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Solvent-Enhanced Diastereo- and Regioselectivity in the Pd^{II}-Catalyzed Synthesis of Six- and Eight-Membered Heterocycles via *cis*-Aminopalladation

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Abstract: The Pd^{II}-catalyzed intramolecular oxidative cyclization of tosyl-protected *cis*- and *trans*-*N*-allyl-2-aminocyclohexanecarboxamides was examined, and efficient syntheses of cyclohexane-fused pyrimidin-4-ones and 1,5-diazocin-6-ones were developed. In the course of the research, a marked solvent effect was observed on both the regio- and diastereoselectivity. Additionally, a novel Pd^{II}-mediated domino oxidation, oxidative amination reaction was discovered. Our experimental and theoretical findings suggest that the reactions proceed via a *cis*-aminopalladation mechanism.

Keywords: allylic compounds · amination · domino reactions · oxidation · palladium

Introduction

The Pd^{II}-mediated intramolecular oxidative "Wacker-type" cyclization is an efficient and valuable method for the construction of diverse nitrogen-containing heterocycles.[1] Since, the olefin moiety is preserved in the product, this type of transformation is also important for target- and diversity-oriented synthesis.[2] However, the exact mechanism underlying this transformation has not been fully revealed to date,[1k] though it would be a powerful tool for the development of enantioselective Pd^{II}-catalyzed cyclizations.[3]

In view of the report by Beccalli et al. on the oxidative Pd^{II}-mediated cyclization of *N*-allylanthranilamides, involving marked solvent and base effects,[4] together with our particular interest in the synthesis and transformation of alicyclic β-amino acid derivatives,[5] the aim of the present work was to investigate the cyclization properties of *cis*- and *trans*-*N*,*N*-diallyl- (**5**, **7**) and *N*-allyl-*N*-methyl-2-tosylaminocyclohexanecarboxamides (**6**, **8**) in Pd^{II}-catalyzed intramolecular oxidative aminations. We have paid special attention to the possible stereochemical outcome of the transformations and to the effects of the marked difference between the calculated pK_a values of the tosyl-protected cyclohexylamine-type nitrogen and the analogous aniline-type nitrogen[4] (9.9 vs 7.2).

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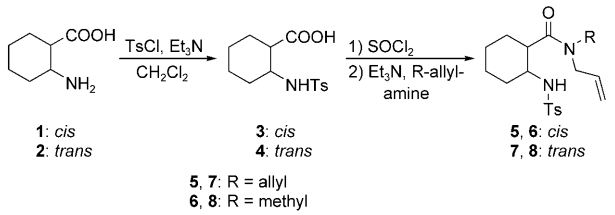
Results and Discussion

The synthetic route towards the starting carboxamides **5**–**8** is depicted in Scheme 1. Tosylation of the starting racemic *cis*- and *trans*-2-aminocyclohexanecarboxylic acids (**1**, **2**), followed by transformation into their acyl chlorides and subsequent reaction with allylamines, led to the desired protected amides **5**–**8** in acceptable overall yields (36–41%).[5]

Application of the cyclization conditions reported by Beccalli et al.[4] (10 mol% $Pd(OAc)_2$, 1 equiv NaOAc, DMSO, 100°C) to **5** resulted in the rapid formation of palladium black and recovery of the unreacted starting material. Since the application of a phase-transfer catalyst had proved beneficial in Pd-mediated transformations,[6] an additional one



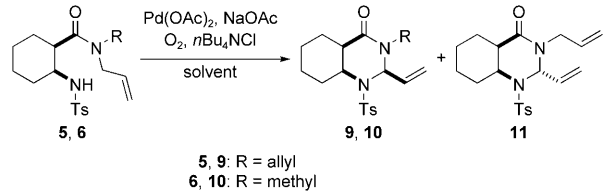
Scheme 1. Synthesis of the starting allyl carboxamides **5**–**8**.

equivalent of nBu$_4$NCl was utilized, which led to the formation of **9** as a single diastereomer in 45% yield (Scheme 2). Finally, performing the reaction under an atmosphere of O_2 (balloon) provided **9** in 69% yield at 110°C (Table 1, entry1).

Table 1. Investigation of the effect of the solvent on the cyclization of *cis*-carboxamides.

Entry	Compound	R	T [°C]	Solvent	Reaction time [h]	Product	Yield [%]
1	**5**	Allyl	110	DMSO	4	**9**	69
2	**5**	Allyl	110	toluene	1.5	**9+11**	76[a]
3	**6**	Me	130	DMSO	20	**10**	52
4	**6**	Me	110	toluene	2.5	**10**	**84**

[a] Combined yield of C-2 epimers.



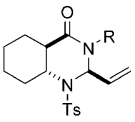
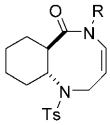
Scheme 2. Pd^{II}-mediated oxidative cyclization of *cis*-carboxamides.

Reaction of *cis*-*N*-allyl-*N*-methyl analogue **6** with the optimized conditions gave the single diastereomer **10** in 52% yield, even after prolonged heating (Table 1, entry 3). Because of the significant solvent effect on this type of transformation,[4] we also performed the reaction in refluxing toluene. Full conversion of **5** was observed within 1.5 h, and a 55:45 C-2 epimeric mixture of **9** and **11** was isolated in 76% combined yield (Table 1, entry 2). In order to exclude the possibility of product isomerization, **9** was subjected to identical conditions as shown in entry 2, but no formation of **11** was detected even after 2 h. The transformation of **6** in refluxing toluene gave **10** in an excellent yield (84%) within 2.5 h (Table 1, entry 4).

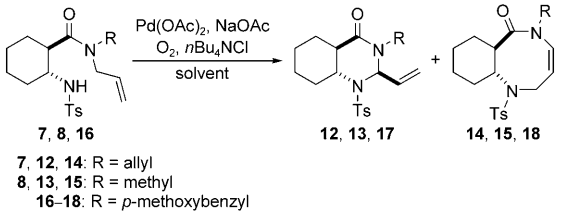
When the optimized conditions were applied to the cyclization of *trans*-amides **7** and **8** (Scheme 3), the reaction was first performed in DMSO at 110°C and reached completion within 2 h (Table 2, entry 1).

The transformation provided a close to 1:1 mixture of two products. The first-eluted compound **12** was identified as the transanellated analogue of **9**. However, the latter-eluted component **14** was identified by two-dimensional NMR

Table 2. Investigation of the effect of the solvent on the cyclization of *trans*-carboxamides.

Entry	Compound	R	T [°C]	Solvent	Reaction time [h]	 12, 13, 17	 14, 15, 18
1	**7**	allyl	110	DMSO	2	42[a] (32)[b]	58 (44)
2	**7**	allyl	110	toluene	0.5	21	79
3	**7**	allyl	**82**	**MeCN**	4	**13 (6)**	**87 (72)**
4	**7**	allyl	110	DMF	1.5	45	55
5	**7**	allyl	110	NMP	1.5	33	66
6	**8**	Me	110	DMSO	3	64 (54)	36 (21)
7	**8**	Me	82	MeCN	4	28 (12)	72 (61)
8	**16**	PMB[c]	82	MeCN	4	15 (9)	85 (67)

[a] Calculated ratio based on ^{1}H NMR. [b] Isolated yields in parenthesis. [c] PMB = *p*-methoxybenzyl.



Scheme 3. Pd^{II}-mediated oxidative cyclization of *trans*-carboxamides.

studies and X-ray crystallography as *trans*-cyclohexane-fused 1,5-diazocin-6-one (Figure 1).

Since, Pd-catalyzed 8-*endo*-*trig* cyclization is rare and the synthesis of medium-sized heterocycles is always a challenging task, we targeted the selective preparation of the diazocinone structure obtained. This uncommon structure is also valuable as concerns natural product[7] and peptidomimetic[8] synthesis. In an investigation of the effect of the reaction medium on the regioselectivity, the ^{1}H NMR spectrum of the crude product indicated that diazocinone **14** was formed as the major product in refluxing toluene in an approximate

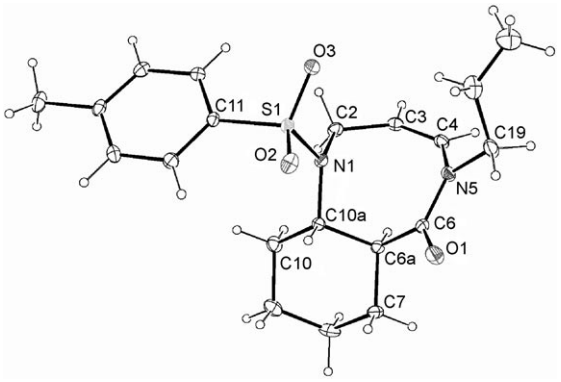
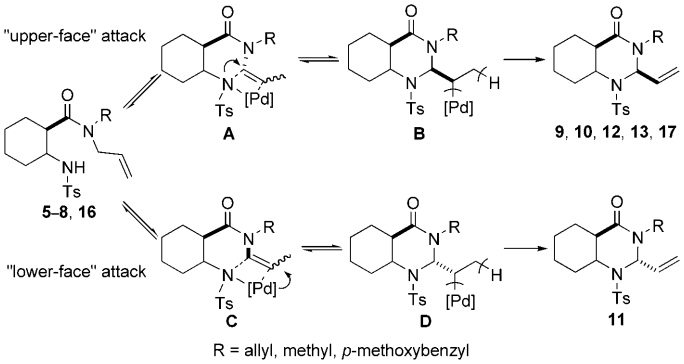


Figure 1. Ortep view of **14**. Thermal displacement parameters are drawn at 20% probability.

ratio of 4:1 with compound **12** (Table 2, entry 2). In refluxing acetonitrile, a ratio of 87:13 was achieved, and diazocinone **14** was isolated in 72% yield (Table 2, entry 3). To confirm that the observed regioselectivity is truly solvent-dependent, but not temperature-dependent, a control experiment was performed in toluene at 80°C. The outcome was a ratio of 4:1, identical to that observed in refluxing toluene. Further efforts to make the reaction more selective resulted in lower ratios (Table 2, entries 4 and 5). In the reaction on the *N*-allyl-*N*-methyl-substituted compound **8**, acetonitrile displayed a lower regioselectivity for compound **15** (Table 2, entry 7). Interestingly, the cyclization of **8** in DMSO gave the pyrimidinone derivative **13** as the major product in a ratio of 64:36 (Table 2, entry 6). In order to broaden the scope of the transformation, *p*-methoxybenzyl-substituted compound **16** was synthesized according to Scheme 1. The cyclization was complete in 4 h (Table 2, entry 8) and diazocinone derivative **18** was isolated in 67% yield together with **17** (9% yield).

With regards the underlying mechanism, if the reactions proceeded via a π-allyl-palladium intermediate, seven-membered heterocycles would also have been formed, in accord with the results of Beccalli et al.[4] In view of the marked difference between the electron density of the tosyl-protected aniline-type nitrogen and the protected cyclohexylamine-type nitrogen, we suggest that, after a Pd-mediated double bond migration,[9,10] the ring-closure towards **9**–**13** and **17** takes place via *cis*-aminopalladation,[1k] due to the stronger coordination of the protected cyclohexylamine-type nitrogen to the palladium moiety. (Scheme 4).

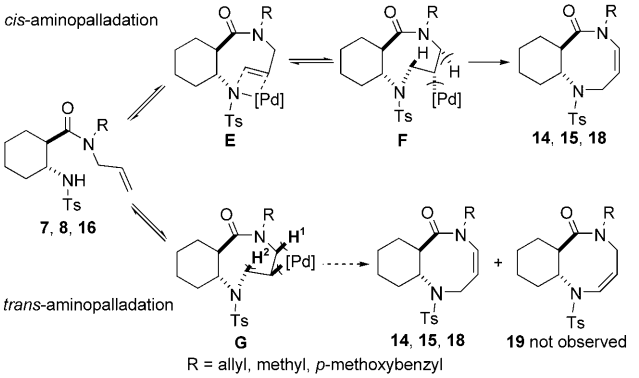


Scheme 4. Proposed mechanism for the formation of quinazolinones **9**–**13** and **17** via *cis*-aminopalladation.

An initial hydropalladation involving β-hydride elimination would give intermediates **A** and **C**; subsequent *cis*-aminopalladation of the isomerized double bond from either the "upper" (**A**) or the "lower" (**C**) face, and a final β-hydride elimination from intermediates **B** and **D** would furnish quinazolinones **9**–**13** and **17**.

For diazocinones **14**, **15** and **18**, we propose the catalytic pathway shown in Scheme 5.

It appears feasible to assume that the reaction takes place via *cis*-aminopalladation rather than *trans*-aminopalladation.



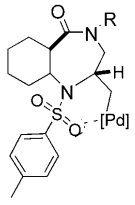
Scheme 5. *cis*- vs *trans*-Aminopalladation in the formation of diazocinones **14**, **15** and **18**.

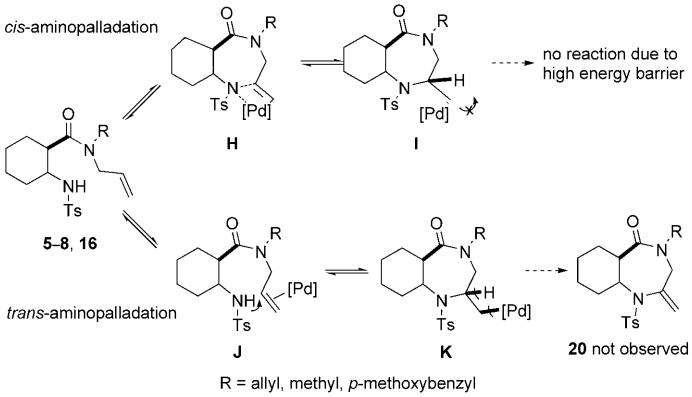
Intermediate **E** is formed via aminopalladation of the double bond, and subsequent *syn*-β-hydride elimination[1k] from intermediate **F** results in compounds **14**, **15** and **18**. In the case of *trans*-aminopalladation, intermediate **G** would form and *syn*-β-hydride elimination could occur with either $\mathbf{H^1}$ or $\mathbf{H^2}$ resulting in the double bond isomer **19** too, but this was not observed in our experiments. However, compounds **14** and **15** are thermodynamically more stable than **19** by 12 and 14 kcal mol^{-1}, respectively.

The presumed mechanisms are supported by gas-phase DFT calculations at the level of b3pw91/lanl2dz for the transition states **A** and **C** shown in Scheme 4 and **E** in Scheme 5. The calculations demonstrated that, for *cis*-carboxamides **5** and **6**, *cis*-aminopalladation is not favored by 15 and 16.7 kcal mol^{-1}, respectively, in the formation of intermediates **5E** and **6E** (see Supporting Information, Table S1). Moreover, the calculations confirmed that in the formation of quinazolines **10**, **12**, **13** and **17**, *cis*-aminopalladation takes place via an "upper-face" attack rather than via the "lower-face". In contrast, for compound **5**, the calculations indicated, that aminopalladation can take place from both the "upper" and the "lower" face (<2 kcal mol^{-1} difference) as we observed in the non-coordinating toluene. The fact that in DMSO only compound **9** can be isolated in 69% yield reveals the dramatic effect of the solvent on the geometry of the transition state, resulting in an "upper-face" attack.

As mentioned above, no formation of diazepine-type product was observed in our experiments, which might serve as further evidence of *cis*-aminopalladation. Our suggested mechanism is depicted in Scheme 6.

The formation of a diazepine-type product via *cis*-aminopalladation would take place by aminopalladation of the double bond in intermediate **H**, though β-hydride elimination would require a 120° rotation of the palladium moiety around the C–C bond (intermediate **I**), which was found to be a critical barrier and thus a potential rate-determining step by Keith et al.[11] Furthermore, the coor-



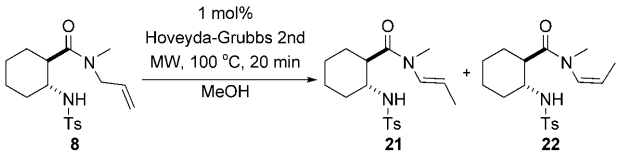


Scheme 6. Mechanistic proposal for the formation of diazepinone-type products.

dination of the non-bonding electron pair of the oxygen atom[1k] in the tosyl group would stabilize intermediate **I**, subsequently increasing the energy barrier of the transformation.

However, *trans*-aminopalladation in intermediate **J** would provide an opportunity for *syn*-β-hydride elimination from intermediate **K**, but diazepinone **20** was not observed in our experiments.

Finally, we set out to obtain experimental evidence to support our theory that no η^3-allyl–palladium complex is involved in these transformations. In view of our finding that, in the presence of the Hoveyda–Grubbs 2nd-generation catalyst, under microwave irradiation, allylamides tend to isomerize to the corresponding propenyl derivatives, we prepared compounds **21** and **22**, in a ratio of 5:1, from **8** (Scheme 7).



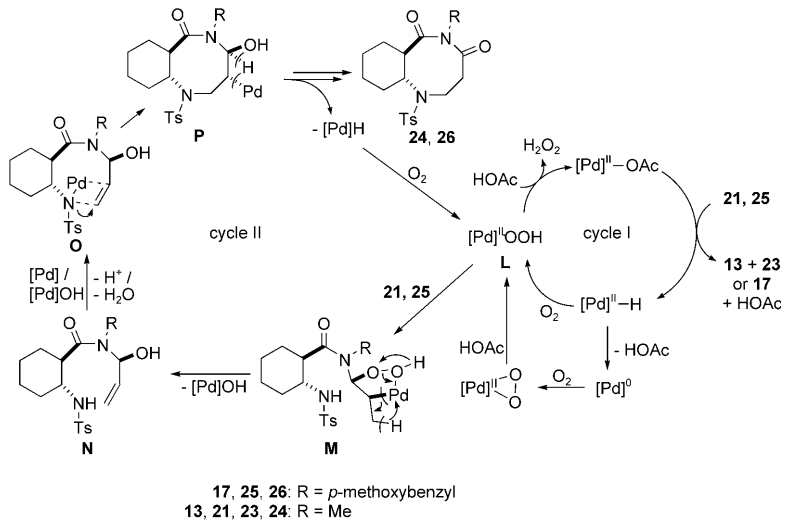
Scheme 7. Microwave-assisted allyl to propenyl isomerization of compound **8**.

It was presumed that subjecting **21** to the conditions shown in Table 2, entry 3 would result in the exclusive formation of **13**. The reaction was complete in 2 h, though it resulted in a mixture of three substances. Two of them were identified as compound **13** and its (2*S**) diastereomer **23**, but they were isolated in a combined yield of only 10%. The third compound, **24**, was isolated in 64% yield and identified as a cyclic imide derivative of **15**. Since no such side-reaction was observed in our previous experiments, we suggest that the oxygen incorporation step takes place prior to the ring-closing aminopalladation step. Accordingly, we presume that **24** is formed via a domino oxidation–oxidative amination cascade reaction. The proposed mechanism is depicted in Scheme 8.

Since quinazolinone-type products **13** and **23** are also formed, we suggest that first an aminopalladation/ring-closure catalytic cycle (cycle I) takes place, identical to that shown in Scheme 4. According to Keith et al.[12] and Popp et al.,[13] at the end of such a cycle, re-oxidation of the catalyst can take place via either direct oxygen insertion or a palladium peroxo species. Both of these pathways result in the palladium hydroperoxo intermediate **L** before regeneration of the original catalyst. On the basis of literature data,[14] we propose that this species can undergo a 1,3-dipolar cycloaddition to result in intermediate **M**, which is transformed to the allylic alcohol derivative **N** via *syn*-β-hydride elimination. Next, allylic alcohol derivative **N** undergoes ring-closure aminopalladation[15] similar to that shown in Scheme 5, to produce the diazocinedione derivative **24**. The fact that the formerly introduced hydroxy group is not eliminated in the final β-elimination step (intermediate **P**) suggests that the 1,3-dipolar cycloaddition step is diastereoselective and creates steric hindrance for the aminopalladation step (intermediate **O**), which thus occurs from the opposite side. Piera et al. recently reported a palladium-catalyzed oxidative transformation in which water was the source of oxygen built into the final product.[16] In order to investigate this possibility, a control experiment was performed in the presence of water, although all our previous experiments were performed in dry media. However, the addition of one equivalent of water did not improve the yield or the ratio of compound **24**. Performance of the reaction with stoichiometric $Pd(OAc)_2$[17] under argon to exclude any source of oxygen yielded quinazolinone derivatives **13** and **23** exclusively, in a close to 1:1 ratio. Hereby, experimental evidence has been provided for our theory that a π-allyl–palladium intermediate is not involved in these transformations. Otherwise, diazocine **15** would also have been formed in the stoichiometric reaction. As proposed by one of the Referees, we prepared the *cis*-analogue of **21**, but its reaction failed to furnish the *cis*-analogue of **24**, as we had expected from our theoretical calculations, which had indicated that *cis*-anellation of a six- and eight-membered ring system is thermodynamically less favored than *trans*-anellation. On the other hand, compound **25** (the PMB-substituted analogue of **21**), isomerized from **16** according to Scheme 7, gave the corresponding diazocinedione **26** in 63% yield.

Conclusion

In conclusion, a highly diastereoselective and efficient Pd^{II}-catalyzed method is reported for the preparation of cyclohexane *cis*-fused 2-vinylpyrimidinones in an O_2 atmosphere. Starting from *trans*-carboxamide derivatives, a highly solvent-dependent and unexpected formation of 1,5-diazocin-6-ones was observed. Both the experimental findings and the theoretical considerations suggest that the reactions proceed via *cis*-aminopalladation, favoring "upper-face" attack, thereby controlling the stereochemical outcome of the transformation. Experimental evidence is presented that no π-



Scheme 8. Proposed mechanism for the formation of diazocine-dione **24** and **26**.

allyl–palladium intermediate is involved in these transformations. Furthermore, a novel Pd^{II}-catalyzed domino oxidation, oxidative amination reaction was discovered, resulting in an eight-membered cyclic imide compound. These results may facilitate a better understanding of Pd^{II}-mediated oxidative transformations, particularly stereoselective ones.

Experimental Section

General methods: ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 400, DRX 500 or AV600 spectrometer. Chemical shifts are expressed in ppm (δ) relative to TMS as internal reference. J values are given in Hz. Melting points were determined on a Kofler apparatus and are uncorrected. FT-IR spectra were recorded on KBr plates on a Perkin-Elmer Spectrum 100 instrument. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS elemental analyser. Low-resolution CR = 1000–1500 mass spectra were run on a Finnigan MAT95S double-focusing mass spectrometer. Samples were introduced directly into the ion source. The electron impact ion source conditions were: temperature 170 °C; electron energy 20 eV; ion current 150 mA. Merck aluminium oxide 90 active neutral (0.063–0.200 mm) was used for column chromatography and Merck Kieselgel 60F_{254} plates for thin-layer chromatography. Anhydrous toluene was distilled from sodium metal and stored over sodium wire. Anhydrous CH_2Cl_2 was distilled from phosphorus pentoxide and stored over 4 Å molecular sieve. $Pd(OAc)_2$ and Hoveyda–Grubbs 2nd-generation catalyst were purchased from Sigma-Aldrich.

CCDC 709671 (**14**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

Starting materials: *cis*- and *trans*-2-Aminocyclohexanecarboxylic acids (**1**, **2**) and 2-tosylaminocyclo-hexanecarboxylic acids (**3**, **4**) were prepared according to literature processes.[5]

General procedure for the preparation of 2-tosylaminocyclohexanecarboxamides 5–8 and 16: To a stirred solution of **3** or **4** (16.8 mmol) in anhydrous toluene (125 mL), $SOCl_2$ (1.3 equiv) was added dropwise. After stirring for 3 h at 60 °C, the solution was evaporated to dryness under reduced pressure. The residue was taken up in anhydrous CH_2Cl_2 (80 mL) and the solution was added dropwise to a stirred solution containing the appropriate allylamine (2 equiv) and Et_3N (2 equiv) in of anhydrous CH_2Cl_2 (50 mL). After completion of the reaction according to TLC, the solution was extracted with cold 5% HCl solution (2×75 mL) and with cold 5% NaOH solution (2×75 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. Isopropyl ether (15 mL) was added to the crude product and the solid was filtered off, resulting in compounds **5**–**8** and **16**.

General procedure for the cyclization of carboxamides 5–8, 16 and 21: A 100 mL three-necked round-bottomed flask was charged with carboxamide **5**–**8** or **16** (1.3 mmol), NaOAc (106 mg, 1.3 mmol), nBu$_4$NCl (362 mg, 1.3 mmol), $Pd(OAc)_2$ (29 mg, 0.13 mmol) and the appropriate solvent (20 mL) and placed under an atmosphere of O_2 (balloon). After heating at 110 °C (reflux in the event of MeCN) for the time specified in Tables 1 and 2, the mixture was quenched with brine (25 mL), filtered through a short pad of Celite and extracted with Et_2O (2×25 mL) and EtOAc (1×25 mL). The combined organic phase was dried over anhydrous Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was purified by column chromatography (n-hexane/ethyl acetate 4:1), which provided pure compounds **9**–**15**, **17**, **18**, **23** and **24**.

(2*R,4a*R**,8a*R**)-3-Allyl-1-tosyl-2-vinyl-2,3,4a,5,6,7,8,8a-octahydro-1*H*-quinazolin-4-one (9)**: Prepared in DMSO according to the general procedure for 4 h. White solid (336 mg, 69%); m.p. 95–97 °C; ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.75 (d, J = 8.3 Hz, 2H, Ar), 7.43 (d, J = 8.0 Hz, 1H, Ar), 5.98 (ddd, J = 17.2, 10.1, 7.5 Hz, 1H, C*H*-CH$_2$), 5.63–5.56 (m, 1H, CH$_2$-C*H*-CH$_2$), 5.37 (d, J = 16.9 Hz, 1H, CH-C*H*$_2$), 5.34 (d, J = 10.1 Hz, 1H, CH-C*H*$_2$), 5.16 (dd, J = 10.3, 1.2 Hz, 1H, CH$_2$-CH-C*H*$_2$), 4.97 (dd, J = 17.3, 1.4 Hz, 1H, CH$_2$-CH-C*H*$_2$), 4.43–4.38 (m, 1H, C*H*$_2$-CH-CH$_2$), 4.13–4.09 (m, 1H, C*H*-NH), 3.43 (dd, J = 15.7, 6.9 Hz, 1H, C*H*$_2$-CH-CH$_2$), 2.40 (s, 3H, Me), 2.18 (d, J = 13.3 Hz, 1H, CH$_2$), 1.98 (s, 1H, CH-CO), 1.67–1.61 (m, 2H, CH$_2$), 1.61–1.53 (m, 1H, CH$_2$), 1.36 (d, J = 13.2 Hz, 1H, CH$_2$), 1.26–1.18 (m, 2H, CH$_2$), 0.86 ppm (tq, J = 13.3, 3.1 Hz, 1H, CH$_2$); ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 21.0, 21.4, 24.7, 24.9, 30.9, 39.9, 45.3, 53.0, 69.8, 117.5, 119.9, 126.8, 130.1, 132.4, 136.4, 136.9, 144.0, 166.7 ppm; IR (KBr): $\tilde{\nu}$ = 3079, 2960, 2942, 2865, 1935, 1655, 1445, 1343, 1246, 1168, 1090 cm^{-1}; MS m/z: 374 [M^+]; elemental analysis calcd (%) for $C_{20}H_{26}N_2O_3S$: C 64.14, H 7.00, N 7.48; found: C 64.02, H 7.12, N 7.33.

***trans*-5-Allyl-1-tosyl-1,2,6a,7,8,9,10,10a-octahydro-5*H*-benzo[*b*]-[1,5]diazocin-6-one (14)**: Prepared in MeCN according to the general procedure for 4 h. White solid (351 mg, 72%); m.p. 136–138 °C; ^{1}H NMR (600 MHz, [D$_6$]DMSO): δ = 7.62 (d, J = 8.3 Hz, 2H, Ar), 7.38 (d, J = 8.0 Hz, 2H, Ar), 5.77 (td, J = 9.9, 1.9 Hz, 1H, N-CH$_2$-CH-C*H*-N), 5.73–5.65 (m, 1H, CH$_2$-C*H*-CH$_2$), 5.13 (dd, J = 17.3, 1.6 Hz, 1H, CH$_2$-CH-C*H*$_2$), 5.07 (dd, J = 10.3, 1.5 Hz, 1H, CH$_2$-CH-C*H*$_2$), 5.04 (ddd, J = 9.9, 3.7, 2.5 Hz, 1H, N-CH$_2$-C*H*-CH-N), 4.24 (d, J = 20.1 Hz, 1H, N-C*H*$_2$-CH-CH-N), 3.86–3.80 (m, 3H, N-C*H*$_2$-CH-CH-N, C*H*$_2$-CH-CH$_2$), 3.72 (dt, J = 11.7, 3.4 Hz, 1H, CH-N), 2.89 (dt, J = 11.3, 4.0 Hz, 1H, CH-CO), 2.38 (s, 3H, Me), 1.70–1.49 (m, 4H, CH$_2$), 1.17–1.28 (m, 3H, CH$_2$), 1.16–1.07 ppm (m, 1H, CH$_2$); ^{13}C NMR (150 MHz, [D$_6$]DMSO): δ = 21.4, 23.9, 24.9, 28.6, 28.7, 41.9, 44.4, 49.4, 58.2, 117.1, 118.1, 126.9, 127.0, 130.3, 134.1, 138.8, 143.4, 171.8 ppm; IR (KBr): $\tilde{\nu}$ = 3085, 3067, 2924, 2864, 1935, 1834, 1654, 1445, 1396, 1336, 1221, 1154, 1090 cm^{-1}; MS m/z: 374 [M^+]; elemental analysis calcd (%) for $C_{20}H_{26}N_2O_3S$: C 64.14, H 7.00, N 7.48; found: C 64.01, H 6.82, N 7.30.

***trans*-5-Methyl-1-tosyl-2,3,6a,7,8,9,10,10a-octahydro-1*H*,5*H*-benzo[*b*]-[1,5]diazocine-4,6-dione (24)**: Prepared according to the general procedure for the cyclization of carboxamides, starting from **21** (100 mg, 0.285 mmol) in refluxing dry MeCN (8 mL). Colorless oil (66 mg, 64%);

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.59–7.55 (m, 2H, Ar), 7.29–7.25 (m, 2H, Ar), 4.12–3.99 (m, 2H, N-CH_2-CH_2-CO, CH-N), 3.56–3.47 (m, 1H, N-CH_2-CH_2-CO), 3.44–3.38 (m, 1H, N-CH_2-CH_2-CO), 3.24 (dt, J = 3.4, 11.4 Hz, 1H, CH-CO), 2.99 (s, 3H, N-Me), 2.94–2.82 (m, 1H, N-CH_2-CH_2-CO), 2.43–2.39 (m, 4H, Me, CH_2), 2.07–0.78 ppm (m, 7H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.0, 24.3, 24.7, 29.3, 29.4, 31.2, 38.1, 39.2, 49.7, 58.4, 126.7, 129.3, 135.5, 143.2, 170.7, 174.0 ppm; IR (KBr): $\tilde{\nu}$ = 2925, 2854, 1704, 1655, 1465, 1373, 1328, 1158, 1066 cm^{-1}; MS m/z: 364 [M^+]; elemental analysis calcd (%) for $C_{18}H_{24}N_2O_4S$: C 59.32, H 6.64, N 7.69; found: C 59.19, H 6.75, N 7.81.

Microwave-assisted allyl to propenyl isomerization of compound 8 to 21 and 22: A 10 mL CEM Discover microwave vial was charged with **8** (100 mg, 0.285 mmol), Hoveyda–Grubbs 2nd-generation catalyst (1.8 mg, 1 mol %), dry MeOH (2 mL) and a magnetic stir bar. The vial was irradiated at 100 °C for 20 min. After completion of the reaction, the solvent was evaporated off and the residue was dissolved in EtOAc (20 mL) and extracted with water (2 × 15 mL). The organic phase was dried over anhydrous Na_2SO_4, evaporated to dryness and purified by column chromatography, using *n*-hexane/ethyl acetate 2:1, to yield **21** and **22**.

***trans*-*N*-Methyl-*N*-((*E*)-prop-1-enyl)-2-tosylaminocyclohexanecarboxamide (21)**: White solid (72 mg, 72 %); m.p. 71–73 °C; two rotamers in a ratio of 1:0.4; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76–7.68 (m, 4H, Ar), 7.31–7.25 (m, 4H, Ar), 7.08 (d, J = 14.7 Hz, 1H, N-C*H*=CH), 6.54 (d, J = 13.3 Hz, 1H, N-C*H*=CH), 5.11–5.03 (m, 1H, N-CH=C*H*), 5.02–4.94 (m, 1H, N-CH=C*H*), 4.75 (d, J = 6.1 Hz, 1H, NH), 4.67 (d, J = 6.1 Hz, 1H, NH), 3.50–3.41 (m, 2H, C*H*-NH), 3.03 (s, 3H, N-Me), 2.91 (s, 3H, N-Me), 2.78–2.70 (m, 2H, CH-CO), 2.41 (s, 6H, Me), 2.13–2.04 (m, 2H, CH_2), 1.81–1.65 (m, 12H, N-CH=CH-*Me*, CH_2), 1.49–1.16 ppm (m, 6H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9, 21.9, 25.0, 25.1, 29.4, 29.6, 30.1, 31.0, 32.7, 32.9, 47.0, 47.4, 55.4, 55.5, 106.7, 109.2, 127.5, 128.5, 129.0, 129.8, 138.8, 143.4, 172.3 ppm; IR (KBr): $\tilde{\nu}$ = 3211, 2927, 2858, 1621, 1451, 1330, 1161, 1095 cm^{-1}; MS m/z: 350 [M^+]; elemental analysis calcd (%) for $C_{18}H_{26}N_2O_3S$: C 61.69, H 7.48, N 7.99; found: C 61.78, H 7.35, N 7.91.

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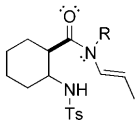

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[17] In the presence of benzoquinone as catalyst oxidant, no cyclization took place and only unreacted starting material was isolated from the mixture.

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