131.1, 129.1, 127.1, 119.9, 60.6, 40.5, 21.3, 14.3; HRMS (ESI-TOF) m/z Calcd for $C_{14}H_{17}NNaO_3$ $[M + Na]^+$ 270.1101, found 270.1108.

(E)-3-(2-Carbamoylmethyl-4-fluoro-phenyl)-acrylic acid ethyl ester (4e): Following **GP-A** the title compound was isolated as white solid (34 mg, 34% yield); R_f (6:4 Hexanes/EtOAc) = 0.3; Mp 144-146 ^oC; IR (ATR) 3388, 3199, 1711, 1650, 1462, 1180, 657 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 16.0 Hz, 1H), 7.33-7.32 (m, 1H), 7.13-7.08 (m, 2H), 6.58 (d, J = 16.0 Hz, 1H), 5.51 (brs, 2H), 4.25 (q, J = 8.0 Hz, 2H), 3.72 (s, 2H), 1.33 (t, J = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.9, 166.9, 163.08 and 160.56 (J_{C-F} = 252.0 Hz), 136.53 and 136.50 (d, J_{C-F} = 3.0 Hz), 134.9, 130.86 and 130.77 (d, J_{C-F} = 9.0 Hz), 127.0, 125.42 and 125.29 (d, J_{C-F} = 13.0 Hz), 122.43 and 122.31 (d, J_{C-F} = 12.0 Hz), 115.72 and 115.49 (d, J_{C-F} = 23.0 Hz), 60.8, 40.6, 14.3; HRMS (ESI-TOF) m/z Calcd for $C_{13}H_{14}FNNaO_3$ $[M + Na]^+$ 274.0850, found 274.0850.

(E)-Diethyl 2-(2-amino-2-oxoethyl)-5-methylstyrylphosphonate (4f): Following **GP-A** the title compound was isolated as brownish sticky solid (52 mg, 42% yield); R_f (EtOAc) = 0.2; IR (ATR) 3352, 3199 , 2986, 1668, 1198, 1021, 965; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 (t, J = 16.0 Hz, 1H), 7.38 (s, 1H), 7.18 (s, 2H), 6.19 (t, J = 16.0 Hz, 1H), 5.79 (brs, 2H), 4.12 (m, 4H), 3.65 (s, 2H), 2.35 (s, 3H), 1.33 (t, J = 8.0 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.9, 145.8, 137.7, 134.22 and 134.00 (d, J = 22.0 Hz), 131.4, 131.3, 131.2, 127.3, 117.18 and 115.23 (d, J = 189.0 Hz), 62.12, 62.07, 39.9, 21.0, 16.39, 16.32; HRMS (ESI-TOF) m/z Calcd for $C_{15}H_{22}NNaPO_4$ $[M + Na]^+$ 334.1179, found 334.1185.

(E)-2-[2-(2-Benzenesulfonyl-vinyl)-4-methyl-phenyl]-acetamide (4g): Following **GP-A** the title compound was isolated as brownish solid (86 mg, 68% yield); R_f (6:4 Hexanes/EtOAc) = 0.25; Mp 172-174 ^oC; IR(ATR) 3429, 3302, 3187, 2926, 1662, 1298, 1139; ^1H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, J = 8.0 Hz, 2H), 7.88 (d, J = 16.0 Hz, 1H), 7.74-7.70 (m, 1H), 7.67-7.63 (m, 2H), 7.60 (s, 1H), 7.56 (brs, 1H), 7.45 (d, J = 16.0 Hz, 1H), 7.20 (s, 2H), 7.00 (brs, 1H), 3.58

(s, 2H), 2.26 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 171.7, 140.8, 140.0, 136.4, 134.0, 133.5, 131.5, 131.4, 131.3, 129.5, 128.9, 127.6, 127.2, 39.0, 20.4; HRMS (ESI-TOF) m/z Calcd for $C_{17}H_{18}NO_3S$ $[M + H]^+$ 316.1002, found 316.1025.

(E)-2-[2-(2-Benzenesulfonyl-vinyl)-4-methoxy-phenyl]-acetamide (4h): Following **GP-A** the title compound was isolated as brownish solid (77 mg, 61% yield); R_f (6:4 Hexanes/EtOAc) = 0.25; Mp 153-155 ^{o}C; IR (ATR) 3394, 3177, 2922, 1654, 1402, 1143 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6 + $CDCl_3$) δ 7.93-7.91 (m, 2H), 7.86 (d, J = 15.2 Hz, 1H), 7.72-7.63 (m, 1H), 7.65-7.61 (m, 2H), 7.54 (s, 1H), 7.50 (s, 1H), 7.28 (d, J = 2.8 Hz, 1H), 7.22 (d, J = 8.4 Hz, 1H), 6.95-6.92 (m, 2H), 3.76 (s, 3H), 3.55 (s, 2H); $^{13}C\{^{1}H\}$ NMR (400 MHz, DMSO-d_6 + $CDCl_3$) δ 171.8, 158.2, 140.8, 139.9, 133.4, 132.43, 132.38, 129.4, 129.2, 128.5, 127.2, 117.4, 111.2, 55.3, 38.6; HRMS (ESI-TOF) m/z Calcd for $C_{17}H_{18}NO_4S$ $[M + H]^+$ 332.0951, found 332.0951.

(E)-3-(2-Carbamoylmethyl-5-bromo-phenyl)-acrylic acid ethyl ester (4i): Following **GP-A** the title compound was isolated as brownish solid (58 mg, 38% yield); R_f (6:4 Hexanes/EtOAc) = 0.3; Mp 158-160 ^{o}C; IR(ATR) 3458, 3301, 1682, 1292, 1143, 609 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.0 (s, 1H), 7.93 (d, J = 7.6 Hz, 2H)), 7.82-7.73 (m, 2H), 7.69-7.65 (m, 3H), 7.62 (brs, 1H), 7.50-7.56 (m, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.07 (brs, 1H), 3.63 (s, 2H); $^{13}C\{^{1}H\}$ NMR (100 MHz, DMSO-d_6) δ 171.1, 140.5, 138.2, 136.1, 134.0, 133.6, 133.4, 133.2, 129.9, 129.5, 127.2, 120.3, 38.8; HRMS (ESI-TOF) m/z Calcd for $C_{16}H_{15}BrNO_3S$ $[M + H]^+$ 379.9951, found 379.9956.

(E)-3-(2-Carbamoylmethyl-5-chloro-phenyl)-acrylic acid ethyl ester (4j): Following **GP-A** the title compound was isolated as brownish solid (44 mg, 33% yield); R_f (6:4 Hexanes/EtOAc) = 0.3; Mp199-201 ^{o}C; IR(ATR) 3427, 3190, 2921, 1661, 1304, 1143, cm^{-1}; ^{1}H NMR (400 MHz,

DMSO-d_6) δ 7.93 (d, J = 7.2 Hz, 2H), 7.87 (s, 1H), 7.82-7.72 (m, 2H), 7.68-7.64 (m, 3H), 7.61 (brs, 1H), 7.45-7.43 (m, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.06 (brs, 1H), 3.64 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 171.6, 141.0, 138.8, 136.2, 134.1, 133.7, 132.4, 130.7, 130.4, 130.0, 127.7, 127.1, 39.3; HRMS (ESI-TOF) m/z Calcd for $C_{16}H_{15}ClNO_3S$ [M + H]$^+$ 336.0456, found 336.0445

(E)-2-(4-methyl-2-styrylphenyl)acetamide (4k): Following **GP-A** the title compound was isolated as white solid (35 mg, 35% yield); R_f (6:4 Hexanes/EtOAc) = 0.35; Mp 194-196 ^oC; IR (ATR) 3406, 3197, 2913, 1651, 1403 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 6.4 Hz, 3H), 7.38 (t, J = 8.0 Hz, 2H), 7.31-7.26 (m, 2H), 7.17-7.11 (m, 2H), 7.06 (d, J = 16.0 Hz, 1H), 5.68 (brs, 1H), 5.45 (brs, 1H), 3.72 (s, 2H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.6, 137.9, 137.0, 136.8, 131.5, 131.0, 129.6, 129.0, 128.7, 128.0, 126.9, 126.7, 125.0, 41.0, 21.2; HRMS (ESI-TOF) m/z Calcd for $C_{17}H_{18}NO$ [M + H]$^+$ 252.1383, found 252.1376.

(E)-2-(4-methoxy-2-styrylphenyl)acetamide (4l): Following **GP-A** the title compound was isolated as white solid (38 mg, 36% yield); R_f (6:4 Hexanes/EtOAc) = 0.35; Mp 151-153 ^oC; IR (ATR) 3386, 3196, 2924, 1651, 1500, 1400 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 6.4 Hz, 2H), 7.38-7.35 (m, 2H), 7.30 (s, 1H), 7.22-7.16 (m, 3H), 7.03 (d, J = 16.4 Hz, 1H), 6.85-6.33 (m, 1H), 5.48 (brs, 1H), 5,39 (brs, 1H), 3.86 (s, 3H), 3.68 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.7, 159.4, 138.2, 136.9, 132.2, 131.9, 128.8, 128.2, 126.8, 125.0, 113.9, 111.5, 55.4, 40.6; HRMS (ESI-TOF) m/z Calcd for $C17H18NO_2$ [M + H]$^+$ 268.1332, found 268.1333.

(E)-3-[2-(1-Carbamoyl-ethyl)-phenyl]-acrylic acid ethyl ester (6a): Following **GP-A** the title compound was isolated as white solid (62 mg, 64 % yield); R_f (6:4 Hexanes/EtOAc) = 0.35; Mp 105-107 ^oC; IR(ATR) 3361, 3175, 2926, 1705, 1658, 1452, 1191 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$) δ 8.03 (d, *J* = 16.0 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.43-7.37 (m, 2H), 7.31-7.28 (m, 1H), 6.35 (s, *J* = 8.0 Hz, 1H), 5.70 (brs, 1H), 5.50 (brs, 1H), 4.26 (q, *J* = 8.0 Hz, 2H), 3.99 (q, *J* = 8.0 Hz, 1H), 1.51 (d, *J* = 8.0 Hz, 3H), 1.34 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 176.0, 166.7, 141.3, 140.4, 133.3, 130.6, 127.7, 127.3, 127.5, 60.8, 42.2, 18.5, 14.3; HRMS (ESI-TOF) m/z Calcd for $C_{14}H_{17}NNaO_3$ [M + Na]$^+$ 270.1101, found 270.1095.

(E)-2-[2-(2-Benzenesulfonyl-vinyl)-phenyl]-propionamide (6b): Following **GP-A** the title compound was isolated as brownish solid (77 mg, 61% yield); R_f (6:4 Hexanes/EtOAc) = 0.25; Mp 149-151 ^oC; IR(ATR) 3428, 3310, 1666, 1299, 1140, 745 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6 + $CDCl_3$) δ 8.04 (d, *J* = 16 Hz, 1H), 7.95-7.93 (m, 2H), 7.73-7.69 (m, 1H), 7.67-7.62 (m, 3H), 7.46 (brs, 1H), 7.44-7.40 (m, 2H), 7.39-7.36 (m, 1H), 7.27-7.22 (m, 1H), 6.96 (brs, 1H), 3.98 (q, *J* = 8.0 Hz, 1H), 1.31 (d, *J* = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (400 MHz, DMSO-d_6 + $CDCl_3$) δ 174.8, 142.3, 140.6, 139.4, 133.4, 130.8, 130.6, 129.45, 129.38, 127.5, 127.4, 127.1, 126.8, 41.3, 19.0; HRMS (ESI-TOF) m/z Calcd for $C_{17}H_{18}NO_3S$ [M + H]$^+$ 316.1002, found 316.0995.

(E)-Diethyl 2-(1-amino-1-oxopropan-2-yl)styrylphosphonate (6c): Following **GP-A** the title compound was isolated as brownish sticky solid (56 mg, 45% yield); R_f (EtOAc) = 0.2; IR(ATR) 3350, 3197, 2980, 1671, 1222, 1018, 958; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95-7.85 (m, 1H), 7.52-7.44 (m, 2H), 7.39-7.35 (m, 1H), 7.29-7.25 (m, 1H), 6.22-6.17 (m, 1H), 6.13 (brs, 1H), 5.92 (brs, 1H), 4.15-4.06 (m, 4H), 4.01 (q, *J* = 8.0 Hz, 1H), 1.47 (d, *J* = 8.0 Hz, 3H), 1.35-1.31 (m, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 176.2, 146.10, 140.13, 133.81 and 133.59 (d, $J_{C\text{-}P}$ = 22.0 Hz), 130.6, 127.7, 127.5, 126.5, 126.8, 118.01 and 116.12 (d, $J_{C\text{-}P}$ = 189.0 Hz), 62.08, 62.03, 41.7, 18.6, 16.38, 16.32; HRMS (ESI-TOF) m/z Calcd for $C_{15}H_{22}NNaPO_4$ [M + Na]$^+$ 334.1179, found 334.1183.

(E)-2-(2-Styryl-phenyl)-propionamide (6d): Following **GP-A** the title compound was isolated as white solid (42 mg, 42% yield); R_f (6:4 Hexanes/EtOAc) = 0.4; Mp 114-116 ^oC; IR(ATR) 3397, 3202, 2921, 1621, 1461, 762 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.52 (d, *J* = 6.4 Hz, 2H), 7.40-7.31 (m, 7H), 7.99 (d, *J* = 16.0 Hz, 1H), 5.49 (brs, 1H), 5.30 (brs, 1H), 3.97 (q, *J* = 7.2 Hz, 1H), 1.57 (d, *J* = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 176.7, 138.6, 137.1, 136.6, 132.2, 128.8, 128.4, 128.0, 127.7, 127.5, 126.8, 126.7, 125.4, 43.1, 17.8; HRMS (ESI-TOF) m/z Calcd for $C_{17}H_{18}NO$ [M + H]$^+$ 252.1383, found 252.1392.

Procedure for preparative scale synthesis: In an oven dried 100 mL round bottom flask equipped with magnetic stir bar was sequentially added phenylacetamide (4.0 mmol, 1 equiv, 540 mg), $Pd(OAc)_2$ (10 mol %, 89.8 mg), benzoquinone (0.4 mmol, 1equiv, 432 mg). Then ethyl acrylate (12 mmol, 3.0 equiv,1.27 mL) followed by trifluoroacetic acid (40 mL) was added to reaction mixture. The reaction mixture was purged with oxygen thrice. The flask was connected to oxygen balloon through the condenser. The reaction mixture was placed in preheated oil bath of 100 ^oC and vigorously stirred for 36 h. After cooling to room temperature, thesolvent was evaporated under reduced pressure and diluted with ethyl acetate followed by neutralization with asaturated solution of sodium bicarbonate. After extraction with ethyl acetate (100 mL x 3) organic layer was washed with brine solution and filtered through ashort pad of celite and dried over sodium sulfate and concentrated under *vaccum*. The crude mixture was purified by silica gel column chromatography and ethyl acetate/hexanes as eluent to give **3a** 57% (530 mg) of alkenylated derivative.

Synthesis of (E)-ethyl 3-(2-(Cyanomethyl)phenyl)acrylate (7a) By following a reported procedure[16a] 3a (0.2 mmol, 46 mg) in a mixture of CH_3CN/H_2O (1:1) was treated with $PdCl_2$ (10 mol%, 3.5 mg) at 50 ^oC for 12 h. After completion, reaction mixture was quenched with water

and extracted with ethyl acetate (10 mL x 3). Solvent was removed in *vacuum* and crude product was purified by column chromatography.

(E)-3-(2-Cyanomethyl-phenyl)-acrylic acid ethyl ester (7a): white solid (35 mg, 82% yield); R_f (1:10 Hexanes/EtOAc) = 0.5; Mp 69-71 ^oC; IR(ATR) 2941, 2220, 1703, 1632, 3112, 1175, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 16.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.44-7.36 (m, 2H), 6.39 (d, J = 16.0 Hz, 1H), 4.28 (q, J = 7.2 Hz, 2H), 3.86 (s, 2H), 1.34 (t, J = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.3, 139.7, 133.3, 130.6, 129.3, 128.90, 128.86, 127.4, 122.1, 117.1, 60.9, 21.8, 14.3; HRMS (ESI-TOF) m/z Calcd for $C_{13}H_{13}NNaO_2$ $[M + Na]^+$ 238.0838, found 238.0851.

3-[2-(Methoxycarbonylamino-methyl)-phenyl]-acrylic acid methyl ester (7b) By following a reported procedure[16b] a mixture of oxone (0.4 mmol, 122.8 mg) and iodobenzene (0.2 mmol, 33 μL) was prepared in methanol (2.0 mL), 3a (0.2 mmol, 46 mg) was added in reaction mixture and stir for 24 h at 100 ^oC. After completion reaction mixture solvent was evaporated in vacuo and extracted with ethyl acetate (10 mL x 3). Solvent was removed in *vacuum* and crude product was purified by column chromatography.

3-[2-(Methoxycarbonylamino-methyl)-phenyl]-acrylic acid methyl ester (7b): colorless liquid R_f (10:1 Hexanes/EtOAc) = 0.4;(35 mg, 70% yield); IR (ATR) 2952, 1714, 1634, 1434, 1318, 1167, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 16.0 Hz, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.34-7.28 (m, 3H), 6.37 (d, J = 16.0 Hz, 1H), 3.80 (s, 3H), 3.78 (s, 2H). 3.69 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 171.4, 167.2, 141.9, 134.0, 133.6, 131.1, 130.2, 127.9, 126.9, 120.1, 52.2, 51.8, 38.6. HRMS (ESI-TOF) m/z Calcd for $C_{13}H_{14}NaO_4$ $[M +Na]^+$ 257.0784, found 257.0797.

3-(2-Carboxymethyl-phenyl)-acrylic acid (7c) By following a reported procedure[16c] a mixture of 3a (0.2 mmol, 46 mg) was prepared in 20% (v/v) H_2SO_4 (2.5 mL) and heated at 100 ^oC for 6 h. After completion of reaction, mixture was cooled to room temperature and diluted with water then extracted with ethylacetate (15 mL x 3). Organic layer was dried in *vacuum*. Recrystallization with dichloromethane and hexane produced white solid.

3-(2-Carboxymethyl-phenyl)-acrylic acid (7c) white solid (30 mg, 73 %), Mp 130-132 ^oC IR(ATR) 2925 (br), 1682, 1619, 1220, 974; ^1H NMR (400 MHz, DMSO-d_6) δ 7.78-7.74 (m, 2H), 7.38-7.29 (m, 3H), 6.43 (d, J = 16.0 Hz, 2H), 3.75 (s, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 172.3, 167.5, 141.1, 134.8, 133.6, 131.5, 130.0, 127.6, 126.7, 38.5; HRMS (ESI-TOF) m/z Calcd for $C_{11}H_{10}NaO_4$ $[M + Na]^+$ 229.0471, found 229.0501.

(E)-ethyl 3-(2-(2-(benzylamino)-2-oxoethyl)phenyl)acrylate (9): Following **GP-A** the title compound was isolated as white solid (16 mg, 25% yield); R_f (7:3 Hexanes/EtOAc) = 0.4; Mp 105-107 ^oC; IR(ATR) 3285, 2924, 1708, 1640, 1542, 1316, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ7.92 (d, J = 16.0 Hz, 1H), 7.59 (m, 1H), 7.35-7.26 (m, 6H), 7.26-7.16 (m, 2H), 6.35 (d, J = 16.0 Hz, 1H), 5.70 (brs, 1H), 4.40(d, J = 4.0 Hz, 2H), 4.26 (q, J = 8/0 Hz, 2H), 3.77 (s, 2H), 1.33 (t, J = 8.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ168.9, 166.5, 140.9, 137.0, 134.1, 131.4, 130.5, 128.6, 128.2, 127.5, 127.4, 127.2, 121.1, 60.7, 43.6, 41.2; HRMS (ESI-TOF) m/z Calcd for $C_{20}H_{21}NNaO_3$ $[M + Na]^+$ 346.1414, found 346.1459.

Procedure for intermolecular competition experiment between 1d and 1e: A suspension of $Pd(OAc)_2$ (10 mol %, 3.5 mg) BQ (1 equiv, 16.2 mg) ethyl acrylate (3 equiv, 48 µL), **1d** (0.15 mmol, 22.3 mg, 1 equiv) and **1e** (0.15 mmol, 23 mg, 1 equiv) was stirred in TFA (2.0 mL) under oxygen for 36 h at 100 ^oC. After cooling to room temperature, solvent was evaporated in

vacuum. Reaction mixture was dilute with ethyl acetate, followed by neutralization with aqueous solution of sodium bicarbonate. After extraction with ethyl acetate organic layer was washed with brine solution and filtered through short pad of celite and dried over sodium sulphate. Combined organic layer was concentrated under vacuum. The crude mixture was purified by column chromatography using ethyl acetate/hexanes as eluent. Compounds **4d** and **4e** were obtained in 48% and 13% respectively.

Procedure for intermolecular competition experiment between 2a and 2g: A suspension of **1a** (0.2 mmol, 27 mg), $Pd(OAc)_2$ (10 mol%, 4.5 mg) BQ (1 equiv, 21.6 mg), ethyl acrylate (3 equiv, 64 μL) and phenyl vinyl sulfone (3.0 equiv, 100 mg) was stirred in TFA (3.0 mL) under oxygen for 36 h at 100^{o}C. After cooling to room temperature, thesolvent was evaporated in vacuum. The reaction mixture was diluted with ethyl acetate and followed by neutralization with anaqueous solution of sodium bicarbonate. After extraction with ethyl acetate organic layer was washed with brine solution and passed through ashort pad of celite and dried over sodium sulfate. Combined organic layer was concentrated under vacuum. The crude mixture was purified by column chromatography using ethyl acetate/hexanes as eluent. Compounds **3a** and **3g** were obtained in 43% and 48% respectively.

Kinetic isotope effect experiment:Procedure for intermolecular competitive experiment between 1a and 1a-d_5: A mixture of **1a** (0.15 mmol) and **1a-**d_5(0.15 mmol), $Pd(OAc)_2$ (10 mol %, 6.7 mg), BQ (1 equiv, 32.4 mg), (3 equiv, 48 μL) was strirred in TFA (3.0 mL) under oxygen for 3 h at 100 ^{o}C. After cooling to room temperature, thesolvent was evaporated in vacuum. The reaction mixture was diluted with ethyl acetate, followed by neutralization with anaqueous solution of sodium bicarbonate. After extraction with ethyl acetate organic layer was washed with brine solution and filtered through ashort pad of celite and dried over sodium sulfate.

Combined organic layer was concentrated under vacuum. The crude mixture was purified by column chromatography using ethyl acetate/hexanes as eluent to give **3a**/**3a**-d_4 (15 mg, 24%). The ratio of **3a** and **3a**-d_4 was determined by ^{1}H NMR. The kinetic isotope effect of the reaction was determined to be $k_H/k_D = 4.0$ (see SI for details).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Additional screening data, mechanistic experimental details, ^{1}H and ^{13}C NMR spectra of all new products

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Notes

The authors declare no competing financial interest.

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