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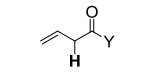
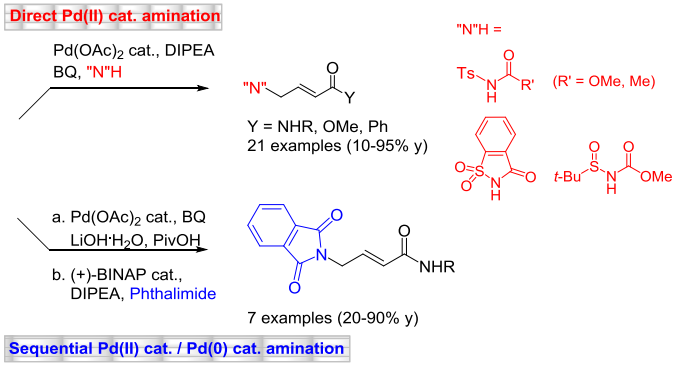
Dedicated to Professor Jean Normant on the occasion of his 80th birthday.





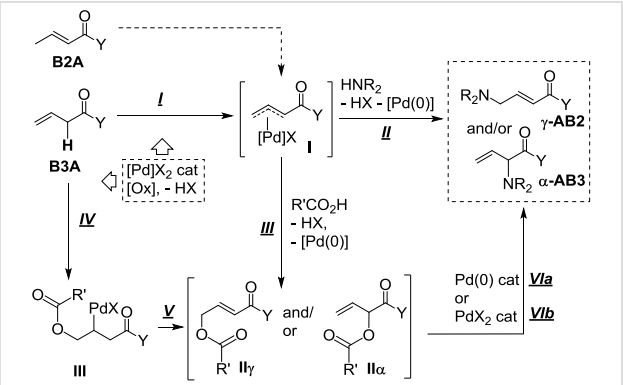
Abstract Two complementary Pd-catalyzed protocols enabling the γ-selective intermolecular allylic amination of but-3-enoic acid derivatives are reported. These transformations could be successfully achieved via, either a direct Pd(II)-catalyzed protocol or an one-pot Pd(II)/Pd(0)-catalyzed sequence, depending on the nature of the nitrogen nucleophile used.

Keywords palladium, catalysis, C-H activation, allylic amination, allylic acyloxylation, but-3-enoic acid derivatives.

Owing to the abundance of C-N bonds in a wide range of natural substances, biological frameworks (*e.g.* amino-acids), as well as in polymers and pharmaceutical products, several studies have been devoted to the development of efficient and selective amination reactions.[2] Traditional methods for N-C bond formation rely on the substitution reaction of an organohalide (or pseudohalide) by a nitrogen-based nucleophile (Gabriel-type reaction) or reductive amination.[2a] While these methods are reliable and robust, they require the pre-oxidation of the precursor in order to install the appropriate leaving group or carbonyl moiety, respectively. Thus, reactions that directly and selectively convert a C-H bond into a C-N bond significantly simplify synthetic sequences, avoiding preparation and handling pre-oxidized materials.[3] In this context, alpha-olefins and their derivatives are ideal low-cost starting materials for their catalytic functionalization to produce more complex structures for fine chemistry purposes such as allyl-amines.[4] Although some Pd-catalyzed[5] dehydrogenative allylic amination reactions on simple alpha-olefins have already been reported,[6,7] several challenging variations are still waiting for implementation. In particular, the direct intermolecular oxidative allylic amination[8] of but-3-enoic acid (B3A) derivatives is a thus far unknown synthetic transformation, whose development would be desirable.[9] Indeed, this substrate appears to be ideally biased for a C-H activation, its allylic position being at the same time α to a carboxyl function (Scheme 1).[10,11]

In particular, we reasoned that allylic C-H activation of a generic B3A derivative to give the corresponding η^3-allylpalladium complex **I** (step ***I***) could be more easily reached from a B3A derivative than from the isomeric but-2-enyl B2A one for two reasons: a) the former non conjugated isomer is thermodynamically less stable and thus expected to be more reactive than the latter; b) Pd-catalyzed allylic C-H activations on linear alkenes are almost exclusively known on terminal alkenes. Subsequent direct *in situ* trapping of the η^3-allyl complex **I** with an appropriate nitrogen nucleophile[12] may then afford the desired allylic amination product (step ***II***). Alternatively, analogous oxidative conditions in the presence of an acyloxy donor ligand may lead to α- and/or γ- allylic acylation products **IIα** and/or **IIγ** via either trapping of **I** by the acyloxy ligand (step ***III***) or through an acyloxypalladation / dehydropalladation sequence (steps ***IV*** + ***V***).[13] Finally, these allylic esters may undergo *in situ* conversion into α- and/or γ-amino but-2-enoic (γ-AB2) derivatives via a redox neutral Pd(0)- or Pd(II)-catalyzed allylic amination (step ***VI***). Worthy of note, the Pd-catalyzed direct allylic acyloxylation of but-3-enoates, (steps ***I*** + ***III***) has been recently reported by the group of Szabò using hypervalent iodine as the terminal oxidant.[10] Furthermore, a related strategy based on the one-pot two-step (Pd/Ir catalysis) conversion of terminal alkenes into enantioenriched branched allylic amines through the intermediacy of linear allyic benzoates was recently reported by Hartwig and coworkers.[14] However, this very elegant strategy targets only branched allylic amines, and it does not addresses B3A derivatives.

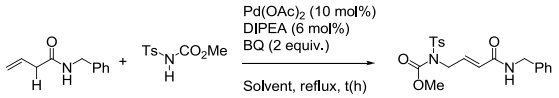
Following our constant interest in the synthesis of nitrogen-based scaffolds via Pd-catalyzed allylic amination,[15] we describe here the synthesis of γ-AB2 derivatives from B3A derivatives via a direct oxidative path {***I*** + ***II***; Pd(II)/[Ox]} as well as a one-pot consecutive path {***I*** + ***III***; Pd(II)/[Ox] (→**IIγ**) + ***VIa***; Pd(0)}. Optimizations, scope and limitations of these two complementary routes, which depend on the nature of the nitrogen nucleophile used, are reported.



Scheme 1 Possible synthetic routes to allylic amination of but-3-enoic acid derivatives.

Focusing first on the direct Pd(II)-catalyzed strategy, we chose the reaction between B3A benzyl amide **1a** and *N*-Ts-carbamate **A** as our first model transformation to study. The reaction conditions developed by White[16] for an intermolecular allylic amination using the same carbamate **A** as nucleophile were first selected, namely $Pd(OAc)_2$ (10 mol%), $PhS(O)CH_2CH_2S(O)Ph$ (15 mol%), DIPEA (6.0 mol%), and benzoquinone (BQ) (2.0 equiv) (Table 1). The first experiments, performed in TBME at reflux for 72 h, gave the desired γ-AB2 amide **2a** with similar yields, whether the reaction was run with or without disulfoxide ligand (entries 1-2). Furthermore, no trace of the α-AB3 isomer was detected. Use of THF as the solvent, with (entry 3) or without (entry 4) disulfoxide ligand, or use of DMSO (entry 5) did not improve the yields. Gratifyingly, use of CH_3CN at reflux gave **2a** in 95% yield in only 24 hours (entry 6).[17]

Table 1 Optimization of Pd(II)-catalyzed direct amination.

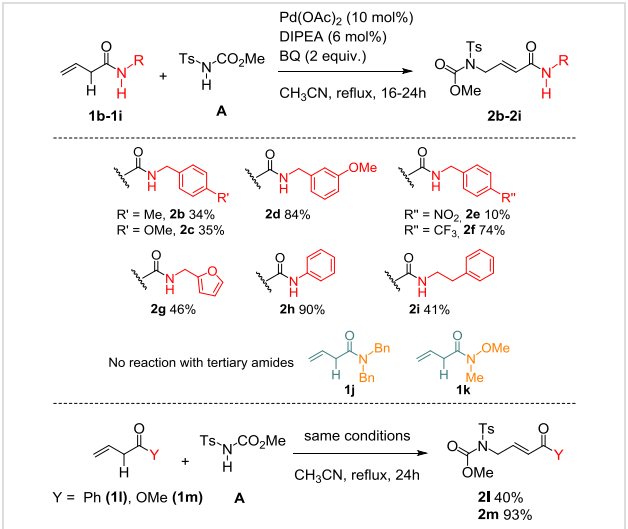


1a A 2a

Entry	Ligand	Solvent	Time (h)	Yield (%)[b]
1	yes[a]	TBME	72	72
2	no	TBME	72	75
3	yes[a]	THF	72	53
4	no	THF	18	66
5	no	DMSO	24	50
6[c]	**no**	**CH_3CN**	**24**	**95**

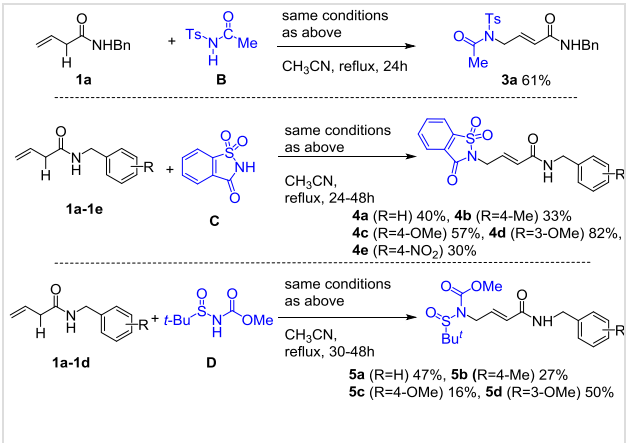
[a] Ligand: $PhSO(CH_2)_2SOPh$ (15 mol%). [b] Isolated Yields. [c] Reaction conditions: **1a** (1.0 equiv), $TsNHCO_2Me$ **A** (2.0 equiv), $Pd(OAc)_2$ (10 mol%), DIPEA (6 mol%), BQ (2 equiv) in CH_3CN (0.2 M).

With optimal conditions in hand [$Pd(OAc)_2$ 10 mol%, DIPEA 6 mol%, BQ (2.0 equiv), in CH_3CN, reflux], we explored the scope of the Pd(II)-catalyzed amination with *N*-Ts-carbamate **A** (Scheme 2). The effect of the substitution on the aryl ring of various *N*-benzyl-3-butenamides was investigated first. Electron-donors in *para*-position (**1b-c**) led to the corresponding γ-AB2 amides with moderate yields (~35% yield), the disappointing yield being probably due to the instability of the products in the oxidizing medium. Nevertheless, a satisfactory 84% yield was obtained with the *meta*-methoxy derivative (**1d**). Electron-withdrawing *para*-substitution, such as nitro (**1e**) also gave the desired γ-AB2 amide in low yield, due to difficulties in product isolation, whereas a *para*-trifluoromethyl-group (**1f**) was well tolerated. *N*-furfuryl (**1g**), *N*-phenyl (**1h**) and *N*-phenylethyl B3A secondary amides (**1i**) led to the expected γ-AB2 derivatives in good to moderate yields, while no reaction occurred with B3A tertiary amides (**1j-k**). Finally, this protocol is not limited to amides. Indeed, a ketone (**1l**) and an ester (**1m**) could also be aminated under these conditions.



Scheme 2 Scope of the Pd(II)-catalyzed allylic amination with *N*-Ts-carbamate **A**.

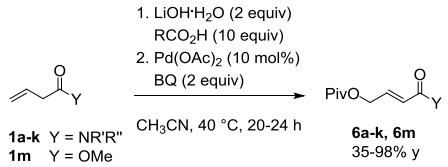
The behavior of other nitrogen nucleophiles was investigated next (Scheme 3). Accordingly, *N*-Ts-acetamide **B,** electronically and sterically not too different from **A**, reacted with **1a** to give the corresponding γ-AB2 amide **3a** in 61% yield. The acylated sultame, saccharin **C** gave the desired γ-AB2 derivatives (**4a-e**), too. Similarly, the γ-AB2 amides (**5a-d**) could be isolated when using *N*-sulfinyl-carbamate **D**. On the other hand, *N*-Ts-amine, phthalimide and camphorsultam did not react. These results suggest that NH acidity of the nucleophile is crucial for the coupling, the ideal pK_a being in the range of 5-6.



Scheme 3 Scope of Pd(II)-catalyzed allylic amination of B3A amides **1a-1d** with *N*-Ts-amide, saccharin and *N*-sulfinyl-carbamate.

We surmised that an alternative Pd-catalyzed sequence, involving this time an initial oxidative allylic acyloxylation, followed by an isohypsic amination (Scheme 1), {***I*** + ***III***; Pd(II)/[Ox] (→**IIγ**) + ***VIa***; Pd(0)} might overcome the drawbacks associated to the former route.

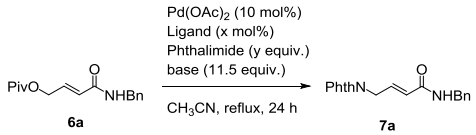
Indeed, the Pd(0)-catalyzed allylation of less acidic N-H based nucleophiles, such as N-phthalimide (pK_a = 8.3), is well known.[18] Nevertheless, merging these two Pd-catalyzed protocols in a single synthetic operation is a deceptively simple task. First of all, we surmised that a buffered medium for the acyloxylation step was mandatory to ensure the compatibility of the two protocols. Accordingly, we adopted the conditions reported by Le Bras and coworkers, who used the couple $LiOH/RCO_2H$ for analogous dehydrogenative Pd(II)-catalyzed acyloxylations.[19] Preliminary experiments were first conducted on the model B3A amide **1a**, to assess the influence of the nature and the amount of the added carboxylic acid (see SI), the optimal choice being: pivalic acid (10.0 equiv), $LiOH{\cdot}H_2O$ (2.0 equiv), $Pd(OAc)_2$ (10 mol%), BQ (2.0 equiv), in CH_3CN (Scheme 4). This slightly modified Le Bras protocol turned out to be effective for all - secondary as well as tertiary - B3A amides **1a-k**, and for the ester **1m**, affording the corresponding γ-oxylated but-2-enyl acid derivatives (γ-OB2A) in satisfactory yields (scheme 4).[20] However, ketone **1l** gave a mixture of the expected 4-pivaloxy-1-phenylbut-2-en-1-one **6la** and 3,4-dipivaloxy-1-phenylbutan-1-one **6lb**, this latter deriving from conjugate addition of pivalate anion onto the α,β-unsaturated ketone **6la**.



Scheme 4 Pd(II)-catalyzed allylic pivaloxylation. [c] Reaction conditions: pivalic acid (10.0 equiv), $LiOH{\cdot}H_2O$ (2.0 equiv), $Pd(OAc)_2$ (10 mol%), BQ (2.0 equiv), **1** (1.0 equiv), CH_3CN (0.2 M).

We next focused our attention on the second step, *i.e.* the globally isohypsic[21] Pd(0)-catalyzed amination using phthalimide as nucleophile. In order to ultimately merge the two protocols in a single synthetic operation, we decided to optimize this step in CH_3CN, and using $Pd(OAc)_2$ as catalyst. Worth mentioning, Pd(0)-catalyzed allylations require the presence of a ligand (usually a phosphine), to prevent dimerization of the transient η^3-allyl complex (and to bring about ionization in some instances), and when a PdX_2 precatalyst is used, to reduce it to the competent Pd(0) catalyst. Furthermore, when the counterion of the ensuing η^3-allyl complex is not basic enough to carry out pro-nucleophile deprotonation, a base is also needed.[22] Accordingly, given the important amount of pivalic acid needed in the first step, an excess of base (11.5 equivalents) was planned for the one-pot protocol, so as to obtain a buffered medium. Allylation of phthalimide with γ-OB2A **6a** was then considered, to investigate the influence of the nature of the ligand, of the base, as well as of the amount of pro-nucleophile used. The results are presented in Table 2.

Table 2 Optimization of the Pd(0)-catalyzed amination of **6a** with phthalimide.[23]



Entry	Ligand (x)	PhthNH (y)	base	Yield (%) [a]
1	PPh_3 (40)	1.5	NEt_3	SM
2	DPPE (20)	1.5	NEt_3	SM
3	DPPF (20)	1.5	NEt_3	28
4	XANTPHOS (20)	1.5	NEt_3	25
5	BINAP (20)	1.5	NEt_3	30
6[b]	BINAP (20)	1.5	NEt_3	34
7	BINAP (20)	1.5	DIPEA	40
8[c]	**BINAP (20)**	**3.0**	**DIPEA**	**83**

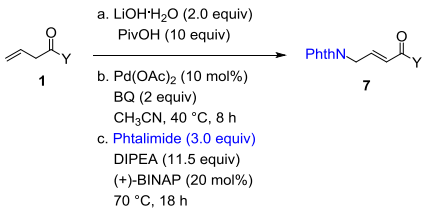
[a] Isolated yields. [b] Reaction time = 48 h. [c] Reaction conditions: **6a** (1.0 equiv), phthalimide (3.0 equiv), $Pd(OAc)_2$ (10 mol%), (+)-BINAP (20 mol%), DIPEA (11.5 equiv), CH_3CN (0.2 M).

The role of the phosphine ligand was first examined, in the presence of NEt_3 and phthalimide (1.5 equiv). While the monodentate PPh_3 and the bidentate DPPE brought about no reaction (entries 1-2), the use of other bidentate ligands such as XANTPHOS, DPPF and BINAP did afford the desired γ-AB2A amide **7a**, although in modest yields (entries 3-5). BINAP was thus selected as the most suitable ligand for the subsequent tests. Increasing the reaction time did not significantly improve the reaction yield (entry 6). Hünig's base (DIPEA) was also able to promote the amination, affording a slight increase of yield (entry 7). Finally, use of 3.0 equivalents of phthalimide allowed to obtain **7a** in 83% yield by (entry 8).

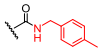
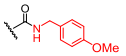
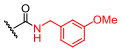
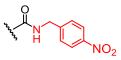
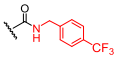
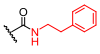
With satisfactory protocols for both the separated steps in hand, we passed to merge the two protocols into a single operation (Table 3). Allylic pivaloxylation was carried out according to the conditions reported in scheme 4, during 8 h. Then, DIPEA (11.5 equiv), phthalimide (3.0 equiv) and BINAP (20 mol%) were added to the reaction mixture, and heating to reflux was kept for additional 18 h. Treatment of B3A **1a** according to the above combined one-pot protocol, gave γ-AB2 **7a** in 90% yield (entry 1).

These new conditions were then tested on other B3A amides. Electron-donor groups in *para*-position of a B3A N-benzyl amide (**1b-c**) gave the desired γ-AB2 products with moderate yields (entries 2-3), while a *meta*-methoxy group (**1d**) afforded the corresponding product in a more satisfactory 76% yield (entry 4). *N*-furfuryl- (**1g**), *N*-phenyl- (**1h**) and *N*-phenylethyl (**1i**) B3A amides led to the corresponding γ-AB2 products in moderate to good yields (entries 7-9). However, B3A N-benzyl amide with electron withdrawing *para*-substitution were not tolerated (entries 5-6), only pivaloxylated compounds being detected in this case in the final crude mixture. As previously observed in the direct amination, no reaction occurred with tertiary amides (**1j**). Furthermore, ester (**1m**) also met with failure, the second step being once more the halted stage (entries 10-11).[24]

Table 3 Scope of the sequential one-pot Pd(II)/Pd(0)-catalyzed allylic amination with phthalimide.[a]



Entry	substrate	product	Yield (%)[b]

1		**1a**	**7a**	90
2		**1b**	**7b**	22
3		**1c**	**7c**	53
4		**1d**	**7d**	76
5		**1e**	**7e**	traces [c]
6		**1f**	**7f**	0[c]
7		**1g**	**7g**	20
8		**1h**	**7h**	32[d]
9		**1i**	**7i**	82
10		**1j**	**7j**	0[c]
11		**1m**	**7m**	0[c]

[a] Reaction conditions: a) pivalic acid (10.0 equiv), $LiOH{\cdot}H_2O$ (2.0 equiv), $Pd(OAc)_2$ (10 mol%), BQ (2.0 equiv), **1** (1 equiv) in CH_3CN (0.2 M) b) Phthalimide (3.0 equiv), (+)-BINAP (20 mol%), DIPEA (11.5 equiv). [b] Isolate Yields. [c] Only pivaloxylated compound **6** was detected at the end of the reaction. [d] 1.5 equiv of phthalimide were used.

Although at present only speculative, the results of Table 3 can be accounted for on the basis of an H-bond directed addition of phthalimide enolate at the distal allyl terminus of the transient η^3-allylpalladium complex.[25] Such an H-bond, however, is disrupted if the amide substituent is too electron-withdrawing, as in the case of the γ-OB2A derivatives **1e** and **1f** (Table 3, entries 5 and 6). This rationale would also justify the inertness of the tertiary amide **1j** and of the ester **1m** that lack the directing N-H.

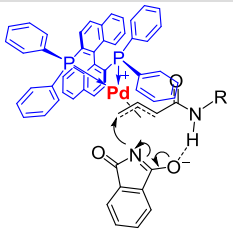


Figure 1 Working model for the Pd(0)-catalyzed addition of phthalimide enolate to η^3-allylpalladium moiety of the transient intermediate.

In conclusion, two new complementary strategies for Pd-catalyzed dehydrogenative aminations of B3A derivatives have been developed. Depending of the type of nitrogen nucleophiles, and more precisely of the acidity of the NH function in these nucleophiles, a direct Pd(II)-catalyzed allylic amination, or a sequential one-pot [direct Pd(II)-catalyzed pivaloxylation / Pd(0)-catalyzed amination] allowed building-up various γ-AB2 derivatives. Extension of this methodology to direct the reaction toward the α-AB3 isomers as well as to obtain more elaborated nitrogen-containing frameworks is currently underway in our laboratories.

Unless special mention, all reactions were carried out under an argon atmosphere. Glassware was flame-dried under an argon gas flow prior to use. Reactions were run in flasks or sealed tubes with magnetic stirring. Reagents and solvents were purchased from commercial sources and used as received. DCM, THF, CH_3CN and DMF were dried on a Mbraun purification system MB SPS-800. Nucleophiles were synthesized according to literature procedures: TsNHCOOMe,[8d] TsNHCOMe,[26] *t*BuSONHCOOMe.[27] NMR spectra (^1H, ^{13}C) were recorded on a Bruker AM 300 MHz or a Bruker AVANCE 400 MHz. NMR experiments were carried out in deuterochloroform ($CDCl_3$) and deuterodimethylsulfoxide (DMSO-d_6). Chemical shifts are given in parts per million (ppm), using the $CDCl_3$ residual signal as reference or the DMSO-d_6 residual signal as reference. Coupling constants (*J*) are given in Hertz (Hz). IR spectra were recorded on a Bruker Tensor 27 (ATR diamond) Bruker spectrophotometer and reported as characteristic bands (cm^{-1}). High resolution mass spectra (HRMS) were recorded at the Institut Parisien de Chimie Moléculaire (FR 2769) (electrospray source). Melting points were measured in capillary tubes on Stuart Scientific SMP3 apparatus and are uncorrected. TLC were performed on Merck 60 F254 silica gel and revealed with either a ultra-violet lamp (254 nm) or a specific color reagent (potassium permanganate, p-anisaldehyde, etc.). A silica gel Merck Geduran® SI 60 (40-63 mm) was used for flash column chromatography. Preparative thin layer chromatography was realized with PLC silica gel 60 F254 (1 mm, 20x20 cm.).

Synthesis of allyl-amides 1a-1j: General procedure (GP1)

To a stirred solution of the proper amine (1.0 or 2.0 equiv) in CH_2Cl_2 (0.2 M) were added at 0 °C DCC (1.3 equiv), DMAP (0.13 equiv) and 3-butenoic acid (1.3 equiv). The reaction mixture was stirred for 10 minutes at 0 °C, then for 24 hours at room temperature. The precipitate was filtered off and washed with CH_2Cl_2 (25 mL). The organic layer was hydrolyzed with saturated aqueous $NaHCO_3$, extracted and dried over $MgSO_4$ and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding allyl-amide **1**.

***N*-Benzyl-3-butenamide (1a)**

Following GP1 with benzylamine (1.0 equiv, 1.02 mL, 9.3 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **1a** in quantitative yield (1.9 g, 10.8 mmol). White solid.

^1H NMR ($CDCl_3$, 300 MHz): δ 7.40-7.29 (m, 5H), 6.07-5.91 (m, 2H), 5.29-5.23 (m, 2H), 4.48 (d, 2H, *J* = 5.7 Hz), 3.09 (td, 2H, *J* = 1.3, 7.2 Hz).

These spectroscopic data are in good agreement with those reported in the literature.[28]

***N*-(4-methylbenzyl)-3-butenamide (1b)**

Following GP1 with 4-methylbenzylamine (1 equiv, 500 mg, 4.1 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **1b** in 76% yield (588 mg, 3.11 mmol). White solid, mp: 100-102 °C.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.10-7.05 (m, 4H), 5.86 (ddt, 1H, J = 16.7, 10.5, 7.2 Hz), 5.77 (br s, 1H), 5.17-5.11 (m, 2H), 4.32 (d, 2H, *J* = 5.6 Hz), 2.97 (dt, 2H, *J* = 7.1, 1.3 Hz), 2.26 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2, 137.3, 135.1, 131.3, 129.4, 127.1, 119.9, 43.4, 41.6, 21.1.

IR (cm^{-1}) γ: 3291, 1626, 1532, 1412.

HRMS (ESI) *m/z* calcd for $C_{12}H_{15}NNaO$ $[M+Na]^+$: 212.1046, found 212.1046.

***N*-(4-methoxybenzyl)-3-butenamide (1c)**

Following GP1 with 4-methoxybenzylamine (1.0 equiv, 0.47 mL, 3.64 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **1c** in 96% yield (715 mg, 3.5 mmol). White solid, mp: 88-90 °C.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.25-7.20 (m, 2H), 6. 91-6.87 (m, 2H), 6.01-5.90 (m, 1H), 5.81 (br s, 1H), 5.26-5.21 (m, 2H), 4.40 (d, 2H, *J* = 5.6 Hz), 3.82 (s, 3H), 3.06 (dt, 2H, *J* = 7.2, 1.3 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2, 159.1, 131.3, 130.2, 129.1, 119.9, 114.1, 55.3, 43.2, 41.6.

IR (cm^{-1}) γ: 3285, 1636, 1548, 1511, 1300, 1173.

HRMS (ESI) *m/z* calcd for $C_{12}H_{15}NNaO_2$ $[M+Na]^+$: 228.0995, found 228.0992.

***N*-(3-methoxybenzyl)-3-butenamide (1d)**

Following GP1 with 3-methoxybenzylamine (1.0 equiv, 0.47 mL, 3.6 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **1d** in 82% yield (611 mg, 2.97 mmol). Orange oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28-7.23 (m, 1H), 6.87-6.82 (m, 3H), 6.01 (m, 1H), 5.99-5.91 (m, 1H), 5.26-5.21 (m, 2H), 4.42 (d, 2H, *J* = 5.7 Hz), 3.81 (s, 3H), 3.06 (dt, 2H, *J* = 7.1, 1.3 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 159.8, 139.7, 131.3, 129.7, 119.9, 119.8, 113.3, 112.9, 55.2, 43.6, 41.6.

IR (cm^{-1}) γ: 3180, 1575, 1541, 1320.

HRMS (ESI) *m/z* calcd for $C_{12}H_{15}LiNO_2$ $[M+Li]^+$: 212.1258, found 212.1264.

***N*-(4-nitrobenzyl)-3-butenamide (1e)**

Following GP1 with 4-nitrobenzylamine hydrochloride (1.0 equiv, 300 mg, 1.6 mmol) and DMAP (1.2 equiv, 233 mg, 1.9 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **1e** in 60% yield (200 mg, 0.91 mmol). White solid, mp: 83-84 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.23-8.19 (m, 2H), 7.47-7.44 (m, 2H), 6.05 (br s, 1H), 5.98 (tdd, 1H, *J* = 7.2, 10.2, 17.3 Hz), 5.32-5.27 (m, 2H), 4.57 (d, 2H, *J* = 6.1 Hz), 3.13 (dt, 2H, *J* = 7.2, 1.2 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 145.7, 145.1, 130.9, 128.2, 123.9, 120.5, 42.8, 41.5.

IR (cm^{-1}) γ: 3229, 3055, 2926, 1638, 1601, 1545, 1509, 1345.

HRMS (ESI) *m/z* calcd for $C_{11}H_{12}N_2NaO_3$ $[M+Na]^+$: 243.0740, found 243.0743.

***N*-(4-(trifluoromethyl)benzyl)but-3-enamide (1f)**

Following GP1 with 4-(trifluoromethyl)benzylamine (1.0 equiv, 500 mg, 5.81 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **1f** in 70% yield (990 mg, 4.07 mmol). White solid, mp: 118-120 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60 (d, 2H, *J* = 7.9 Hz), 7.39 (d, 2H, *J* = 8.0 Hz), 6.09 (br s, 1H), 5.96 (ddt, 1H, *J* = 17.3, 10.3, 7.2 Hz), 5.29-5.23 (m, 2H), 4.50 (d, 2H, *J* = 6.0 Hz), 3.09 (dt, 1H, *J* = 7.1, 1.3 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.6, 142.3, 129.8 (*J* = 33.3 Hz), 131.1, 127.8, 125.7, 124.2 (*J* = 270 Hz), 120.2, 43.0, 41.5.

^{31}F NMR ($CDCl_3$): δ - 62.54.

IR (cm^{-1}) γ: 3476, 1647, 1545, 1328, 1029.

HRMS (ESI) *m/z* calcd for $C_{12}H_{12}F_3NNaO$ $[M+Na]^+$: 266.0763, found 266.0761.

***N*-(2-furanylmethyl)-3-butenamide (1g)**

Following GP1 with furfurylamine (2.0 equiv, 1.03 mL, 11.6 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **1g** in 52% yield (490 mg, 2.97 mmol). White solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27 (q, 1H, *J* = 2.4 Hz), 6.95 (br s, 1H), 6.27-6.25 (m, 1H), 6.14 (q, 1H, *J* = 3.2 Hz), 5.95-5.74 (m, 1H), 5.15-5.09 (m, 2H), 4.38-4.31 (m, 2H), 2.96 (t, 2H, *J* = 5.4 Hz).

These spectroscopic data are in good agreement with those reported in the literature.[29]

***N*-phenyl-3-butenamide (1h)**

Following GP1 with aniline (2.0 equiv, 1.05 mL, 5.8 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 4:6) to afford **1h** in 68% yield (630 mg, 3.9 mmol). White solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.56-7.53 (m, 3H), 7.37-7.29 (m, 2H), 7.13 (t, 1H, *J* = 7.4 Hz), 6.06 (tdd, 1H, *J* = 7.1, 10.8, 16.0 Hz), 5.37-5.31 (m, 2H), 3.21 (td, 2H, *J* = 1.2, 7.0 Hz).

These spectroscopic data are in good agreement with those reported in the literature.[30]

***N*-phenethyl-3-butenamide (1i)**

Following GP1 with phenylethylamine (2.0 equiv, 1.46 mL, 11.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **1i** in 40% yield (424 mg, 2.24 mmol). Pale yellow solid, mp: 63-65 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.17 (m, 5H), 6.08 (br s, 1H), 5.89 (tdd, 1H, *J* = 7.1, 10.3, 17.3 Hz), 5.23-5.16 (m, 2H), 3.50 (q, 2H, *J* = 6.7 Hz), 2.97 (td, 2H, *J* = 1.3, 7.1 Hz), 2.83 (t, 2H, *J* = 7.1 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 138.8, 131.3, 128.7, 128.6, 126.5, 119.8, 41.7, 40.6, 35.6.

IR (cm^{-1}) γ: 3264, 3078, 2930, 1633, 1552.

HRMS (ESI) *m/z* calcd for $C_{12}H_{15}NNaO$ $[M+Na]^+$: 212.1046, found 212.1039.

***N,N*-dibenzyl-3-butenamide (1j)**

Following GP1 with dibenzylamine (1.0 equiv, 0.31 mL, 1.6 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **1j** in 69% yield (290 mg, 1.1 mmol). Yellow oil.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.35-7.03 (m, 10H), 5.96 (tdd, 1H, *J* = 6.6, 10.2, 16.9), 5.13-4.97 (m, 2H), 4.52 (s, 2H), 4.36 (s, 2H), 3.15 (dt, 2H, *J* = 6.6, 1.6 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.5, 137.3, 136.4, 131.7, 129.0, 128.6, 128.4, 127.7, 127.5, 126.4, 117.9, 50.0, 48.2, 38.7.

IR (cm^{-1}) γ: 3027, 2919, 1646, 1418, 696.

HRMS (ESI) *m/z* calcd for $C_{18}H_{19}NNaO$ $[M+Na]^+$: 288.1359, found 288.1361.

***N*-methoxy-*N*-methylbut-3-enamide (1k)**

A mixture of N,O-dimethylhydroxylamine hydrochloride (1.0 equiv, 604 mg, 6.2 mmol) and triethylamine (2.0 equiv, 12.4 mmol, 1.72 mL) in dichloromethane (30 mL) was stirred for 2 hours at room temperature. Then, at 0 °C, but-3-enoyl chloride (1 equiv, 648 mg, 6.2 mmol) freshly prepared [from thionyl chloride (2.0 equiv) and 3-butenoic acid (1.0 equiv) was stirred for 4 hours at 60 °C, carefully evaporated and immediately used without purification] was added dropwise. The mixture was stirred for 10 minutes at 0 °C, then at room temperature overnight. The reaction was hydrolyzed with a HCl 1N solution, then with a saturated aqueous $NaHCO_3$ solution and water. The organic layer was extracted with dichloromethane and dried over $MgSO_4$, filtered and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography (eluent: AcOEt/CycloHexane 6:4) to afford the amide **1k** in 54% yield (430 mg, 3.33 mmol). Pale yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.02-5.92 (m, 1H), 5.19-5.18 (m, 1H), 5.16-5.15 (m, 1H), 3.69 (s, 3H), 3.23 (d, 2H, *J* = 6.7 Hz), 3.18 (s, 3H).

Major Rotamer: ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.4, 131.2, 118.1, 61.3,. 37.2, 25.2.

IR (cm^{-1}) γ: 2969, 1664, 1381, 1176, 1002.

HRMS (ESI) *m/z* calcd for $C_6H_{11}NNaO_2$ $[M+Na]^+$: 152.0687, found 152.0682.

Phenyl Allyl Ketone (1l)

Under air atmosphere, to a solution of 1-phenylbut-3-en-1-ol (1.0 equiv, 300 mg, 2.02 mmol) in acetone (10 mL) at 20 °C was added a solution of Jones reagent (1,5 mL) via a dropping funnel. After 10 minutes, (color change from orange to blue), the reaction mixture was treated with water and extracted with diethyl ether. The organic layer was washed with saturated aqueous $NaHCO_3$, extracted and dried over $MgSO_4$ and concentrated at reduced pressure. The crude product was purified by

silica gel column chromatography (eluent: AcOEt/CycloHexane 1:1) to afford the ketone **1l** in 80% yield (235mg, 1.61 mmol). Colorless oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97 (d, 2H, *J* = 7.5 Hz), 7.57 (t, 1H, *J* = 7.5 Hz), 7.47 (t, 2H, *J* = 7.5 Hz), 6.09 (tdd, 1H, *J* = 6.8, 10.4, 17.3 Hz), 5.18-5.27 (m, 2H), 3.76 (td, 2H, *J* = 1.4, 8.2 Hz).

These spectroscopic data are in good agreement with those reported in the literature.[31]

Pd(II)-catalyzed direct amination (2a-i, 2l-m, 3a, 4a-e and 5a-d): General procedure (GP2)

In a sealed tube, B3A derivative **1** (1 equiv) was dissolved in CH_3CN (0.2 M), and subsequently $Pd(OAc)_2$ (10 mol%), the nucleophile (2 equiv), DIPEA (6 mol%) and BQ (2 equiv) were added to the mixture. Then, the reaction was stirred at reflux for 16-24 hours and, after cooling to r.t., was hydrolyzed with a saturated aqueous K_2CO_3 solution and diluted with Et_2O. The organic layer was extracted, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent: AcOEt/CycloHexane) to afford the aminated compound **2**, **3**, **4** or **6** depending on the nucleophile used.

Methyl (*E*)-(4-(benzylamino)-4-oxobut-2-en-1-yl)(tosyl)carbamate (2a)

Following GP2 with amide **1a** (1.0 equiv, 100 mg, 0.57 mmol) and methyl tosylcarbamate **A** (2.0 equiv, 260 mg, 1.13 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **2a** in 95% yield (219 mg, 0.54 mmol). White solid, mp: 145-146 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.88-7.82 (m, 2H), 7.42-7.30 (m, 7H), 6.91 (dt, 1H, *J* = 15.2, 5.3 Hz), 6.03 (dt, 1H, *J* = 15.2, 1.7 Hz), 5.84 (br s, 1H), 4.63 (dd, 2H, *J* = 5.2, 1.7 Hz), 4.55 (dd, 2H, *J* = 5.8, 1.9 Hz), 3.73 (s, 3H), 2.46 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.5, 152.4, 145.0, 138.3, 137.9, 136.0, 129.4, 128.8, 128.6, 128.0, 127.6, 125.4, 54.0, 47.4, 43.8, 21.6.

IR (cm^{-1}) γ: 3317, 1737, 1673, 1634, 1440, 1165, 981, 700.

HRMS (ESI) m/z calcd for $C_{20}H_{22}N_2NaO_5S$ $[M+Na]^+$: 425.1142, found 425.1149.

Methyl (*E*)-(4-((4-methylbenzyl)amino)-4-oxobut-2-en-1-yl)(tosyl)carbamate (2b)

Following GP2 with amide **1b** (1.0 equiv, 100 mg, 0.53 mmol) and methyl tosylcarbamate **A** (2.0 equiv, 242 mg, 1.06 mmol) for 16 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **2b** in 34% yield (34 mg, 0.082 mmol). Beige solid, mp: 171-172 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86-7.83 (m, 2H), 7.33-7.28 (m, 2H), 7.22-7.16 (m, 4H), 6.78 (td, 1H, *J* = 5.3, 15.3 Hz), 6.00 (td, 1H, *J* = 1.7, 15.2 Hz), 5.82 (br s, 1H), 4.60 (dd, 2H, *J* = 1.7, 5.3 Hz), 4.48 (d, 2H, *J* = 5.6 Hz), 3.71 (s, 3H), 2.44 (s, 3H), 2.36 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.5, 152.4, 144.9, 138.2, 137.4, 136.0, 134.9, 129.4, 128.6, 128.0, 125.5, 54.1, 47.4, 43.6, 21.6, 21.1.

IR (cm^{-1}) γ: 3292, 2926, 1623, 1359, 1232, 1168.

HRMS (ESI) *m/z* calcd for $C_{21}H_{24}N_2NaO_5S$ $[M+Na]^+$: 439.1298, found 439.1305.

Methyl (*E*)-(4-((4-methoxybenzyl)amino)-4-oxobut-2-en-1-yl)(tosyl) carbamate (2c)

Following GP2 with amide **1c** (1.0 equiv, 100 mg, 0.49 mmol) and methyl tosylcarbamate **A** (2.0 equiv, 223 mg, 0.97 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **2c** in 35% yield (73 mg, 0.17 mmol). White solid, mp: 158-159 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86-7.82 (m, 2H), 7.33-7.24 (m, 4H), 6.92-6.85 (m, 3H), 6.00 (td, 1H, *J* = 1.7, 15.2 Hz), 5.73 (br s, 1H), 4.61 (dd, 2H, *J* = 1.7, 5.3 Hz), 4.47 (d, 2H, *J* = 5.7 Hz), 3.83 (s, 3H), 3.71 (s, 3H), 2.44 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.4, 159.2, 152.4, 145.0, 138.2, 136.0, 130.0, 129.5, 129.4, 128.6, 125.5, 114.1, 55.3, 54.1, 47.4, 43.3, 21.7.

IR (cm^{-1}) γ**:** 3297, 2960, 1744, 1624, 1515, 1358, 1168, 770.

HRMS (ESI) *m/z* calcd for $C_{21}H_{24}N_2NaO_6S$ $[M+Na]^+$: 455.1247, found 455.1260.

Methyl (*E*)-(4-((3-methoxybenzyl)amino)-4-oxobut-2-en-1-yl)(tosyl)carbamate (2d)

Following GP2 with amide **1d** (1.0 equiv, 100 mg, 0.49 mmol) and methyl tosylcarbamate **A** (2 equiv, 223 mg, 0.97 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **2d** in 84% yield (176 mg, 0.4 mmol). White solid, mp: 127-128 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.83-7.80 (m, 2H), 7.31-7.28 (m, 3H), 6.88-6.83 (m, 4H), 6.22 (t, 1H, *J* = 5.8 Hz), 6.04 (td, 1H, *J* = 1.7, 15.3 Hz), 4.58 (dd, 2H, *J* = 1.7, 5.4 Hz), 4.46 (d, 2H, *J* = 5.7 Hz), 3.79 (s, 3H), 3.68 (s, 3H), 2.42 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.7, 159.9, 152.3, 145.0, 139.6, 138.1, 135.9, 129.7, 129.5, 128.5, 125.6, 120.1, 113.5, 113.0, 55.2, 54.0, 47.4, 43.6, 21.6.

IR (cm^{-1}) γ**:** 3292, 2955, 1744, 1627, 1357, 1165, 765.

HRMS (ESI) *m/z* calcd for $C_{21}H_{24}N_2NaO_6S$ $[M+Na]^+$: 455.1247, found 455.1232.

Methyl (*E*)-(4-((4-nitrobenzyl)amino)-4-oxobut-2-en-1-yl)(tosyl)carbamate (2e)

Following GP2 with amide **1e** (1.0 equiv, 100 mg, 0.45 mmol) and methyl tosylcarbamate **A** (2.0 equiv, 208 mg, 0.98 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **2e** in 10% yield (16 mg, 0.036 mmol). Pale yellow solid, mp: 182-184 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.14-8.10 (m, 2H), 7.76-7.74 (m, 2H), 7.40-7.38 (m, 2H), 7.24 (d, 2H, *J* = 8.0 Hz), 6.86 (td, 1H, *J* = 5.0, 15.2 Hz), 6.05-6.00 (m, 2H), 4.55-4.52 (m, 4H), 3.62 (s, 3H), 2.37 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.9, 153.3, 147.4, 145.5, 145.1, 139.4, 135.9, 129.5, 128.5, 128.4, 124.7, 123.9, 54.1, 47.5, 43.0, 21.7.

IR (cm^{-1}) γ: 3304, 2921, 1743, 1626, 1517, 1346, 1164, 776.

HRMS (ESI) *m/z* calcd for $C_{20}H_{21}N_3NaO_7S$ $[M+Na]^+$: 470.0992, found 470.1004.

Methyl (*E*)-(4-oxo-4-((4-(trifluoromethyl)benzyl)amino)but-2-en-1-yl)(tosyl)carbamate (2f)

Following GP2 with amide **1f** (1.0 equiv, 100 mg, 0.41 mmol) and methyl tosylcarbamate **A** (2.0 equiv, 188 mg, 0.82 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **2f** in 74% yield (142 mg, 0.30 mmol). White solid, mp: 173-174 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76-7.74 (m, 2H), 7.54-7.52 (m, 2H), 7.36-7.33 (m, 2H), 7.24-7.22 (m, 2H), 6.83 (dt, 1H, *J* = 15.3, 5.2 Hz), 5.98 (dt, 1H, *J* = 15.2, 1.6 Hz), 5.91 (br s, 1H), 4.52 (dd, 2H, *J* = 5.2, 1.7 Hz), 4.49 (d, 2H, *J* = 6.0 Hz), 3.62 (s, 3H), 2.35 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.8, 152.3, 145.0, 142.0, 138.9, 135.9, 129,7 (*J* = 32.0 Hz), 129.5, 128.5, 128.0, 125.7 (*J* = 3.7 Hz), 125.0, 122.9 (*J* = 272.0 Hz), 54.1, 47.4, 43.2, 21.6.

^{19}F NMR ($CDCl_3$, 282 MHz): δ - 62.53.

IR (cm^{-1}) γ**:** 3316, 2925, 1737, 1676, 1636, 1361, 1169, 911, 733.

HRMS (ESI) *m/z* calcd for $C_{21}H_{21}F_3N_2NaO_5S$ $[M+Na]^+$: 493.1015, found 493.1012.

Methyl (*E*)-(4-((furan-2-ylmethyl)amino)-4-oxobut-2-en-1-yl)(tosyl)carbamate (2g)

Following GP2 with amide **1h** (1 equiv, 100 mg, 0.60 mmol) and methyl tosylcarbamate **A** (2 equiv, 277 mg, 1.2 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent:

AcOEt/CycloHexane 7:3) to afford **2g** in 46% yield (109 mg, 0.28 mmol). Brown oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76-7.73 (m, 2H), 7.28 (dd, 1H, *J* = 0.8, 1.9 Hz), 7.24-7.22 (m, 2H), 6.78 (td, 1H, *J* = 5.2, 15.3 Hz), 6.25 (dd, 1H, *J* = 1.9, 3.2 Hz), 6.19-6.17 (m, 1H), 5.96 (br s, 1H), 5.93 (td, 1H, *J* = 1.7, 15.3 Hz), 4.51 (dd, 2H, *J* = 1.7, 5.3 Hz), 4.42 (d, 2H, *J* = 5.5 Hz), 3.61 (s, 3H), 2.35 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.6, 152.4, 150.9,. 145.0, 142.3, 138.5, 135.9, 129.5, 128.5, 125.2, 110.5, 107.7, 54.0, 47.4, 36.6, 21.7.

IR (cm^{-1}) γ**:** 3304, 2956, 1747, 1628, 1357, 1165, 759.

HRMS (ESI) *m/z* calcd for $C_{18}H_{20}N_2NaO_6S$ $[M+Na]^+$: 415.0934, found 415.0938.

Methyl (*E*)-(4-oxo-4-(phenylamino)but-2-en-1-yl) (tosyl)carbamate (2h)

Following GP2 with amide **1h** (1.0 equiv., 50 mg, 0.31 mmol) and methyl tosylcarbamate **A** (2.0 equiv, 142 mg, 0.62 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **2h** in 90% yield (52 mg, 0.14 mmol). Brown solid, mp: 153-155 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78-7.75 (m, 2H), 7.62 (br s, 1H), 7.49 (d, 2H, *J* = 8.0 Hz), 7.26-7.18 (m, 4H), 7.04 (t, 1H, *J* = 7.4 Hz), 6.89 (td, 1H, *J* = 5.2, 15.2 Hz), 6.14 (td, 1H, *J* = 1.7, 15.2 Hz), 4.56 (dd, 2H, *J* = 1.7, 5.1 Hz), 3.63 (s, 3H), 2.34 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.9, 152.4, 145.0, 139.2, 136.3, 135.9, 129.5, 129.0, 128.5, 126.0, 124.4, 119.9, 54.1, 47.5, 21.6.

IR (cm^{-1}) γ: 3353, 2916, 1689, 1536, 1440, 1254, 1185, 1080.

HRMS (ESI) *m/z* calcd for $C_{19}H_{20}N_2NaO_5S$ $[M+Na]^+$: 411.0985, found 411.0975.

Methyl (*E*)-(4-oxo-4-(phenethylamino)but-2-en-1-yl) (tosyl)carbamate (2i)

Following GP2 with amide **1i** (1.0 equiv, 100 mg, 0.53 mmol) and methyl tosylcarbamate **A** (2.0 equiv, 243 mg, 1.01 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **2i** in 41% yield (90 mg, 0.22 mmol). White solid, mp: 145-147 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76-7.73 (m, 2H), 7.27-7.12 (m, 7H), 6.74 (td, 1H, *J* = 5.3, 15.3 Hz), 5.85 (td, 1H, *J* = 1.7, 15.3 Hz), 5.48 (br s, 1H), 4.50 (dd, 2H, *J* = 1.7, 5.3 Hz), 3.61 (s, 3H), 3.56-3.50 (m, 2H), 2.78 (t, 2H, *J* = 7.0 Hz), 2.36 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.7, 152.4, 144.9, 138.7, 137.9, 135.9, 129.4, 128.8, 128.7, 128.5, 126.6, 125.6, 54.0, 47.3, 40.7, 35.6, 21.7.

IR (cm^{-1}) γ**:** 3309, 3026, 2960, 1745, 1627, 1546, 1398, 1128, 907.

HRMS (ESI) *m/z* calcd for $C_{21}H_{24}N_2NaO_5S$ $[M+Na]^+$: 439.1298, found 439.1311.

Methyl (*E*)-(4-oxo-4-phenylbut-2-en-1-yl)(tosyl)carbamate (2l)

Following GP2 with phenyl allyl ketone **1l** (1.0 equiv, 100 mg, 0.68 mmol) and methyl tosylcarbamate **A** (2.0 equiv, 309 mg, 1.35 mmol) for 24 hours. The residue was taken up in DCM and treated with an equal volume of 1N KOH for 15 minutes. After decantation and phase separation, the organic layer was dried over $MgSO_4$ and concentrated in vacuo.The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **2l** in 40% yield (102 mg, 0.27 mmol). Brown oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.95 (td, 2H, *J* = 1.8, 8.7 Hz), 7.93-7.87 (m, 2H), 7.62-7.57 (m, 1H), 7.52-7.49 (m, 2H), 7.37-7.31 (m, 2H), 7.13 (td, 1H, *J* = 1.8, 15.5 Hz), 7.02 (td, 1H, *J* = 6.0, 15.5 Hz), 4.76 (dd, 2H, *J* = 2.0, 6.2 Hz), 3.74 (s, 3H), 2.45 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 189.7, 152.4, 145.1, 141.8, 137.3, 136.0, 133.1, 129.5, 128.7, 128.6, 126.8, 54.2, 47.9, 21.7.

IR (cm^{-1}) γ**:** 2958, 1737, 1676, 1359, 1169, 907, 729.

HRMS (ESI) *m/z* calcd for $C_{19}H_{19}NNaO_5S$ $[M+Na]^+$: 396.0876, found 396.0884.

Methyl (*E*)-4-((*N*-(methoxycarbonyl)-4-methylphenyl) sulfonamido)but-2-enoate (2m)

Following **GP2** with methyl but-3-enoate (1.0 equiv, 50 mg, 0.5 mmol) and methyl tosylcarbamate **A** (2.0 equiv, 228 mg, 0.99 mmol) for 48 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **2m** in 93% yield (137 mg, 0.42 mmol). Beige solid, mp: 132-133 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86-7.84 (m, 2H), 7.36-7.34 (m, 2H), 6.94 (td, 1H, *J* = 5.4, 15.7), 6.04 (td, 1H, *J* = 1.7, 15.7 Hz), 4.62 (dd, 2H, *J* = 1.7, 3.5 Hz), 3.77 (s, 3H), 3.73 (s, 3H), 2.47 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.2, 152.3, 145.1, 142.2, 135.9, 129.5, 128.6, 123.0, 54.1, 51.7, 47.2, 21.6.

IR (cm^{-1}) γ**:** 2955, 1749, 1716, 1435, 1356, 1167.

HRMS (ESI) *m/z* calcd for $C_{14}H_{17}NNaO_6S$ $[M+Na]^+$: 350.0669, found 350.0668.

(*E*)-*N*-benzyl-4-(*N*-tosylacetamido)but-2-enamide (3a)

Following GP2 with amide **1a** (1.0 equiv, 100 mg, 0.57 mmol) and *N*-tosylacetamide **B** (2.0 equiv, 261 mg, 1.14 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **3a** in 61% yield (133 mg, 0.34 mmol). Beige solid, mp: 161-162 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.72-7.69 (m, 2H), 7.30-7.21 (m, 7H), 6.77 (dt, 1H, *J* = 15.2, 5.2 Hz), 5.88 (dt, 1H, *J* = 15.2, 1.7 Hz), 5.69 (br s, 1H), 4.51 (dd, 2H, *J* = 1.7, 5.2 Hz), 4.43 (d, 2H, *J* = 5.7 Hz), 2.36 (s, 3H), 2.24 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.5, 145.3, 138.6, 138.1, 137.9, 136.4, 129.9, 128.8, 128.0, 127.8, 127.7, 125.7, 47.0, 43.8, 24.6, 21.6.

IR (cm^{-1}) γ**:** 3315, 2923, 1705, 1635, 1557, 1355, 1242, 1154.

HRMS (ESI) *m/z* calcd for $C_{20}H_{22}N_2NaO_4S$ $[M+Na]^+$: 409.1192, found 409.1178.

(*E*)-*N*-benzyl-4-(1,1-dioxido-3-oxobenzo[d]isothiazol-2(3H)-yl)but-2-enamide (4a)

Following GP2 with amide **1a** (1.0 equiv, 100 mg, 0.57 mmol) and saccharin **C** (2.0 equiv, 208 mg, 1.14 mmol) for 48 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **4a** in 40% yield (80 mg, 0.02 mmol). White solid, mp: 149-150 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00-7.98 (m, 1H), 7.87-7.75 (m, 3H), 7.27-7.17 (m, 5H), 6.84 (td, 1H, *J* = 5.5, 15.3 Hz), 6.01 (td, 1H, *J* = 1.7, 15.2 Hz), 5.75 (br s, 1H), 4.44-4.40 (m, 4H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.2, 158.5, 137.8, 137.7, 135.6, 135.0, 134.5, 128.7, 127.9, 127.6, 127.1, 126.7, 125.3, 121.1, 43.8, 39.2.

IR (cm^{-1}) γ**:** 3312, 1744, 1625, 1325, 1185, 973, 752.

HRMS (ESI) *m/z* calcd for $C_{18}H_{16}N_2NaO_4S$ $[M+Na]^+$: 379.0723, found 379.0709.

(*E*)-4-(1,1-dioxido-3-oxobenzo[d]isothiazol-2(3H)-yl)-*N*-(4-methylbenzyl)but-2-enamide (4b)

Following GP2 with amide **1b** (1.0 equiv, 100 mg, 0.53 mmol) and saccharin **C** (2.0 equiv, 193 mg, 1.05 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **4b** in 33% yield (64 mg, 0.17 mmol). White solid, mp: 171-172 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.01-7.98 (m, 1H), 7.87-7.77 (m, 3H), 7.10-7.04 (m, 4H), 6.83 (td, 1H, *J* = 5.4, 15.2 Hz), 5.99 (td, 1H, *J* = 1.7, 15.2 Hz), 5.66 (br s, 1H), 4.41 (dd, 2H, *J* = 1.7, 5.4 Hz), 4.37 (d, 2H, *J* = 5.6 Hz), 2.25 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.2, 158.5, 137.7, 137.3, 135.5, 135.0, 134.7, 134.5, 129.4, 127.9, 127.1, 126.8, 125.3, 121.1, 43.6, 39.2, 21.1.

IR (cm^{-1}) γ: 3291, 2922, 1731, 1621, 1334, 1186.

HRMS (ESI) *m/z* calcd for $C_{19}H_{18}N_2NaO_4S$ $[M+Na]^+$: 393.0879, found 393.0876.

(*E*)-4-(1,1-dioxido-3-oxobenzo[d]isothiazol-2(3H)-yl)-*N*-(4-methoxybenzyl)but-2-enamide (4c)

Following GP2 with amide **1c** (1.0 equiv, 100 mg, 0.49 mmol) and saccharin **C** (2.0 equiv, 178 mg, 0.97 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **4c** in 57% yield (106 mg, 0.27 mmol). White solid, mp: 164-165 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.09 (ddd, 1H, *J* = 0.7, 1.5, 7.2 Hz), 7.97-7.85 (m, 3H), 7.23-7.20 (m, 2H), 6.93 (td, 1H, *J* = 5.4, 15.3 Hz), 6.88-6.85 (m, 2H), 6.08 (td, 1H, *J* = 1.7, 15.2 Hz), 5.74 (br s, 1H), 4.51 (dd, 2H, *J* = 1.7, 5.5 Hz), 4.44 (d, 2H, *J* = 5.6 Hz), 3.80 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.1, 159.1, 158.5, 137.7, 135.5, 135.0, 134.5, 129.9, 129.3, 127.1, 126.7, 125.3, 121.2, 114.1, 55.3, 43.3, 39.2.

IR (cm^{-1}) γ: 3293, 2933, 1734, 1513, 1182, 909, 730.

HRMS (ESI) *m/z* calcd for $C_{19}H_{18}N_2NaO_5S$ $[M+Na]^+$: 409.0829, found 409.0836.

(*E*)-4-(1,1-dioxido-3-oxobenzo[d]isothiazol-2(3H)-yl)-*N*-(3-methoxybenzyl)but-2-enamide (4d)

Following GP2 with amide **1d** (1.0 equiv, 100 mg, 0.48 mmol) and saccharin **C** (2.0 equiv, 178 mg, 0.97 mmol) for 48 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **4d** in 82% yield (154 mg, 0.4 mmol). White solid, mp: 138-140 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11-8.02 (m, 1H), 7.95-7.87 (m, 3H), 7.25 (dd, 1H, *J* = 7.5, 9.0 Hz), 6.93 (td, 1H, *J* = 5.4, 15.3 Hz), 6.82-6.84 (m, 3H), 6.10 (td, 1H, *J* = 1.7, 15.2 Hz), 5.80 (br s, 1H), 4.52 (dd, 2H, *J* = 1.7, 5.4 Hz), 4.48 (d, 2H, *J* = 5.7 Hz), 3.80 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.2, 159.9, 158.5, 139.3, 137.8, 135.7, 135.0, 134.5, 129.8, 127.1, 126.7, 125.4, 121.0, 120.2, 113.4, 113.2, 55.2, 43.8, 39.2.

IR (cm^{-1}) γ: 3287, 2921, 1731, 1625, 1331, 1213, 1013.

HRMS (ESI) *m/z* calcd for $C_{19}H_{18}N_2NaO_5S$ $[M+Na]^+$: 409.0829, found 409.0840.

(*E*)-4-(1,1-dioxido-3-oxobenzo[d]isothiazol-2(3H)-yl)-*N*-(4-nitrobenzyl)but-2-enamide (4e)

Following GP2 with amide **1e** (1.0 equiv, 65 mg, 0.29 mmol) and saccharin **C** (2.0 equiv, 108 mg, 0.59 mmol) for 48 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **4e** in 30% yield (35 mg, 0.09 mmol). Beige solid, mp: 168-169 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.11-8.08 (m, 2H), 8.00 (ddd, 1H, *J* = 7.3, 1.4, 0.7 Hz), 7.89-7.77 (m, 3H), 7.39-7.35 (m, 2H), 6.88 (td, 1H, *J* = 5.4, 15.3 Hz), 6.07 (td, 1H, *J* = 1.7, 15.3 Hz), 5.93 (br s, 1H), 4.52 (d, 2H, *J* = 6.3 Hz), 4.44 (dd, 2H, *J* = 1.7, 5.4 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.5, 158.6, 147.4, 145.4, 137.7, 136.6, 135.1, 134.6, 128.3, 127.0, 126.1, 125.4, 123.9, 121.1, 42.9, 39.2.

IR (cm^{-1}) γ: 3291, 2924, 1735, 1519, 1344, 1259, 968, 730.

HRMS (ESI) *m/z* calcd for $C_{18}H_{15}N_3NaO_6S$ $[M+Na]^+$: 424.0574, found 424.0584.

Methyl (*E*)-(4-(benzylamino)-4-oxobut-2-en-1-yl)(tert-butylsulfinyl)carbamate (5a)

Following GP2 with amide **1a** (1.0 equiv, 100 mg, 0.57 mmol) and *N*-*tert*-butanesulfinyl carbamate **D** (2.0 equiv, 204 mg, 1.14 mmol) for 48 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **5a** in 47% yield (93 mg, 0.26 mmol). Yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35-7.27 (m, 5H), 6.80 (td, 1H, *J* = 5.5, 15.4 Hz), 6.08 (br s, 1H), 5.95 (td, 1H, *J* = 1.6, 15.3), 4.46 (d, 2H, *J* = 5.7 Hz), 4.12 (ddd, 1H, *J* = 1.7, 5.4, 16.9 Hz), 3.94 (ddd, 1H, *J* = 1.7, 5.4, 16.9 Hz), 3.77 (s, 3H), 1.21 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.9, 155.4, 139.3, 138.0, 128.7, 127.9, 127.5, 125.7, 60.2, 53.6, 43.7, 39.1, 22.5.

IR (cm^{-1}) γ: 3327, 2951, 1702, 1670, 1494, 1371, 1250, 1033.

HRMS (ESI) *m/z* calcd for $C_{17}H_{24}N_2NaO_4S$ $[M+Na]^+$: 375.1349, found 375.1334.

Methyl (*E*)-(tert-butylsulfinyl)(4-((4-methylbenzyl)amino)-4-oxobut-2-en-1-yl)carbamate (5b)

Following GP2 with amide **1b** (1.0 equiv, 100 mg, 0.53 mmol) and *N*-*tert*-butanesulfinyl carbamate **D** (2.0 equiv, 190 mg, 1.06 mmol) for 30 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 6:4) to afford **5b** in 27% yield (51 mg, 0.14 mmol). Yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.12-7.05 (m, 4H), 6.73 (ddd, 1H, *J* = 5.4, 6.1, 15.4 Hz), 5.83 (td, 1H, *J* = 1.6, 15.3 Hz), 5.73 (br s, 1H), 4.37 (d, 2H, *J* = 5.7 Hz), 4.04 (ddd, 1H, *J* = 1.5, 6.1, 16.9 Hz), 3.87 (ddd, 1H, *J* = 1.7, 5.5, 16.9 Hz), 3.70 (s, 3H), 2.26 (s, 3H), 1.14 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.7, 155.4, 139.3, 137.3, 134.9, 129.4, 128.0, 125.8, 60.2, 53.6, 43.6, 39.1, 29.7, 22.5.

IR (cm^{-1}) γ: 3295, 2925, 1717, 1674, 1634, 1443, 1307, 1089, 907, 729.

HRMS (ESI) *m/z* calcd for $C_{18}H_{26}KN_2O_4S$ $[M+K]^+$: 405.1245, found 405.1232.

Methyl (*E*)-(tert-butylsulfinyl)(4-((4-methoxybenzyl)amino)-4-oxobut-2-en-1-yl)carbamate (5c)

Following GP2 with amide **1c** (1.0 equiv, 100 mg, 0.49 mmol) and *N*-*tert*-butanesulfinyl carbamate **D** (2.0 equiv, 174 mg, 0.97 mmol) for 30 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **5c** in 16% yield (29 mg, 0.08 mmol). Yellow oil.

^{1}H NMR ($CDCl_3$,00 MHz): δ 7.14 (d, 2H, *J* = 8.7 Hz), 6.79 (d, 2H, *J* = 8.7 Hz), 6.72 (td, 1H, *J* = 5.7, 15.3 Hz), 5.83 (td, 1H, *J*= 1.7, 15.2 Hz), 5.68 (br s, 1H), 4.35 (d, 2H, *J* = 5.7 Hz), 4.08-4.01 (m, 1H), 3.87 (ddd, 1H, *J* = 1.7, 5.4, 16.9 Hz), 3.72 (s, 3H), 3.70 (s, 3H), 1.14 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.7, 159.1, 155.4, 139.3, 130.0, 129.3, 125.8, 114.1, 60.2, 55.3, 53.6, 43.3, 39.1, 22.5.

IR (cm^{-1}) γ: 2927, 1717, 1513, 1250, 1089, 909, 731.

HRMS (ESI) *m/z* calcd for $C_{18}H_{26}KN_2O_5S$ $[M+K]^+$: 421.1194, found 421.1199.

Methyl (*E*)-(tert-butylsulfinyl)(4-((3-methoxybenzyl) amino)-4-oxobut-2-en-1-yl)carbamate (5d)

Following GP2 with amide **1d** (1.0 equiv, 100 mg, 0.49 mmol) and *N*-*tert*-butanesulfinyl carbamate **D** (2.0 equiv, 175 mg, 0.97 mmol) for 48 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **5d** in 50% yield (93 mg, 0.24 mmol). Pale brown oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20-7.15 (m, 1H), 6.80-6.69 (m, 4H), 5.90 (br s, 1H), 5.86 (td, 1H, *J* = 1.6, 15.3 Hz), 4.38 (d, 2H, *J* = 5.7 Hz), 4.05 (ddd, 1H, *J* = 1.5, 6.1, 16.9 Hz), 3.87 (ddd, 1H, *J* = 1.7, 5.4, 16.9 Hz), 3.72 (s, 3H), 3.70 (s, 3H),1.14 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.8, 159.8, 155.4, 139.5, 139.4, 129.7, 125.7, 120.2, 113.5, 113.0, 60.2, 55.2, 53.6, 43.7, 39.1, 22.5.

IR (cm^{-1}) γ: 3294, 2958, 1716, 1675, 1634, 1442, 1264, 907, 728.

HRMS (ESI) *m/z* calcd for $C_{18}H_{26}KN_2O_5S$ $[M+K]^+$: 421.1194, found 421.1203.

Sequential Pd(II) / Pd(0) catalyzed amination (7a-d, 7g-i): General procedure (GP5)

A sealed tube was charged with $LiOH{\cdot}H_2O$ (2.0 equiv) and *t*$BuCO_2H$ (10.0 equiv) and was heated at 40 °C for 10 minutes. Then, BQ (2.0 equiv), $Pd(OAc)_2$ (10 mol%) and CH_3CN (0.2 M) were added. The mixture was stirred for 15 minutes at r.t., and then the corresponding amide (**1a-d, 1g-i**) (1.0 equiv) was added. The mixture was stirred at 40 °C for 8 hours. The completion of the reaction was monitored by TLC,

and then DIPEA (11.5 equiv), phthalimide (3.0 equiv) and (+)-BINAP[32] (20 mol%) were added and the mixture was stirred at 70 °C for 18 hours. After cooling to r.t., the mixture was filtered through a SiO_2 pad and washed with AcOEt (20 mL for three times), then concentrated at reduced pressure. The crude product was purified by silica gel column chromatography, to afford the corresponding γ-AB2 amide (**7a-d, 7g-i**).

(*E*)-*N*-benzyl-4-(1,3-dioxoisoindolin-2-yl)but-2-enamide (7a)

Following GP5 with amide **1a** (1.0 equiv, 100 mg, 0.57 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **7a** in 90% yield (142 mg, 0.44 mmol). White solid, mp: 184-185 °C.

^{1}H NMR (DMSO-d_6, 400 MHz) δ 8.39 (t, 1H, *J* = 5.7 Hz), 7.92-7,85 (m, 4H), 7.29-7.27 (m, 2H), 7.22-7.20 (m, 2H), 6.68 (dt, 1H, *J* = 15.4, 4.6 Hz), 5.96 (dt, 1H, *J* = 15.5, 1.8 Hz), 4.33 (dd, 2H, *J* = 4.6, 1.9 Hz), 4.28 (d, 2H, *J* = 5.9 Hz).

^{13}C NMR (DMSO-d_6, 100 MHz): δ 167.4, 164.0, 139.1, 136.3, 134.5, 131.6, 128.3, 127.4, 126.8, 124.4, 123.2, 42.1, 38.0.

IR (cm^{-1}) γ: 3282, 1771, 1701, 1629, 977, 720.

HRMS (ESI) *m/z* calcd for $C_{19}H_{16}N_2NaO_3$ $[M+Na]^+$: 343.1059, found 343.1053.

(*E*)-4-(1,3-dioxoisoindolin-2-yl)-*N*-(4-methylbenzyl)but-2-enamide (7b)

Following GP5 with amide **1b** (1.0 equiv, 100 mg, 0.52 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **7b** in 22% (38 mg, 0.11 mmol). Pale yellow solid, mp: 180-182 °C.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83-7.75 (m, 2H), 7.69-7.62 (m, 2H), 7.12-7.03 (m, 4H), 6.80-6.74 (m, 1H), 5.82 (dt, 1H, *J* = 15.3, 1.6 Hz), 5.58 (brs, 1H), 4.39-4.32 (m, 4H), 2.25 (d, 3H, *J* = 4.3 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.6, 164.5, 137.4, 136.8, 134.8, 134.2, 132.0, 129.4, 127.9, 125.7, 123.5, 43.6, 38.2, 21.0.

IR (cm^{-1}) γ: 3274, 2923, 1771, 1713, 1666, 1623, 1547, 1458, 1351 1218, 1118.

HRMS (ESI) *m/z* calcd for $C_{20}H_{18}N_2NaO_3$ $[M+Na]^+$: 357.1210, found 357.1222.

(*E*)-4-(1,3-dioxoisoindolin-2-yl)-*N*-(4-methoxybenzyl)but-2-enamide (7c)

Following GP5 with amide **1c** (1.0 equiv, 100 mg, 0.48 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **7c** in 53% (90 mg, 0.26 mmol). White solid, mp: 178-180 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81-7.76 (m, 2H), 7.71-7.65 (m, 2H), 7.16-7.10 (m, 2H), 6.80-6.73 (m, 3H), 5.81 (td, 1H, *J* = 1.6, 15.3 Hz), 5.61 (br s, 1H), 4.32-4.36 (m, 4H), 3.71 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.6, 164.4, 159.1, 136.8, 134.2, 131.9, 129.9, 129.3, 125.7, 123.5, 114.1, 55.3, 43.4, 39.2.

IR (cm^{-1}) γ: 3284, 2926, 1708, 1620, 1513, 1247.

HRMS (ESI) *m/z* calcd for $C_{20}H_{18}N_2NaO_4$ $[M+Na]^+$: 373.1159, found 373.1163.

(*E*)-4-(1,3-dioxoisoindolin-2-yl)-*N*-(3-methoxybenzyl)but-2-enamide (7d)

Following GP5 with amide **1d** (1.0 equiv, 100 mg, 0.48 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **7d** in 76% yield (129 mg, 0.37 mmol). White solid, mp: 143-144 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.84-7.75 (m, 2H), 7.75-7.62 (m, 2H), 7.18-7.10 (m, 1H), 6.84-6.70 (m, 4H), 5.83 (dt, 1H, *J* = 15.3, 1.7 Hz), 5.66 (br s, 1H), 4.43-4.31 (m, 4H), 3.72 (d, 3H, *J* = 5.9 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.6, 164.4, 159.9, 139.4, 136.9, 134.2, 131.9, 129.8, 125.5, 123.5, 120.1, 113.4, 113.1, 55.2, 43.7, 38.2.

IR (cm^{-1}) γ: 3275, 2897, 1702, 1631, 1423, 1046, 718.

HRMS (ESI) *m/z* calcd for $C_{20}H_{18}N_2NaO_4$ $[M+Na]^+$: 373.1159, found 373.1157.

(*E*)-4-(1,3-dioxoisoindolin-2-yl)-*N*-(furan-2-ylmethyl)but-2-enamide (7g)

Following GP5 with amide **1g** (1.0 equiv, 85 mg, 0.51 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **7g** in 20% (30 mg, 0.097 mmol). Pale yellow solid, mp: 144-145 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (dd, 2H, *J* = 3.0, 5.4 Hz), 7.66 (dd, 2H, *J* = 3.0, 5.4 Hz), 7.25 (dd, 1H, *J* = 0.9, 1.9 Hz), 6.76 (td, 1H, 5.5, 15.3 Hz), 6.22 (dd, 1H, *J* = 1.9, 3.2 Hz), 6.14 (dd, 1H, *J* = 0.9, 3.3 Hz), 5.82 (td, 1H, *J* = 1.6, 15.3 Hz), 5.75 (br s, 1H), 4.39 (d, 2H, *J* = 5.6 Hz), 4.34 (dd, 2H, *J* = 1.7, 5.5 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.6, 164.3, 150.8, 142.2, 137.1, 134.2, 131.9, 125.4, 123.5, 110.5, 107.7, 38.2, 36.5.

IR (cm^{-1}) γ: 3297, 2917, 1703, 1632, 1556, 1425, 1347, 716.

HRMS (ESI) *m/z* calcd for $C_{17}H_{14}N_2NaO_4$ $[M+Na]^+$: 333.0846, found 333.0857.

(*E*)-4-(1,3-dioxoisoindolin-2-yl)-*N*-phenylbut-2-enamide (7h)

Following GP5 with amide **1h** (1.0 equiv, 80 mg, 0.49 mmol) and with 1.5 equiv of phthalimide (109 mg, 0;744 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **7h** in 32% yield (44 mg, 0.14 mmol). Pale yellow solid, mp: 173-174 °C.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.93-7.84 (m, 2H), 7.75 (dd, 2H, *J* = 5.4, 3.2 Hz), 7.51 (d, 2H, *J* = 7.1 Hz), 7.31 (t, 2H, *J* = 7.9 Hz), 7.19 (s, 1H), 7.10 (t, 1H, *J* = 7.5 Hz), 6.95 (dt, 1H, *J* = 14.7, 5.5 Hz), 6.05 (d, 1H, *J* = 15.0 Hz), 4.48 (d, 2H, *J* = 5.4 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.62, 138. 0, 137.6, 134.3, 132.0, 129.0, 126.1, 124.6, 123.3, 119.9, 38.2.

IR (cm^{-1}) γ: 3366, 1769, 1706, 1388, 947, 756.

HRMS (ESI) *m/z* calcd for $C_{18}H_{14}N_2NaO_3$ $[M+Na]^+$: 329.0897, found 329.0901.

(*E*)-4-(1,3-dioxoisoindolin-2-yl)-*N*-phenethylbut-2-enamide (7i)

Following GP5 with amide **1i** (1.0 equiv, 100 mg, 0.53 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/CycloHexane 1:1) to afford **7i** in 82% yield (145 mg, 0.43 mmol). Pale yellow solid, mp: 148-150 °C.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.78 (dd, 2H, *J* = 3.1, 5.4 Hz), 7.66 (dd, 2H, *J* = 3.1, 5.5 Hz), 7.25-7.09 (m, 5H), 6.71 (td, 1H *J* = 5.6, 15.2 Hz), 5.76 (td, 1H, *J* = 1.6, 15.2 Hz), 5.41 (br s, 1H), 4.33 (dd, 2H, *J* = 1.6, 5.7 Hz), 3.49 (dt, 2H, *J* = 5.9, 6.9 Hz), 2.75 (t, 2H, *J* = 6.9 Hz).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.7, 164.6, 138.7, 136.5, 134.2, 131.9, 128.7, 128.6, 126.5, 125.8, 123.5, 40.6, 38.2, 35.5.

IR (cm^{-1}) γ: 3284, 2929, 1711, 1391, 717.

HRMS (ESI) *m/z* calcd for $C_{20}H_{18}N_2NaO_3$ $[M+Na]^+$: 357.1210, found 357.1211.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/XX.

References and notes

(1) Present address: Università degli Studi dell'Insubria, Como.

(2) (a) Amino Group Chemistry, From Synthesis to the Life Sciences, ed. A. Ricci, Wiley-VCH, Weinheim, 2008. (b) Hili R.; Yudin, A. K. *Nat. Chem. Biol.* **2006**, *2*, 284.

(3) For recent books on C-H bond functionalizations, see: (a) Yu, J.-Q. Catalytic Transformations via C-H Activation, vols 1 and 2, Science of Synthesis, Thieme, 2016. (b) Li, J. J. C-H bond Activation in Organic Synthesis, CRC press 2015.

(4) For a review on allylic amination, see: Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689.

(5) For books on Pd-catalyzed alkene functionnalization, see: (a) Tsuji, J. *Palladium Reagents and Catalysts*, Wiley, 2nd ed. New York, 2004. (b) Hoosokawa, T. *Aminopalladation and Related Reactions Involving Other Group 15 Atom Nucleophiles*: Aminopalladation-Dehydropalladation and Related Reactions, in *Handbook of Organopalladium Chemistry for Organic Synthesis* (ed. E.-i. Negishi), John Wiley & Sons, Inc., New York, **2003**.

(6) For a selection of reviews on allylic C-H functionalization, see: (a) Liron, F.; Oble, J.; Lorion, M. M.; Poli, G. *Eur. J. Org. Chem.*, **2014**, *20*, 1539. (b) Breder, A. *Synlett* **2014**, 899. (c) Ramirez, T. A.; Zhao, B.; Shi, Y. *Chem. Soc. Rev.* **2011**, *41*, 931-942. (d) Engelin, C. J.; Fristrup, P. *Molecules* **2011**, *16*, 951. (e) Jensen, T.; Fristrup, P. *Chem. Eur. J.* **2009**, *15*, 9632.

(7) For reviews on aminoapalladation, see: (a) Kočovský, P.; Bäckvall, J.-E. *Chem. Eur. J.* **2015**, *21*, 36. (b) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981. (c) Keith, J. A.; Henry, P. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 9038. (d) Minatti, A.; Muñiz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142. (e) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318.

(8) For literature precedents on intermolecular Pd(II)-catalyzed allylic amination, see: (a) Patillo, C. C.; Strambeanu, I. I.; Calleja, P.; Vermeulen, N. A.; Mizuno, T.; White, M. C. *J. Am. Chem. Soc.* **2016**, *138*, 1265. (b) Shimizu, Y.; Obora Y.; Ishii, Y. *Org. Lett.* **2010**, *12*, 1372. (c) Yin, G.; Wu and, Y.; Liu, G. *J. Am. Chem. Soc.* **2010**, *132*, 11978. (d) Reed, S. A.; Mazzotti A. R.; White, M. C. *J. Am. Chem. Soc.* **2009**, *131*, 11701. (e) Liu, G.; Yin G.; Wu, L. *Angew. Chem. Int. Ed.* **2008**, *7*, 4733. (f Reed S. A.; White, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 3316. For an recent example on intermolecular Pd(II)-catalyzed allylic azidation, see: (g) Chen, H.; Yang, W.; Wu, W.; Jiang, H. *Org. Biomol. Chem.*, **2014**, *12*, 3340.

(9) For synthesis of α- and/or γ-amino-acid derivatives from dienolates of α,β-unsaturated esters, see: Yamamoto, Y.; Hatsuya, S.; Yamada, J-I. *Tetrahedron. Lett.* **1989**, *30*, 3445.

(10) For a precedent of Pd-catalyzed C-H activation on the ester benzyl but-3-enoate and the ketone 1-phenylbut-3-en-1-one, see: (a) Alam, R.; Pilarski, L. T.; Pershagen, E.; Szabò, K. J. *J. Am. Chem. Soc.* **2012**, *134*, 8778. (b) Pilarski, L. T.; Janson, P. G.;. Szabò, K. J. *J. Org. Chem.* **2011**, *76*, 1503. (c) Pilarski, L. T.; Selander, N.; Bose, D; Szabò, K. J. *Org. Lett.* **2009**, *11*, 5518.

(11) For a precedent of Pd-catalyzed C-H activation on a bis-allylic position, see: Trost, B. M. Hansmann, M. M.; Thaisrivongs D. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 4950.

(12) For a review on the basics of the Pd-catalyzed allylation reaction, see: Poli, G.; Prestat, G.; Liron, F.; Kammerer-Pentier, C.; Kazmaier, U. *Transition Metal Catalyzed Enantioselective Allylic Substitution in Organic Synthesis*. *Top. Organomet. Chem.* **2011**, *38*, 1-63.

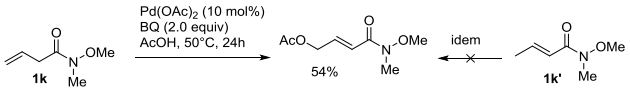
(13) For an example assumed to take place via this mechanism, see: Bottarelli, P.; Costa, M. Della Ca' N.; Fava, E. *Tetrahedron Lett.* **2013**, *54*, 2362.

(14) Sharma, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 17983.

(15) (a) Lorion, M. M.; Duarte, F. J. S.; Calhorda, M. J.; Oble, J.; Poli, G. *Org. Lett.* **2016**, *18*, 1020. (b) Duarte, F. J. S.; Poli, G.; Calhorda M. J. *ACS Catal., ACS Catal.* **2016**, *6*, 1772. (c) Lorion, M. M.; Oble, J. Poli, G. *Pure and Applied Chemistry*. ISSN (Online) 1365-3075, ISSN (Print) 0033-4545, DOI: 10.1515/pac-2015-1102, March 2016. (d) Rajabi, J.; Lorion, M. M.; Ly, V. L.; Liron, F.; Oble, J.; Prestat, G.; Poli, G. *Chem. Eur. J.* **2014**, *20*, 1539. (e) Lorion, M. M.; Nahra, F.; Ly, V. L.; Mealli, C.; Mesaoudi, A.; Liron, F.; Oble, J.; Poli, G. *Chem. Today.* **2014**, *32*, 30. (f) Nahra, F.; Liron, F.; Prestat, G.; Mealli, C.; Messaoudi, A.; Poli, G. *Chem. Eur. J.* **2009**, *15*, 11078.

(16) (a) Qi, X.; Rice, G. T.; Lall, M. S.; Plummer, M. S.; White, M. C. *Tetrahedron* **2010**, *66*, 4816. (b) 8d.

(17) A blank test performed as in table 1, entry 6, but in the absence of the nucleophile gave back the unreacted amide, which confirmed that these reaction conditions do not bring about double bond migration from B3A to B2A. Furthermore, preliminary acetoxylation experiments on Weinreb amides **1k** and **1k'** gave the corresponding γ-acetoxylated product only when starting from A, while only the starting material was recovered when starting from B (see scheme below). This further confirms that, under the above conditions, allylic C-H activation does not take place from the internal alkene.



(18) See for example: Science of Synthesis, Houben-Weyl Methods of Molecular Transformations, Thieme Ed. 2005, Vol 22, Chapt 21.2 F. A. Luzzio, in *Product Class 2: Triacylamines, Imides (Diacylamines), and Related Compounds*, p 259.

(19) Thiery, E.; Aouf, C.; Belloy, J.; Harakat, D.; Le Bras, J.; Muzart, J. *J. Org. Chem.* **2010**, *75*, 1771.

(20) See SI for detailed procedures and full characterization of the pivaloxylated compounds **6a-6k**, and **6m**.

(21) We name it "globally isohypsic" as the global transformation is redox neutral, although the mechanism implies a Pd(0)/Pd(II) redox.

(22) Giambastiani, G.; Poli, G. *J. Org. Chem.* **1998**, *63*, 9608.

(23) Acronyms of the ligands used: 1,2-bis(diphenylphosphino)ethane (DPPE); 1,1'-bis(diphenylphosphino)ferrocene (DPPF); 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (XANTPHOS); 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP).

(24) Given the problematic reactivity of ketone **1l** in the Pd(II)-catalyzed allylic pivaloxylation, this substrate was not tested in the sequential protocol. N-Ts-carbamate **A** and saccharin **C** were unproductive in these sequential conditions.

(25) For a precedent of H-bond directed addition of phthalimide to η^3-allylpalladium moieties, see: Cook, G. R.; Yu, H.; Sankaranarayanan, S.; Shanker, P.S. *J. Am. Chem. Soc*. **2003**, *125*, 5115. (b) Cook, G. R.; Shanker, P. S.; Pararajasingham, K. *Angew. Chem. Int. Ed.* **1999**, *38*, 110.

(26) Xie, W.; Yang, J.; Wang, B.; Li, B. *J. Org. Chem.* **2014**, *79*, 8278.

(27) Mistico, L.; Ay, E.; Huynh, V.; Bourderioux, A.; Chaumeil, H.; Chemla, F.; Ferreira, F.; Oble, J.; Pérez-Luna, A.; Poli, G.; Prestat, G. *J. Organomet. Chem.* **2014**, *76*, 124.

(28) Orliac, A.; Gomez Pardo, D.; Bombrun, A.; Cossy, J. *Org. Lett.* **2013**, *15,* 902.

(29) Jacobi, P.A.; Li, Y. *J. Am. Chem. Soc.* **2001**, *123*, 9307.

(30) Abdou, A.M.; Botros, S.; Hassan, R.A.; Kamel, M.M.; Taber, D.F.; Taher, A.T. *Tetrahedron* **2015**, *71*, 139.

(31) Moriyama, K.; Takemura, M.; Togo, H. *J. Org. Chem.* **2014**, *79*, 6094.

(32) The *R*-configured ligand was used for practical reasons, although its enantiopurity was obviously not needed.