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A new access to 3,5-disubstituted piperazinones via Pd(0)-catalyzed amination

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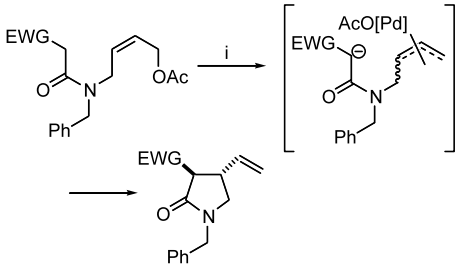
Abstract—An original synthetic route toward 3,5-disubstituted piperazinones has been developed. The method relies upon a 6-*exo* intramolecular process between a sulfonylated nitrogen atom of amino acid derivation and an η^3-allyl-palladium moiety. This cyclization process generates the two possible (*cis* and *trans*) diastereoisomers whose ratio depends on the amino acid employed. The bulkier the amino acid residue, the higher the observed *cis*:*trans* ratio. Convincing evidence for reversible intramolecular addition of the nitrogen nucleophile to the η^3-allyl-palladium complex is put forward.

We recently described a novel access to 3,4-disubstituted pyrrolidones[1] based on the intramolecular interaction between a stabilized acetamide enolate anion and an η^3-allyl-palladium appendage (Scheme 1).

We next thought that an appropriate modification of the above strategy might have enabled the construction of piperazinone derivatives, a family of molecules endowed of a particular pharmacological interest. The piperazine or piperazinone structure is in fact present in compounds possessing antifungal,[2] antidepressant,[3] antimigraine,[4] antithrombotic,[5] antihistaminic,[6] anti-aggregating,[7] or nootropic activity.[8] Accordingly, we envisaged the formal replacement of the active methylene moiety for a suitably *N*-protected amino acid residue in the nucleophilic left-side arm of the precursor. This set the stage for a new 6-*exo* allylic amination process allowing the generation of 3,5-disubstituted piperazinones. Of course, the role of the pre-existing stereogenic center on the diastereoselectivity of the cyclization represented a point of potential interest (Scheme 2).



Scheme 1. *Reagents and conditions*: $Pd_2(dba)_3$, (0.05 equiv.), PPh_3, (0.5 equiv.), BSA (1.2 equiv.) AcOK (0.1 equiv.), THF, reflux, 12 h, 61–93%. EWG: CO_2Me, COMe, CN, SO_2Ph, $PO(OEt)_2$.

According to the above reasoning the known allylic amine **1**[1] has been acylated with three differently *N*-protected L-alanine derivatives **2**–**4**. *N*-Boc L-alanine **2** was commercially available. *N*-Cbz-**3** and *N*-Ts-**4** were instead prepared from L-alanine according to known and/or standard procedures. *N*-Bz-L-alanine precursor **8** was prepared from **5** by Boc-to-Bz exchange (Scheme 3).

A preliminary set of experiments was performed in DMF using $Pd(OAc)_2$ (5%), 1,2-bis(diphenylphosphino)ethane (dppe) (10%) and NaH (1 equiv.) as deprotonating agent.[9] Under these conditions *N*-Boc, *N*-Cbz and *N*-Bz precursors were recovered unchanged. Conversely and quite gratifyingly, the same reaction conditions smoothly and quantitatively converted the *N*-tosyl derivative **7** into the expected piperazinone **11** as a 1:1 mixture of the two possible C_5-epimers. Further optimization experiments confirmed the couple $Pd(OAc)_2$/dppe as the optimal catalytic system, and DMF as the best solvent. Furthermore, it was soon realized that upon thermal activation (80°C), NaH was

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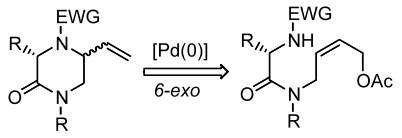
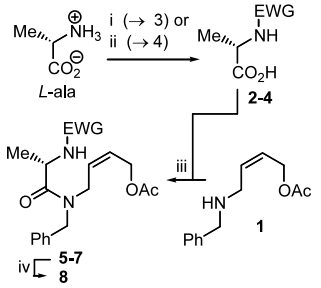


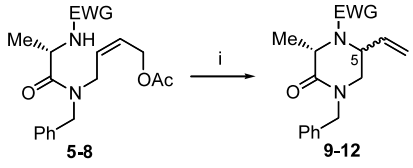
Scheme 2. Retrosynthetic disconnection of the 3,5-disubstituted piperazinone heterocycle.



Scheme 3. *Reagents and conditions*: (i) Cbz-Cl, NaOH, Et_2O/H_2O (**3**, 91%); (ii) TsCl, NaOH, Et_2O/H_2O (**4**, 76%); (iii) DCC, DMAP (5%), THF (**5**: 78%; **6**: 65%, **7**: 90%); (iv) (1) **5**, TMSCl, NaI, CH_3CN, then MeOH, (2) PhCOCl, NEt_3, DMAP (5%), CH_2Cl_2 (**8**, 65% over the two steps).

unnecessary for the success of the cyclization. Under these conditions **11**[10] was obtained in quantitative yield within 3 h with the same diasteromeric ratio as observed at room temperature in the presence of NaH. Moreover, these conditions allowed the cyclization of the *N*-Boc and *N*-Cbz derivatives, albeit in limited yield and longer reaction time (Scheme 4, Table 1).

The reasons for the better cyclization behavior of the *N*-tosyl derivative **7** with respect to the carbamates **5** and **6**, or the amide derivative **8** are still unclear. It should be noted, however, that precedents of Pd(0)-catalyzed aminations using carbamate-protected[11] or sulfonamide-protected[12] amines are rather rare, and examples of failure have been reported.[13]



Scheme 4. *Reagents and conditions*: (i) 5% $Pd(OAc)_2$, 10% dppe, DMF, 80°C.

Table 1. Cyclization outcomes for allylic alanine derivatives

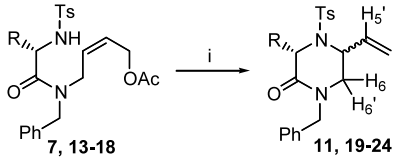
Precursor	EWG	Piperazinone	Yield (%)
5	Boc	**9**	85
6	Cbz	**10**	57
7	Ts	**11**	≥98
8	Bz	**12**	0

Having established the tosyl group as the optimal *N*-derivatization of the cyclization precursor, L-leucine, L-isoleucine, L-phenylglycine, L-phenylalanine, and L-tryptophan were similarly converted into the corresponding allylamides **13**–**18** and tested for cyclization (Scheme 5, Table 2).

Despite the excellent chemical yields, the diastereoselectivities of the cyclization process were variable, spanning from totally random, in the case of the L-alanine derivative (entry 1), to a 95:5 ratio, in the case of the L-isoleucine derivative (entry 3). A careful inspection of the ^1H NMR spectra as well as of the chromatographic behavior of the diastereoisomeric piperazinones revealed that specific features constantly discriminated the set of the major diastereomers from that of the minor ones. In fact, in each series studied the major and more apolar isomer regularly featured a more deshielded $H_{5'}$ as well as a smaller $\Delta\delta$ (H_6–$H_{6'}$). Such indications were thus suggestive of a precise, though variable, diastereoselective trend. Although NOE difference analysis of the resulting piperazinones turned out to be inconclusive, an X-ray diffraction structure of the crystalline major isomer of **21** ($[\alpha]_D^{20}$ (*c* 0.4, $CHCl_3$) −39)[14,15] unambiguously showed its *cis* 3,5-configuration (Fig. 1).[16] Accordingly, we confidently assigned the same *cis* configuration to the other major isomers.

Having established the sense of the diastereoselection, rationalization of its extent as a function of the incorporated amino acid moiety became a tractable task. From a qualitative viewpoint, it is interesting to note that diastereoselectivity augments with increasing of the steric demand of the incorporated amino acid moiety. Although such a result was not unexpected, the thermodynamics of the present cyclization process remained to be ascertained. Accordingly, an equilibration test was performed by re-submission of an equimolar mixture of the isolated piperazinone *trans*-**21** and its precursor **15** to the above cyclization conditions (Scheme 6).[17]

After complete conversion of the precursor to the piperazinone, a 50:50 epimeric mixture *cis*- and *trans*-**21** was obtained. This result implies that 25% of the *trans* epimer has been converted into the *cis* one. We thus conclude that the amination reaction is a reversible process, the equilibration between the two epimers taking place very likely through the corresponding zwitterionic η^3-allylpalladium species **22** (Scheme 7). It is interesting to note that the above behavior strictly parallels that found by Ibuka et al. in the Pd(0)-catalyzed equilibration of *N*-methane- and *N*-arenesulfonyl-



Scheme 5. *Reagents and conditions*: (i) 5% $Pd(OAc)_2$, 10% dppe, DMF, 80°C, 3 h.

Table 2. Synthesis of 3,5-disubstituted *N*-tosyl-piperazinones

Entry	R	Precursor	Piperazinone	(%)	*cis*/*trans*
1	Me	**7**	**11**	≥98	50:50
2	*i*-Bu	**13**	**19**	≥98	60:40
3	*s*-Bu	**14**	**20**	≥98	95:5
4	Ph	**15**	**21**	≥98	74:26
5	Bn	**16**	**22**	≥98	65:35
6	3-CH_2-ind	**17**	**23**	≥98	69:31
7	H	**18**	**24**	≥98	–

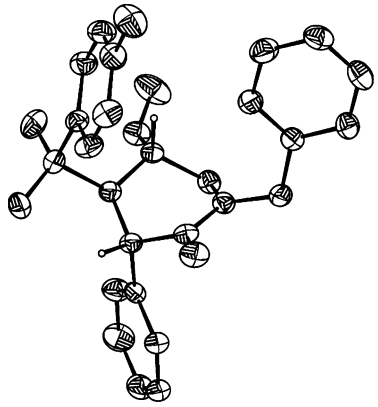
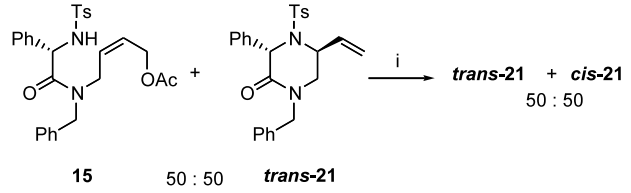
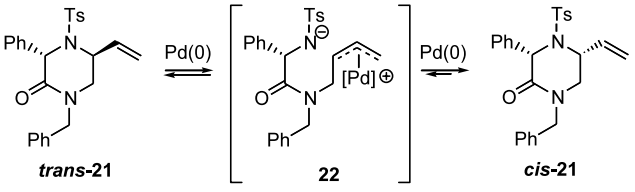


Figure 1. ORTEP drawing of *cis*-**21**.



Scheme 6. *Reagents and conditions*: (i) 5% $Pd(OAc)_2$, 10% dppe, DMF, 80°C, 3 h.



Scheme 7. Reversibility of the Pd(0)-catalyzed amination reaction.

2-alkyl-3-vinylaziridines. Indeed, in these substrates too, the *cis* isomers are constantly found to be more stable than the *trans* ones.[18,19]

Verification of the higher stability of the *cis* piperazinones over the *trans* ones was judged essential to corroborate our rationale. Accordingly, we carried out a molecular mechanics computational analysis of the cyclized products. Conformational searches[20] in MacroModel v. 7.2[21] were performed on both epimers of **11**, **19**–**23**, and the energy differences between the global minima for each pair was calculated. The *cis* and *trans* epimers of all the minimized piperazinones showed nitrogen pyramidalization[22] and the same boat-type conformation as seen in the X-ray structure of *cis*-**21**.[23] More importantly, the *cis* isomers were consistently found to be more stable than the corresponding *trans* ones.[24] Although the calculated values do not quantitatively match the experimental observed *cis*/*trans* ratios, the qualitative trend is respected, with piperazinones **20** featuring the highest energy difference.[25] The overall *cis* preference is expected to be essentially due to the tetrahedral geometry of the sulfonamide nitrogen, which favors the equatorial disposition of the bulky tosyl group and forces the lone pair of electrons on nitrogen in the axial position. As a result, only the *cis* epimer can arrange both the amino acid residue and vinyl group *trans* to the bulky sulfonyl group.

In summary, we have developed a new route to 3,5-disubstituted piperazinones based on an intramolecular Pd(0)-catalyzed allylic amination of *N*-tosylated amino acid derivatives. Piperazinones are obtained in high yields as a mixture of the two possible diastereoisomers. Such a cyclization has been shown to be a reversible process, constantly favoring the thermodynamically more stable *cis* isomer with *cis*/*trans* ratios increasing with the size of the amino acid residue.

Acknowledgements

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9. These cyclization conditions are optimized for the synthesis of pyrrolidones and differ with respect to those used in Ref. 1 ($Pd_2(dba)_3$, PPh_3, BSA, AcOK, THF). See: Poli, G.; Giambastiani, G. *J. Org. Chem.* **2002**, *67*, 9456–9459.
10. Piperazinone **11**: dppe (20 mg, 0.1 mmol) was added to a solution of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) in dry DMF (1 mL) under N_2 atmosphere. After 15 min of stirring, cyclization precursor **7** (0.5 mmol, 222 mg) in DMF (1 mL) was added through cannula to the thus formed Pd(0) complex. The resulting mixture was stirred at 80°C for 3 h before it was cooled to rt. Et_2O was then added and the organic phase was washed with brine (3×20 mL) dried over $MgSO_4$ and concentrated under reduced pressure. Flash chromatography gave the pure piperazinone as a pale yellow oil (188 mg, 98%). ^1H NMR ($CDCl_3$, 400 MHz): *δ cis* compound 1.60 (d, $^3J=7$ Hz, 3 H), 2.44 (s, 3H), 3.17 (dd, $^3J=4.5$ Hz, $^2J=13$ Hz, 2H), 4.36 (d, $^2J=14$ Hz, 1H), 4.39 (m, 1H), 4.54 (d, $^2J=14$ Hz, 1H), 4.59 (q, $^3J=7$ Hz, 1H), 5.06 (dd, $^2J=1.5$ Hz, $^3J=17$ Hz, 1H), 5.17 (dd, $^2J=1.5$ Hz, $^3J=10.5$ Hz, 1H), 5.76 (ddd, $^3J=5$ Hz, $^3J=10.5$ Hz, $^3J=17$ Hz, 1H), 6.98 (m, 2H), 7.24–7.32 (m, 5H), 7.70 (m, 2H); *trans* compound: 1.63 (d, $^3J=6.5$ Hz, 3H), 2.41 (s, 3H), 3.13 (dd, $^3J=3.5$ Hz, $^2J=13$ Hz, 1H), 3.60 (dd, $^3J=3.5$ Hz, $^2J=13$ Hz, 1H), 4.28 (d, $^2J=14.5$ Hz, 1H), 4.37 (q, $^3J=6.5$ Hz, 1H), 4.57 (m, 1H), 4.71 (d, $^2J=14.5$, 1H), 5.04 (d, $^3J=10$ Hz, 1H), 5.15 (d, $^3J=16.5$ Hz, 1H), 5.47 (dd, $^3J=7$ Hz, $^3J=10$ Hz, $^3J=16.5$ Hz, 1 H), 7.18 (m, 2H), 7.23–7.32 (m, 5 H), 7.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): *δ cis* compound 21.0, 21.5, 46.9, 49.9, 52.8, 53.9, 117.8, 127.1, 127.7, 127.9, 128.4, 128.6, 128.7, 129.5, 129.9, 133.7, 135.7, 137.4, 143.6, 168.8; *δ trans* compound 21.3, 21.4, 47.3, 50.4, 53.2, 54.3, 118.3, 127.5, 128.2, 128.6, 129.0, 130.4, 136.1, 136.7, 144.3, 168.5.
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14. Sharp *cis*/*trans* isomer separation of the resulting piperazinones turned out to be rather hard, and traces of the undesired isomer often contaminated the selected one. As a consequence, measurement of the optical rotations values of these compounds was not attempted at this stage, except for the crystalline *cis*-**21**.
15. Check for the full preservation of the enantiomeric integrity in the resulting piperazinones has not been specifically addressed. Nevertheless, related literature precedents clearly indicate that the reaction conditions are not expected to be racemizing. See for example: (a) Verhelst, S. H. L.; Wiednhof, W.; Ovaa, H.; van der Marel, G. A.; Overkleeft, H. S.; van Boeckel, C. A. A.; van Boom, J. H. *Tetrahedron Lett.* **2002**, *43*, 6451–6455; (b) Kinderman, S. S.; Doodeman, R.; van Beijma, J. W.; Russcher, J. C.; Tjen, K. C. M. F.; Kooistra, T. M.; Mohaselzadeh, H.; van Maarseveen, J. H.; Hiemstra, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2002**, *344*, 736–748; (c) Zorn, C.; Gnad, F.; Salmen, S.; Herpin, T.; Reiser, O. *Tetrahedron Lett.* **2001**, *42*, 7049–7053.
16. Crystallographic data (excluding structure factors) for the structures in this paper, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 202406. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
17. An equimolar mixture of the isolated piperazinone *trans*-**21** and its precursor **15** was deliberately chosen for this test in order to reproduce the original reaction conditions. In fact, a potential interaction between the starting acetate and the catalytic system, which would affect the exact nature of the real catalyst, cannot be completely ruled out.
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19. For a related *trans*-to-*cis* equilibration of *N*-Boc-5-alkylpipecolaldehydes, see: (a) Wilkinson, T. J.; Stehle, N. W.; Beak, P. *Org. Lett.* **2000**, *2*, 155–158; (b) Beak, P.; Lee, W. K. *J. Org. Chem.* **1993**, *58*, 1109–1117; (c) Kotsuki, H.; Kusumi, T.; Inoue, M.; Ushio, Y.; Ochi, M. *Tetrahedron Lett.* **1991**, *32*, 4159–4162.
20. Conformational searches were performed by the Monte Carlo method, generating 1000–4000 structures within 10 kJ/mol energy window. The lowest energy structure in each search was found more than 20 times and converged to a low gradient, typically approx. 2 kJ/mol lower in energy than the next most frequently found structure, confirming it as a global energy minimum.
21. http://www.schrodinger.com
22. Belvisi, L.; Carugo, O.; Poli, G. *J. Mol. Struct.* **1994**, *318*, 189–202.
23. The RMS between the calculated global minimum of *cis*-**21** and the X-ray structure is 0.5752, the major difference being the orientation of the phenyl rings.
24. Found *cis*-*trans* relative steric energy differences (kJ/mol) **11**: −14.5; **19**: −12.3; **20**: −22.0; **21**: −14.9; **22**: −9.9; **23**: −14.5.
25. Precipitation of black palladium was constantly observed a few hours after completion of the reaction. As a consequence, further experiments at longer reaction times, in order to reach the final thermodynamic equilibrium, were not attempted.