DOI: 10.1002/adsc.201600813
Advanced Synthesis & Catalysis

(Diacyloxyiodo)benzenes-Driven Palladium-Catalyzed Cyclizations of Unsaturated *N*-Sulfonylamides: Opportunities of Path Selection

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Received: July 25, 2016; Revised: December 6, 2016; Published online: ■■ ■■, 0000

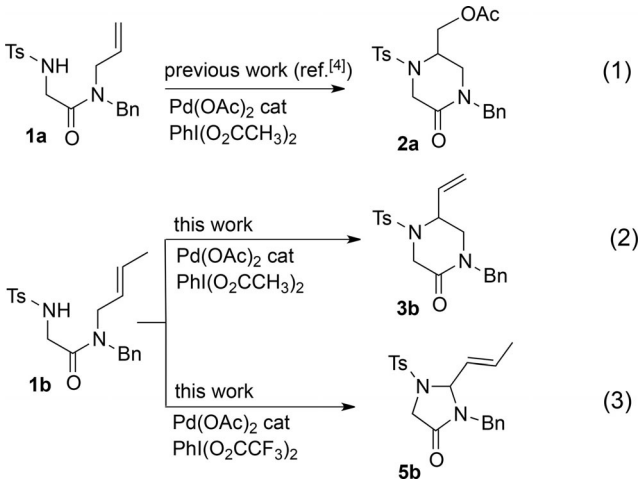
Supporting information for this article can be found under: http://dx.doi.org/10.1002/adsc.201600813.

Abstract: A study of the palladium(II)-catalyzed cyclization of unsaturated *N*-sulfonylamides was undertaken, using (diacyloxyiodo)benzenes as terminal oxidizing agents. Different reactivities were observed as a function of the nature of the unsaturation (terminal *vs.* internal), or of the hypervalent iodine compound used (diacetoxyiodobenzene *vs.* bistrifluoroacetoxyiodobenzene). Proper parameter selection allows the direction of the cyclization to be chosen towards either a global aminoacetoxylation, an allylic amination *via* aminopalladation, or an allylic amination *via* allylic C–H activation.

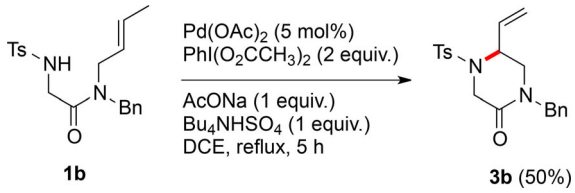
Keywords: allylic compounds; amination; C–H activation; homogeneous catalysis; palladium

The literature devoted to the oxidative Pd(II)-catalyzed addition of nucleophiles to olefins is very extensive and the method allows the construction of a number of synthetically useful compounds starting from simple unsaturated substrates.[1] Although different terminal oxidants have been used for this purpose, the attention was recently directed toward hypervalent iodine reagents.[2,3] In particular, $PhI(O_2CCH_3)_2$, alias PIDA, has been efficiently used to promote 1,2-aminoacetoxylations of unsaturated amine derivatives. In this context, some of us recently described the intra-intermolecular conversion of glycine allylamides into acetoxymethyl-substituted piperazinones [Scheme 1, Eq. (1)].[4] In this contribution, we show that slight modifications of the substrate and/or the oxidizing system can trigger alternative mechanisms [Scheme 1, Eqs. (2) and (3)]. In the frame of our constant interest in the mechanisms of Pd-catalyzed nucleophilic additions to alkenes,[5,6] we envisioned an extension of the above initial study to nitrogen-based substrates bearing terminal as well as internal unsaturations, and to the testing of new reaction conditions. Our new study started with *N*-tosylglycine *N'*-crotyl-*N'*-benzylamide **1b** as the model substrate, using the reaction conditions optimized in our previous study [$Pd(OAc)_2$ 5 mol%, $PhI(O_2CCH_3)_2$ (2.0 equiv.), AcONa (1.0 equiv.) and Bu_4NHSO_4 (1.0 equiv.)].

No reaction occurred when working with CH_2Cl_2 as solvent, either at room temperature or at reflux. However, on changing to DCE at reflux (conditions 1), we obtained the 5-vinylpiperazinone **3b** in 50% yield (Scheme 2, and Table 1, entry 1), instead of the anticipated corresponding aminoacetoxylated product.[4] Performing the cyclization in MeCN at room



Scheme 1. Previous and present studies on Pd(II)-catalyzed cyclizations using $PhI(O_2CR)_2$.



Scheme 2. $Pd(OAc)_2$-catalyzed cyclization of **1b** with $PhI(O_2CCH_3)_2$, Conditions 1.

temperature for 24 h also furnished the product, although in lower yield.

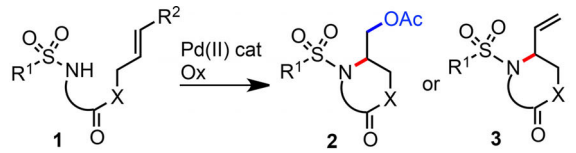
These new conditions were then tested on other differently substituted *N*-sulfonyl-*N*′-allyl or *N*′-crotylamides (Table 1).

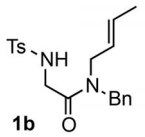
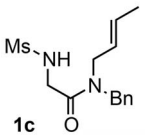
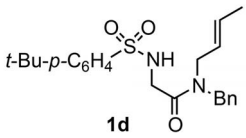
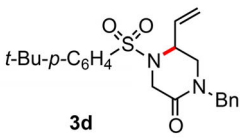
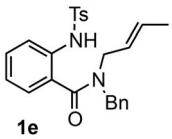
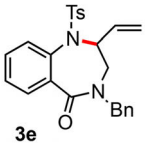
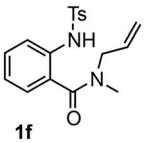
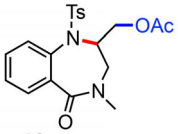
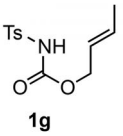
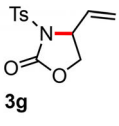
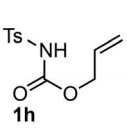
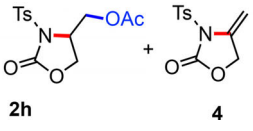
The *N*-mesyl-glycine *N*′-crotyl-*N*′-benzylamide **1c** gave the vinyl piperazinone **3c** in 47% yield (entry 2), while the 4-*tert*-butylphenylsulfonyl derivative **1d** afforded the corresponding 5-vinylpiperazinone **3d** in 35% yield (entry 3). The different behavior between the allyl and the crotyl derivatives was confirmed in the next tests. Indeed, *N*-tosyl-anthranilic acid *N*′-crotyl-*N*′-benzylamide **1e** provided the corresponding vinyl-substituted benzodiazepinone **3e** in 72% yield (entry 4), while the corresponding *N*-allyl-*N*-methyl derivative **1f** gave the 2-acetoxymethyl-benzodiazepinone **2f** in 92% yield (entry 5). Carbamate substrates showed the same behavior. In fact, *N*-tosyl crotyl carbamate **1g** led to the 4-vinyloxazolidinone **3g** in 55% yield (entry 6), while the corresponding allyl derivative **1h** gave the 4-acetoxymethyloxazolidone **2h**, although in this case the β-H elimination product **4** was prevailing (entry 7). Worthy of note, the reaction conditions to convert **1g** into **3g** (Table 1, entry 6) turned out to be more effective than the acidic conditions previously reported by some of us,[7] which led to total degradation of the substrate.

The two different outcomes of the above described reactions can be understood in terms of an initial common aminopalladation step, to afford a transient aminopalladated intermediate **I** (step *1*), from which two alternative paths are possible: a) a $PhI(O_2CCH_3)_2$-promoted oxidative cleavage *via* the high valent species **II**, if a distocyclic β-H elimination is unavailable (clockwise steps *2*+*3*); or b) a distocyclic β-H elimination followed by palladium hydride reoxidation (anticlockwise steps *4*+*5*), if the former step is possible (Scheme 3).[8] Thus, when a distocyclic hydrogen is available (**I**, $R^2 = CH_3$), the β-H elimination path turns out to be faster than the oxidative cleavage. On the other hand, the difficulty of β-H elimination of intermediates **I** and **II** ($R^2 = H$), having only a proxicyclic β-hydrogen available has been already noticed by us.[6d,7]

We then turned our attention to $PhI(O_2CCF_3)_2$, alias PIFA, as alternative oxidizing agent (Conditions 2) (Scheme 4).[9–11]

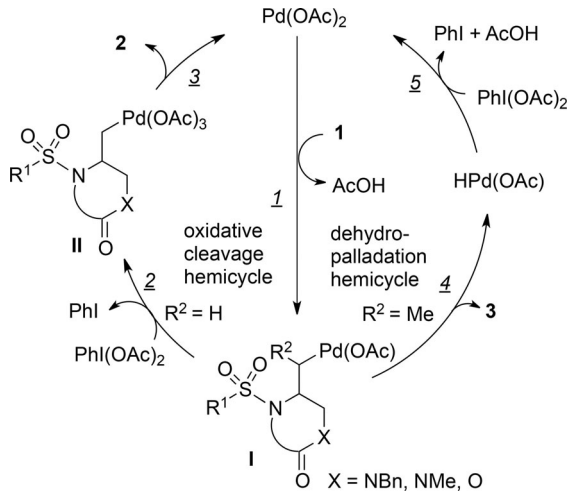
Table 1. Pd(II)-catalyzed cyclization of allyl and crotyl *N*-sulfonyl derivatives with $PhI(O_2CCH_3)_2$ under Conditions 1.[a]



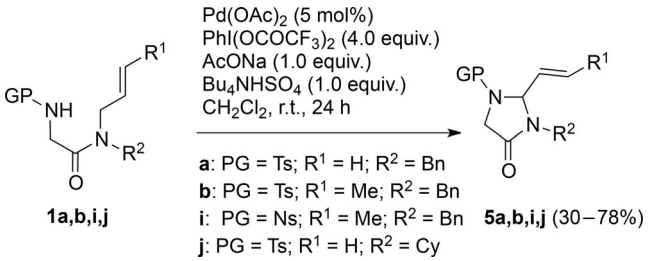
Entry	Substrate	Product	Yield [%]
1			50
2			47
3			35
4			72
5			92
6			55
7			20 (**2h**) 50 (**4**)

[a] *Reaction conditions:* $Pd(OAc)_2$ (5 mol%), $PhI(O_2CCH_3)_2$ (2.0 equiv.), AcONa (1.0 equiv.), Bu_4NHSO_4 (1.0 equiv.) in DCE at reflux, 5 h.

Intriguingly, preliminary cyclization tests on allyl and crotyl amides of *N*-tosyl and Ns-glycine **1a**, **b**, **i**, **j** furnished neither type **3** products (deriving from aminopalladation/dehydropalladation), nor type **2** ones (deriving from aminopalladation/trifluoroacetoxyla-



Scheme 3. Proposed mechanism for the cyclization of *N*-allyl and *N*-crotyl derivatives with Conditions 1, depicted on amide **1b**.

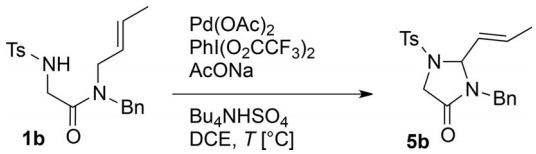


Scheme 4. Preliminary experiments on the cyclization of allyl and crotyl *N*-sulfonylamides using Conditions 2.

tion). Instead, the corresponding 2-vinyl- or 2-propenylimidazolidinones **5a**, **b**, **i**, **j** were unexpectedly obtained (Scheme 4). On the basis of this general behavior, optimization of this reaction on *N*-tosylglycine *N*′-crotyl-*N*′-benzylamide **1b** was next undertaken (Table 2). Use of $Pd(OAc)_2$ (5 mol%), $PhI(O_2CCF_3)_2$ (2.0 equiv.), NaOAc (1.0 equiv.), and Bu_4NHSO_4 (1.0 equiv.) in DCE at room temperature for 3 h gave the 2-vinylimidazolidinone **5b** in 78% yield (entry 1). No reaction occurred in the absence of either the palladium catalyst (entry 2),[12] or of Bu_4NHSO_4 (entry 3). Reduction of the amount of $PhI(O_2CCF_3)_2$ from 4.0 to 1.0 equivalents, or of the molar ratio $PhI(O_2CCF_3)_2/Bu_4NHSO_4$ from 4.0/1.0 to 2.0/0.2 (at reflux of the solvent), or to 4.0/0.2 brought about considerable yield erosions, too (entries 4, 5, and 6). Finally, by employing $Pd(OAc)_2$ (5 mol%), $PhI(O_2CCF_3)_2$ (2.0 equiv.), NaOAc (1.0 equiv.), and Bu_4NHSO_4 (1.0 equiv.) in DCE at reflux, we were able to increase the yield to 85% (entry 7).

With the optimal conditions in hand, we proceeded to explore the scope of this cyclization on different *N*-sulfonylated amino acid allylamide substrates

Table 2. Optimization of the Pd(II)-catalyzed cyclization of *N*-tosylamide **1b** with Conditions 2.

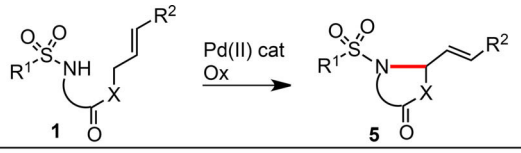


Entry	$Pd(OAc)_2$ (mol%)	Oxidant (equiv.)	Bu_4NHSO_4 (equiv.)	*T* [°C]	Yield [%]
1	5	4.0	1.0	25	78
2	–	4.0	1.0	25	s.m.
3	5	4.0	–	25	<5
4	5	1.0	1.0	25	40
5	5	2.0	0.2	80	18
6	5	4.0	0.2	25	45
7	5	2.0	1.0	80	85

(Table 3). The reaction was effective on glycine *N*-crotyl-*N*-benzylamides protected at the nucleophilic nitrogen with sulfonyl groups other than tosyl or nosyl groups, such as **1c** and **1d**, to give the corresponding imidazolidinones **5c** and **5d** in 31% and 35% yield (entries 2 and 3). *N*-Tosyl-anthranilic acid *N*′-crotyl-*N*′-benzylamide **1e** and *N*′-allyl-*N*′-methyl **1f** afforded the corresponding dihydroquinazolinones **5e** and **5f** in 40% and 26% yield (entries 4 and 5). Analogously, *N*-tosylglycine *N*′-cyclohexenyl-*N*′-benzylamide **1k** provided the spiranic compound **5k** in 37% yield (entry 6), while *N*-tosylglycine *N*′-benzyl-*N*′-cinnamylamide **1l** afforded the corresponding imidazolidinone in 44% yield (entry 7).

Several spectroscopic experiments (^{1}H NMR, ^{13}C NMR, IR, and UV, see the Supporting Information) were conducted to detect the putative generation of $Pd(O_2CCF_3)_4$ from oxidation of $Pd(O_2CCH_3)_2$ or $Pd(O_2CCF_3)_2$ by $PhI(O_2CCF_3)_2$. However, no experiment revealed conclusive findings. Although more work will be required to clarify this point, we believe that oxidation of the metal by the hypervalent reagent is more likely to take place on a more electron-rich organometallic Pd(II) intermediate, or on Pd(0). Accordingly, we propose that under the reaction conditions 2, an initial, rapid, although reversible, aminopalladation/Pd(II)-to-Pd(IV) oxidation sequence might still be possible (Scheme 5), (step *1*). However, in this case, and in contrast to what was observed with $PhI(O_2CCH_3)_2$, neither dehydropalladation ($R^2 = CH_3$) nor reductive elimination from the Pd(IV) intermediate ($R^2 = H$) are permitted from the resulting aminopalladated intermediate **II**. In particular, the reductive elimination may be forbidden by the highly withdrawing power of the trifluoroacetyl ligand,[13] while the absence of available vacant sites on the metal in $\mathbf{II}_{(n=1)}$ may account for the blockage of dehy-

Table 3. Pd(II)-catalyzed cyclization of allyl and crotyl *N*-sulfonyl derivatives with $PhI(O_2CCF_3)_2$ with Conditions 1.[a]



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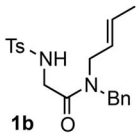
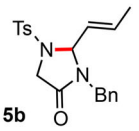
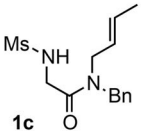
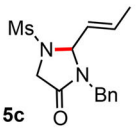
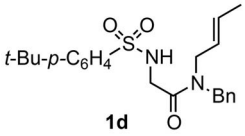
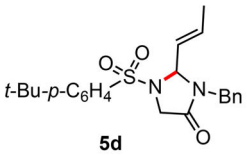
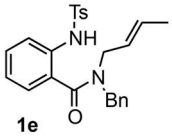
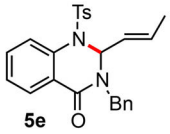
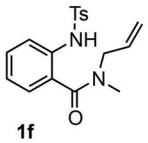
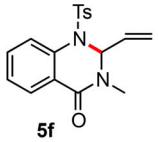
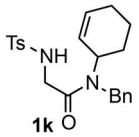
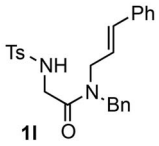
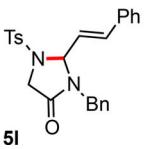
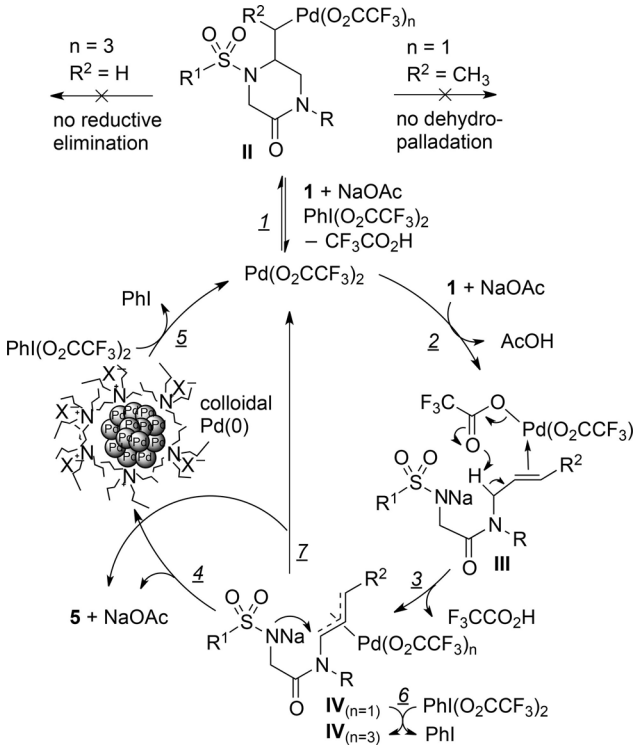
1			85
2			31
3			35
4			40
5			26
6			37
7			44

[a] *Reaction conditions:* $Pd(OAc)_2$ (5 mol%), $PhI(O_2CCF_3)_2$ (2.0 equiv.), AcONa (1.0 equiv.), Bu_4NHSO_4 (1.0 equiv.) in DCE at reflux, 3–7 h.

dropalladation step.[14] As a result, a slower, but irreversible allylic C–H activation (steps 2+3)[15,16] generates the η^3-allylcomplex $\mathbf{IV}_{(n=1)}$, *via* **III**. Subsequent intramolecular addition of the sodium salt of the *N*-sulfonylated nitrogen atom onto the proximal position of



Scheme 5. Proposed mechanism for the cyclization of *N*-allyl and *N*-crotyl amides with Conditions 2.

the η^3-allyl system generates the cyclic product **5** and colloidal Pd(0) (step 4),[17] which can be reoxidized to $Pd(O_2CCF_3)_2$ by $PhI(O_2CCF_3)_2$ (step 5). However, an alternative or competitive oxidation of $\mathbf{IV}_{(n=1)}$ to $\mathbf{IV}_{(n=3)}$, by $PhI(O_2CCF_3)_2$, (step 6) before the cyclization (step 7) cannot be ruled out. Thus, the competition between the former [Pd(0)/Pd(II)] and the latter [Pd(II)/Pd(IV)] mechanism will depend on the relative rates between oxidation and cyclization of intermediate $\mathbf{IV}_{(n=1)}$.

Worthy of note, with these substrates the cyclization step is favored over the alternative trifluoroacetoxylating reductive elimination step, observed by Szabó and co-workers.[10a]

In conclusion, in the framework of our continuing research project devoted to the study of Pd-catalyzed cyclizations, we have shown that *N*-sulfonylamides exhibit different reactivity patterns, when using (diacyloxyiodo)benzenes as the terminal oxidizing agents. Indeed, as a function of the position of the unsaturation, or of the nature of the hypervalent iodine compound used, as well as of the judicious selection of the reaction conditions, a global aminoacetoxylation, an allylic amination *via* aminopalladation, or an allylic amination *via* allylic C–H activation, can be predictably obtained at will.

Experimental Section

General Procedure for the Palladium-Catalyzed Amination Reactions with $PhI(OAc)_2$ (Conditions 1)

A mixture of $Pd(OAc)_2$ (5 mol%, 0.02 mmol, 5.0 mg), $PhI(O_2CCH_3)_2$ (2 equiv., 0.6 mmol, 0.193 g), AcONa (1.0 equiv., 0.3 mmol, 25 mg), $Bu_4N^+HSO_4^-$ (1 equiv., 0.3 mmol, 0.102 g) and substrate **1b–h** (1 equiv., 0.3 mmol) in DCE (0.02 M, 15 mL) was heated at reflux for 5 h. The solvent was evaporated and the mixture was taken up with 5 mL of CH_2Cl_2 and aqueous $Na_2S_2O_3$ was added (5 mL). The two phases were separated, the organic extract was washed with brine (5 mL), and the brine layer was extracted with CH_2Cl_2 (5 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography.

1-Benzyl-4-tosyl-5-vinylpiperazin-2-one (3b): Eluent: (6/4 AcOEt/ petroleum ether); yield: 50%; white solid; mp 100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.44 (s, 3H), 3.13 (dd, J = 12.5 Hz, J = 2.1 Hz, 1H), 3.45 (dd, J = 12.5 Hz, J = 4.7 Hz, 1H), 3.78 (d, J = 17.4, 1H), 4.26 (d, J = 17.4 Hz, 1H), 4.34 (d, J = 14.4 Hz, 1H), 4.63 (m, 1H), 4.68 (d, J = 14.4 Hz, 1H), 5.02 (dd, J = 17.3 Hz, J = 1.4 Hz, 1H), 5.14 (dd, J = 10.6 Hz, J = 1.4 Hz, 1H), 5.45–5.49 (m, 1H), 7.14–7.16 (m, 2H), 7.27–7.31 (m, 5H), 7.69 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5 (q), 45.1 (t), 48.7 (t), 49.9 (t), 52.7 (d), 119.4 (t), 127.4 (d), 127.9 (d), 128.4 (d), 128.7 (d), 129.8 (d), 131.9 (d), 135.5 (s), 135.6 (s), 144.1 (s), 164.1 (s); anal. calcd. for $C_{20}H_{22}N_2O_3S$: C 64.84, H 5.99, N 7.56; found: C 65.01, H 5.87, N 7.39.

4-Benzyl-1-tosyl-2-vinyl-1,2,3,4-tetrahydrobenzo[*e*][1,4]diazepin-5-one (3e): Eluent: (6/4 AcOEt/ etroleum ether); yield: 72%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.42 (s, 3H), 3.02–3.12 (m, 2H), 3.62 (d, J = 14.8 Hz, 1H), 4.74 (d, J = 14.8 Hz, 1H), 4.92–4.99 (m, 1H), 5.25 (d, J = 10.4 Hz, 1H), 5.44 (d, J = 17.2 Hz, 1H), 5.65–5.74 (m, 1H), 7.27–7.73 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6 (q), 46.1 (t), 49.1 (t), 63.2 (d), 118.1 (t), 127.3 (d), 127.8 (d), 128.6 (d), 128.7 (d), 129.2 (d), 129.8 (d), 130.3 (d), 131.9 (d), 132.3 (d), 132.6 (d), 132.8 (s), 135.0 (s), 136.2 (s), 136.6 (s), 143.8 (s), 167.9 (s); anal. calcd. for $C_{25}H_{24}N_2O_3S$: C 69.42, H 5.59, N 6.48; found: C 69.55, H 5.37, N 6.66.

General Procedure for Palladium-Catalyzed Amination Reactions with $PhI(OCOCF_3)_2$ (Conditions 2)

A mixture of $Pd(OAc)_2$ (5 mol%, 0.02 mmol, 5.0 mg), $PhI(O_2CCF_3)_2$ (2 equiv., 0.6 mmol, 0.260 g), AcONa (1 equiv., 0.3 mmol, 25 mg), $Bu_4N^+HSO_4^-$ (1 equiv., 0.3 mmol, 0.102 g) and substrate **1b–f, l** (1 equiv., 0.3 mmol) in DCE (0.02 M, 15 mL) was heated at reflux for 3–7 h. The solvent was evaporated and the mixture was taken up with 5 mL of CH_2Cl_2 and aqueous $Na_2S_2O_3$ was added (5 mL). The two phases were separated, the organic extract was washed with brine (5 mL), and the brine layer was extracted with CH_2Cl_2 (5 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography.

(*E*)-3-Benzyl-2-(prop-1-en-1-yl)-1-tosyl-2,3-dihydroquinazolin-4-one (5e): Reaction time: 5 h; eluent: (1/1 AcOEt/petroleum ether); yield: 40%; orange oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54 (d, J = 6.5 Hz, 3H), 2.28 (s, 3H), 4.04 (d, J = 14.2 Hz, 1H), 4.86 (d, J = 14.2 Hz, 1H), 5.30 (ddd, J = 15.2, 5.8, 1.6 Hz, 1H), 5.57–5.66 (m, 1H), 6.07 (d, J = 5.8 Hz, 1H), 7.22–7.39 (m, 10H), 7.50–7.55 (m, 1H), 7.78 (dd, J = 8.1, 1.0 Hz, 1H), 7.94 (dd, J = 7.7, 1.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.3 (q), 21.5 (q), 48.8 (t), 71.1 (d), 124.2 (s), 125.0 (d), 125.4 (d), 126.7 (d), 126.9 (d), 128.0 (d), 128,3 (d), 128.7 (d), 129.4 (d), 129.8 (d), 131.2 (d), 132.9 (d), 134.4 (s), 135.9 (s), 136.0 (s), 144.1 (s), 160.9 (s); anal. calcd. for $C_{25}H_{24}N_2O_3S$: C 69.42, H 5.59, N 6.48; found: C 69.23, H 5.84, N 6.75.

1-Benzyl-4-tosyl-1,4-diazaspiro[4.5]dec-6-en-2-one (5k): Reaction time: 7 h; eluent: (6/4 AcOEt/petroleum ether, then 9/1 CH_2Cl_2/MeOH); yield: 37%; orange oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.75–2.22 (m, 4H), 2.35–2.40 (m, 2H), 2.43 (s, 3H), 4.08 (s, 2H), 4.27 (d, J = 15.8 Hz, 1H), 4.47 (d, J = 15.8 Hz, 1H), 5.15 (d, J = 10.1 Hz, 1H), 6.25 (d, J = 10.1 Hz, 1H), 7.09–7.11 (m, 2H), 7.21–7.32 (m, 3H), 7.71 (d, J = 8.3 Hz, 2H), 7.81 (d, J = 8.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.9 (t), 21.6 (q), 23.8 (t), 34.8 (t), 43.9 (t), 49.1 (t), 80.9 (s), 124,6 (d), 127.1 (d), 127.8 (d), 128.5 (d), 129.7 (d), 132.9 (d), 136.9 (s), 137.0 (s), 138.3 (d), 144.0 (s), 167.5 (s): anal. calcd. for $C_{22}H_{24}N_2O_3S$: C 66.64, H 6.10, N 7.07; found: C 66.53, H 6.34, N 6.81.

Acknowledgements

We thank Omar Khaled (UPMC) for HR-MS analyses. The Università degli Studi dell'Insubria, CNRS, UPMC, and Labex Michem are acknowledged for financial support. Support through CMST COST Action, CM1205 (CARISMA) and CMST COST Action, CA15106 (CHAOS) is also gratefully acknowledged.

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