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Polyfunctionalized Pyrrolidines by Ugi Multicomponent Reaction Followed by Palladium-Mediated S_N2' Cyclizations

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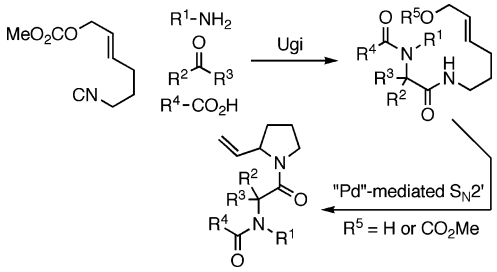
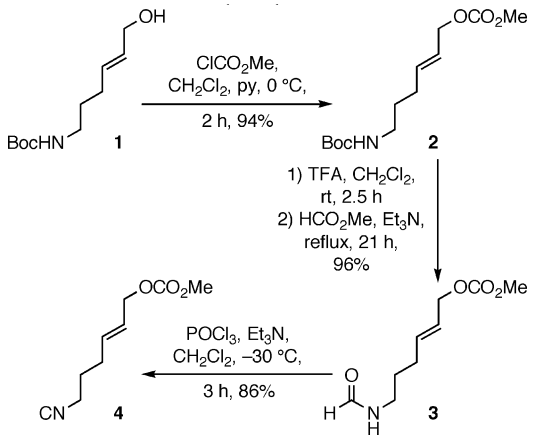


A 4-component Ugi reaction with a suitable isocyanide, followed by a novel secondary transformation involving a Pd(II)-mediated (R^5 = H) or a Pd(0)-mediated (R^5 = CO_2Me) S_N2' cyclization to give highly functionalized *N*-acyl-2-vinylpyrrolidines, is reported. The overall yields are usually good and in most cases the Pd(0)-catalyzed reaction gave the final product in almost quantitative yield.

The pyrrolidine ring is an important moiety present in many natural products and is often included in bicyclic scaffolds and peptide mimetics.[1] Therefore the possibility to obtain highly and differentially functionalized derivatives in a convergent way is an important tool in diversity oriented synthesis.[2]

We recently optimized a very simple method for the preparation of *N*-acyl-2-vinylpyrrolidines using a base-promoted cyclization (LiHMDS) of an acetamide onto an allylic bromide through an S_N2' reaction.[3] We now decided to extend the same protocol to more functionalized secondary amides, accessible in a multicomponent way through the isocyanide-based[4] Ugi reaction. For this purpose we first synthesized the special isocyanide **4**, one of the four inputs in the Ugi MCR, as summarized in Scheme 1. The alcohol **1**, readily obtained in excellent overall yield by a known procedure from 2-pyrrolidone,[5] was therefore submitted to a deprotection−formylation−dehydration protocol.[6]

SCHEME 1. Synthesis of Key Isocyanide 4



Isocyanide **4** was then used, together with a variety of carbonyl compounds (usually aldehydes, but also ketones) (Table 1), primary amines, and carboxylic acids, for preparing in excellent yield a small library of Ugi derivatives. After hydrolysis of the carbonate **5a**, we attempted to convert the alcohol **6a** into the corresponding allyl bromide, needed for the previously reported base-mediated cyclization. However, surprisingly, all our efforts to achieve this simple transformation were unsuccessful.[7]

For this reason we planned an alternative approach for the cyclization, taking advantage of the catalytic activity of different palladium complexes. We first focused our attention on the Pd(II) derivatives, which have been used in the past for the synthesis of *N*-heterocycles through cyclization of suitable nitrogen nucleophiles onto allylic alcohols both free and protected.[8−10] The nitrogen nucleophiles were, in those examples, mostly carbamates or oxazolidinones. To the best of our knowledge, only one example dealing with amides has been reported.[11]

We therefore started with alcohol **6a**, choosing first $PdCl_2(PhCN)_2$ as catalyst. After a careful optimization (reaction conditions and use of additives, as reported in the Supporting Information) we found the best conditions which are reported

(1) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789−12854.

(2) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46−58.

(3) Banfi, L.; Basso, A.; Guanti, G.; Riva, R. *Tetrahedron* **2006**, *62*, 4331−4341.

(4) (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210. (b) Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Wiley: Weinheim, Germany, 2005. (c) Dömling, A. *Chem. Rev.* **2006**, *106*, 17−89. (d) Concerning only the related Passerini reaction see: Banfi, L.; Riva, R. *Org. React.* **2005**, *65*, 1−140.

(5) Hara, O.; Sugimoto, K.; Makino, K.; Hamada, Y. *Synlett* **2004**, 1625−1627.

(6) The formamide formation step was crucial and only the reported conditions were successful.

(7) Every attempt to employ different leaving groups failed too.

(8) (a) Hirai, Y.; Terada, T.; Amemiya, Y.; Momose, T. *Tetrahedron Lett.* **1992**, *33*, 7893−7894. (b) Hirai, Y.; Watanabe, J.; Nozaki, T.; Yokoyama, H.; Yamaguchi, S. *J. Org. Chem.* **1997**, *62*, 776−777. (c) Hirai, Y.; Shibuya, K.; Fukuda, Y.; Yokoyama, H.; Yamaguchi, S. *Chem. Lett.* **1997**, 221−222. (d) Yokoyama, H.; Otaya, K.; Yamaguchi, S.; Hirai, Y. *Tetrahedron Lett.* **1998**, *39*, 5971−5974. (e) Yokoyama, H.; Otaya, K.; Kobayashi, H.; Miyazawa, M.; Yamaguchi, S.; Hirai, Y. *Org. Lett.* **2000**, *2*, 2427−2429. (f) Lei, A.; Liu, G.; Lu, X. *J. Org. Chem.* **2002**, *67*, 974−980. (g) Makabe, H.; Kong, L. K.; Hirota, M. *Org. Lett.* **2003**, *5*, 27−29. (h) Eustache, J.; Van de Weghe, P.; Le Nouen, D.; Uyehara, H.; Kabuto, C.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4043−4053.

(9) Hirai, Y.; Nagatsu, M. *Chem. Lett.* **1994**, 21−22.

(10) Yokota, W.; Shindo, M.; Shishido, K. *Heterocycles* **2001**, *54*, 871−885.

(11) Harrington, P. J.; Hegedus, L. S.; McDaniel, K. F. *J. Am. Chem. Soc.* **1987**, *109*, 4335−4338.

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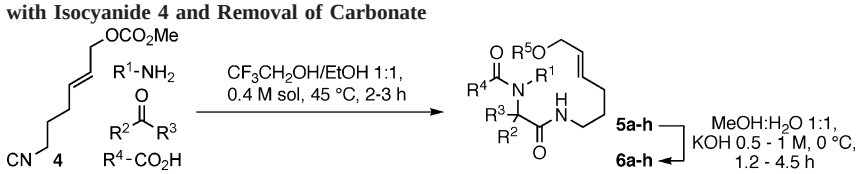
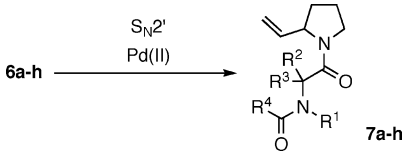
TABLE 1. Ugi Reaction with Isocyanide 4 and Removal of Carbonate



					isolated yield	
entry	R^1	R^2	R^3	R^4	**5** ($R^5 = CO_2Me$)[a,b]	**6** ($R^5 = H$)
1[c]	CH_2Ph	Ph	H	Et	**5a**: 100	**6a**: 100
2	Ph	Ph	H	Et	**5b**: 73 (80)	**6b**: 98
3	CH_2Ph	H	H	Et	**5c**: 94	**6c**: 92
4[d]	CH_2Ph	*i*-Pr	H	CH_2NHBoc	**5d**: 86	**6d**: 85
5[d]	*n*-Bu	*i*-Pr	H	Ph	**5e**: 99	**6e**: 94
6[d]	*n*-Bu	*t*-Bu	H	Ph	**5f**: 79 (92)	**6f**: 99
7[d]	*n*-Bu	*o*-(OMe)-C_6H_4	H	$CH_2CH_2CH_2Ph$	**5g**: 88	**6g**: 85
8[c]	CH_2Ph	Me	Me	Et	**5h**: 100	**6h**: 100

[a] Based on the isocyanide. [b] The yield based on recovered **4** is given in parentheses. [c] Imine was preformed. [d] The reaction was run in the presence of 4 Å molecular sieves.

TABLE 2. S_N2' Reaction Promoted by Pd(II)



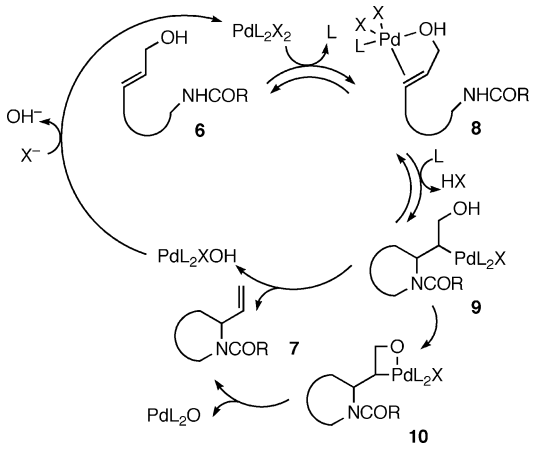
entry	substrate (product)	catalyst[a,b]	time (h)	yield (%)[c]	dr[d]
1	**6a** (**7a**)	$PdCl_2$[e]	118	47 (68)	35:65[h]
2	**6a** (**7a**)	$PdCl_2(PhCN)_2$[f]	24	65 (67)	37:63[h]
3	**6a** (**7a**)	$PdCl_2(MeCN)$[f]	30.6	71 (80)	29:71[h]
4	**6a** (**7a**)	$PdCl_2(MeCN)_2$[g]	2.2	77 (89)	35:65[h]
5	**6b** (**7b**)	$PdCl_2(MeCN)_2$[g]	3	75	29:71[h]
6	**6c** (**7c**)	$PdCl_2(MeCN)_2$[g]	5.5	67 (80)	
7	**6d** (**7d**)	$PdCl_2(MeCN)_2$[g]	6.2	36 (45)	73:27[i]
8	**6e** (**7e**)	$PdCl_2(MeCN)_2$[g]	20.3	27 (37)	38:62[h]
9	**6f** (**7f**)	$PdCl_2(MeCN)_2$[g]	5.7	40 (52)	62:38[h]
10	**6g** (**7g**)	$PdCl_2(MeCN)_2$[g]	3.2	58	87:13[i]
11	**6h** (**7h**)	$PdCl_2(MeCN)_2$[e]	20		

[a] 30% with respect to **5**. [b] All reactions were run in the presence of 4 Å molecular sieves in THF (entries 2−11) or MeCN (entry 1). [c] The yield based on recovered starting material is given in parentheses. [d] Diastereoisomer with minor t_R was reported first. [e] Room temperature (71 h, entry 1; 5 h, entry 11), then reflux (47 h, entry 1; 15 h, entry 11). [f] Room temperature. [g] Reflux. [h] By GC-MS. [i] By HPLC.

in entry 2, Table 2. Then we explored different catalysts. The cheaper $PdCl_2$ gave unsatisfactory results (entry 1), while the more expensive $PdCl_2(MeCN)_2$ (entries 3 and 4) was shown to be the best. Actually, on **6a** this catalyst afforded **7a** in slightly better yield (see entries 2 and 3) and the reaction time and yield were even improved when the cyclization was run at reflux, instead of rt (entry 4). In all cases, however, the diastereomeric ratio was only poor.

Even if detailed studies on the mechanism of this reaction have not been reported, a possible catalytic cycle, based upon experimental findings, is reported in Scheme 2. After an activating complexation of the alkene **6** with Pd(II), a completely regioselective addition of the nucleophile takes place to give **9**. The transformation into the final product is ensured by a β-elimination step from the β-hydroxy organopalladium intermediate **9**, affording a palladium hydroxide that can enter again the catalytic cycle after a suitable ligand exchange. Also an alternative syn elimination from the intermediate palladaoxabutane **10**, as previously reported,[12] cannot be excluded. The possible elimination of palladium hydride does not occur.

SCHEME 2. Proposed Mechanism for the Pd(II) Cyclization



In that case Pd(II) would be converted into Pd(0) at the end of the cycle and so the addition of a cooxidant to the reaction would be necessary; moreover the structure of the products would be an aldehyde and not a terminal alkene.

At least 30% catalyst was necessary for an appreciable rate and this seems consistent with a rapid pre-equilibrium during the cyclization, followed by a slow β-elimination.

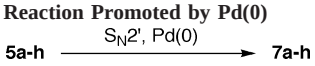
Also a certain passivating effect on the catalyst was observed and this may be responsible for the usually incomplete transformation of the substrate **6** into **7**. Addition of a stoichiometric oxidant (*p*-benzoquinone) or working under air instead of argon atmosphere led to inferior yields. Moreover, when the Pd(II) was employed in a stoichiometric amount, an improvement of the rate, but not of the yield, was observed, in accord with a catalytic reaction with a low turnover number.

We then studied the scope of the reaction on other Ugi adducts. With the exception of derivatives **6b**,**c** (entries 5 and 6), in all other cases the yields were only moderate, but in one case a remarkable diastereoselection was observed (entry 10).[13]

On the contrary alcohol **6h**, coming from an Ugi reaction employing acetone as carbonyl input, did not afford the desired

(12) Hacksell, U.; Daves, G. D, Jr. *Organometallics* **1983**, *2*, 772−775.

TABLE 3. S_N2' Reaction Promoted by Pd(0)



entry[a]	substrate (product)	time (h)	yield (%)[b]	overall yield from **4** (%)	dr[c]
1	**5a** (**7a**)	2	100	100	54:46[d]
2	**5b** (**7b**)	3.3	100	73	46:54[d]
3	**5c** (**7c**)	1.8	86	81	
4	**5d** (**7d**)	3	92	79	25:75[e]
5	**5e** (**7e**)	3	80 (85)	79	89:11[d]
6	**5f** (**7f**)	2	86	68	87:13[d]
7	**5g** (**7g**)	3	100	88	58:42[e]
8	**5h** (**7h**)	17.5			

[a] All reactions were run in the presence of 10% $Pd(PPh_3)_4$, 2 equiv (with respect to Pd(0)) of diphenyphosphinoethane (dppe), in MeCN at 60 °C. [b] The yield based on recovered starting material is given in parentheses. [c] Diastereoisomer with minor t_R was reported first. [d] By GC-MS. [e] By HPLC.

7h. We experienced a slow reacting rate and initially a new product, most likely **7h**, was observed in TLC. However, it did not increase with time and, upon bringing the reaction to completion, it disappeared completely, probably because of an hydrolytic cleavage of the pyrrolidine−CO bond. The resulting 2-vinylpyrrolidine and 2-(*N*-benzylpropionamido)-2-methylpropanoic acid have indeed been isolated.

This protocol, although well-suited for some secondary amides, was shown to be dramatically affected by the nature of groups R^1−R^4, thus limiting its scope. So we turned our attention to a different strategy. Although Pd(0)-catalyzed reactions are a well-known method for the intermolecular formation of N−C bonds exploiting an allylic carbonate,[14] there are, to the best of our knowledge, only very few examples of the intramolecular version involving amidic nitrogens as nucleophiles. One of them uses a highly functionalized α-ketoamide[15] as nucleophile and a carbonate as leaving group, whereas two other examples employ an oxazolidinone as nucleophile and a chloride as leaving group, in the absence[10] or in the presence[16] of an alkaline hydride, used to enhance the nucleophilicity of the N atom.

For our reaction, tested on carbonate **5a**, we used $Pd(PPh_3)_4$ in the presence of dppe, working in acetonitrile at 60 °C (Table 3). This time we experienced a complete, fast, and very clean reaction, isolating **7a** in quantitative yield (entry 1).[17] The same protocol on **5b**−**g** gave the expected products **7b**−**g** with excellent, and in some cases even quantitative, yield. In all examples employing branched aliphatic aldehydes as carbonyl inputs in the Ugi condensation, we observed a moderate to good stereoselectivity (entries 4−6), while aromatic aldehydes gave poor stereoselection (entries 1, 2, and 8). It should be noted that in previously reported highly stereoselective Pd-catalyzed cyclizations,[8,10,15,16] the inducing stereocenter was always located in the incoming heterocyclic ring, contrary to our present case.

Also in this case, while the reaction on Ugi products coming from aldehydes gave excellent results in the Pd(0)-mediated cyclization, the same strategy applied to **5h** did not work. This time the outcome of the reaction was different with respect to the Pd(II)-mediated cyclization. Actually, **5h** slowly reacted to give only a terminal conjugated diene (30−40% isolated yield, as a *E*/*Z* mixture referred to the internal double bond), arising from the formal elimination of $HOCO_2Me$. Most likely the cyclization of **5h** was prevented by steric reasons and so a competitive reaction occurred.

In this note we have reported the first example of an Ugi reaction followed by an intramolecular S_N2' cyclization, leading to a series of densely functionalized *N*-heterocycles. This protocol represents a further example of how secondary transformations can expand the scope of isocyanide-based multicomponent reactions. In this case the isocyanide derived secondary amide has been transformed into a tertiary one, converting at the same time the classical acyclic Ugi scaffold into a heterocyclic one.

Although compounds **7** could be in principle prepared by acylation of vinyl pyrrolidine with α-aminoacid derivatives followed by further acylation with synthetic equivalents of R^4-CO_2H, this alternative approach would be undoubtly longer and less convergent. Moreover it would be limited to easily accessible *N*-alkylated α-aminoacid derivatives. On the contrary, our procedure gives access, in a very short (2 steps), convergent, and high-yielding manner, to compounds **7** with the introduction of three diversity inputs R^1, R^2, and R^4, including also R^2 groups different from the ones typical of natural α-aminoacids.

The possible preparation of a family of isocyanide analogues to **4** will allow the introduction of a fourth diversity input, concerning either the substituents on the pyrrolidine or the ring size. The presence of stereogenic centers on the isocyanide may also be helpful for a better control of the stereoselectivity of the cyclization step.

Finally the mildness of the Pd(0) conditions will probably allow the easy introduction, on R^1, R^2, or R^4 groups, of further additional functionalities that, in combination with the vinyl moiety, could be exploited for the synthesis of bicyclic systems. Our results in this field will be reported in due course.

Experimental Section

General Procedure for the Ugi Reaction. A solution of isocyanide **4** (0.5−2 mmol) in dry EtOH/CF_3CH_2OH 1:1 (≈0.4 M solution) was treated with activated 4 Å powdered molecular sieves (25 mg/mmol of aldehyde) (entries 2 and 4−7, Table 1). Then aldehyde (1.5 equiv) and amine (1.65 equiv) (entries 2−7) or preformed imine (1.5 equiv) (entries 1 and 8) and carboxylic acid (1.2 equiv) were added. The reaction was stirred at 45 °C until complete (2−3 h). After filtration of the sieves (when required), the mixture was diluted with AcOEt and the organic layer was washed with saturated aq $NaHCO_3$ solution, dried, and concentrated in vacuo. The crude was purified by chromatography with the appropriate PE/AcOEt mixture.

Compound 5a: pale yellow oil, 100% yield. R_f 0.42 (PE/AcOEt 3:7, UV, molibdic reagent). Anal. found C 69.15, H 7.20, N 6.25; $C_{26}H_{32}N_2O_5$ requires C 69.01, H 7.13, N 6.19. IR ν_{max} 3431, 3000, 1744, 1641, 1447, 1270, 1067, 971, 940. GC-MS t_R 13.71; *m/z* 395 ($M^+ - 57$, 1.5), 291 (23), 280 (10), 252 (19), 215 (9.8), 197 (16), 196 (100), 162 (21), 118 (9.5), 106 (22), 98 (5.6), 92 (8.3), 91 (90), 65 (5.4), 57 (8.1). ^1H NMR ($CDCl_3$) δ 1.10 (3H, t, J = 7.4 Hz), 1.57 (2H,

(13) Diastereoisomers of **7** have been separated and independently fully characterized in some cases (**7a**,**b**,**g**). Diastereoisomers of **7d**,**e**,**f** could not be separated and therefore they have been characterized as a mixture, although an accurate determination of the diastereomeric ratio was always possible (see the Supporting Information).

(14) See, for example: Zumpe, F. L.; Kazmaier, U. *Synthesis* **1999**, 1785−1791 and references therein.

(15) Bulusu, M. A. R. C.; Waldstätten, P.; Tricotet, T.; Rochais, C.; Steck, A.; Bacher, M. *Tetrahedron Lett.* **2004**, *45*, 5833−5836.

(16) Takao, K.; Nigawara, Y.; Nishino, E.; Takagi, I.; Maeda, K.; Tadano, K.; Ogawa, S. *Tetrahedron* **1994**, *50*, 5681−5704.

(17) Working at a lower temperature required a noticeably longer reaction time and furnished **7a** with less satisfactory yield and no improvement with respect to the diastereomeric ratio.

center of m), 2.04 (2H, q, J = 7.0 Hz), 2.18−2.46 (2H, m), 3.25 (2H, center of m), 3.77 (3H, s), 4.52 (2H, d, J = 6.3 Hz), 4.55 and 4.73 (2H, AB system, J_{AB} = 19.0 Hz), 5.50−5.79 (2H, m), 5.90 (2H, two overlapped s), 6.99−7.35 (10H). ^{13}C NMR ($CDCl_3$) δ 9.2 (CH_3), 27.1 (CH_2), 28.3 (CH_2), 29.5 (CH_2), 39.0 (CH_2), 49.8 (CH_2), 54.6 (CH_3), 62.7 (CH), 68.3 (CH_2), 123.9, 125.9, 126.7, 128.2, 128.4, 128.6, 129.6, 135.8 (12C, CH), 135.1 (C), 137.6 (C), 155.5 (C), 169.8 (C), 175.6 (C).

General Procedure for Pd(II)-Promoted Cyclization (entries 3−11, Table 2). A solution of $PdCl_2(MeCN)_2$ (30% with respect to **6**) in dry THF (2 mL) was treated with activated 4 Å powdered molecular sieves (40% weight with respect to **6**) and the suspension was carefully degassed and kept under Ar. The alcohol **6** (200−300 μmol), dissolved in dry THF (6 mL), was added and the reaction was stirred at rt (entry 3) or refluxed (entries 4−11) for the appropriate time. The sieves were filtered and the reaction was diluted with water and extracted with AcOEt. After drying and solvent removal the crude was purified by chromatography with the appropriate PE/AcOEt mixture to give **7**.

General Procedure for Pd(PPh$_3$)$_4$-Promoted Cyclization. A solution of carbonate **5** (150−200 μmol) in dry MeCN (5 mL) was carefully degassed and kept under Ar. Then dppe (20% with respect to **5**) and $Pd(PPh_3)_4$ (10%) were added and the reaction was stirred at 60 °C until complete. The solution was diluted with water and extracted with AcOEt. After drying and solvent removal the crude was purified by chromatography with the appropriate PE/AcOEt mixture to give **7**.

Compound 7a: 77% (89% on recovered starting material) [Pd(II)] and 100% [Pd(0)] yield. Anal. found C 76.25, H 7.45, N 7.45; $C_{24}H_{28}N_2O_2$ requires C 76.56, H 7.50, N 7.44. Dr (see Table 2 for values) by GC-MS [differences with respect to the usual method (see the Supporting Information: final temperature = 230 °C, final time = 7 min, then to 290 °C in 40 deg/min and final time = 0); t_R 13.99 (**7aF** = faster running in TLC) and 14.30 (**7aS** = slower running in TLC) min]. **7aF**: pale yellow oil. R_f 0.45 (PE/AcOEt 1:9, UV, molibdic reagent). At rt: 56:44 mixture of rotamers (C*H*Ph signal in ^{1}H NMR; M = major, m = minor); at 120 °C one rotamer, but most signals are very broad. IR ν_{max} 3417, 3060, 1635, 1410, 1169, 1075, 717. GC-MS t_R 13.99; *m/z* 319 (M^+ − 57, 0.91), 252 (7.3), 216 (7.3), 215 (49), 214 (8.3), 197 (11), 196 (70), 124 (8.1), 118 (8.7), 106 (5.4), 98 (5.2), 96 (5.6), 92 (8.6), 91 (100), 90 (6.6), 81 (7.7), 65 (8.0), 57 (10), 41 (5.2). ^{1}H NMR (DMSO-d_6, temperature = 120 °C) δ 1.02 (3H, t, J = 7.5 Hz), 1.66−1.91 (4H, m), 2.20−2.38 (2H, m), 3.11 (1H, apparent br d, J = 6.0 Hz), 3.47 (1H, br s), 4.67 (3H, apparent asymmetric s), 4.99 (1H, d, J = 10.5 Hz), 5.08 (1H, d, J = 17.1 Hz), 5.77 (1H, ddd, J = 17.1, 10.2, 5.7 Hz), 6.34 [1H, br s; at rt 2 clearly prevailing signals in 56:44 ratio at 6.38 (s) and 6.51 (s), respectively], 6.99−7.28 (10H, m). ^{13}C NMR (DMSO-d_6) δ 9.16 (m) and 9.24 (M) (CH_3), 20.9 (M) and 22.7 (m) (CH_2), 26.0 (*M*) and 26.4 (m) (CH_2), 29.6 (m) and 31.6 (M) (CH_2), 45.6 (m) and 45.8 (M) (CH_2), 47.6 (M) and 48.1 (m) (CH_2), 57.0 (M) and 60.2 (m) (CH), 58.4 (m) and 59.0 (M) (CH), 113.9 (m) and 114.7 (M) (CH_2), 125.3, 125.6, 126.2, 126.4, 126.6, 126.8, 127.2, 127.8, 128.0, 128.16, 128.23, 128.4, 129.5, 129.9 (10C, CH), 133.7, 136.3 and 138.2 (2C, C), 137.3 (m) and 138.8 (M) (CH), 167.87 (M) and 167.93 (m) (C), 174.4 (m) and 174.6 (M) (C). **7aS**: white solid. Mp 80.1−82.5 °C. R_f 0.31 (PE/AcOEt 1:9, UV, molibdic reagent). At rt 64:36 mixture of two highly prevailing rotamers (^{13}C NMR); at 120 °C one rotamer, but almost all very broad signals (^{1}H NMR). IR ν_{max} 3430, 3018, 2967, 1632, 1411, 1072, 1048, 790. GC-MS t_R 14.30; 319 (M^+ − 57, 1.8), 252 (8.9), 216 (7.2), 215 (49), 214 (7.8), 197 (13), 196 (77), 124 (8.1), 118 (8.1), 106 (5.2), 92 (7.9), 91 (100), 90 (6.0), 81 (8.2), 65 (7.4), 57 (10). ^{1}H NMR (DMSO-d_6, temperature = 120 °C): δ 1.01 (3H, t, J = 7.4 Hz), 1.65−1.92 (4H, m), 2.19 (1H, center of m), 2.34 (1H, center of m), 3.07−3.38 (1H, m), 3.60 (1H, center of m), 4.48−4.78 (3H, m), 4.97−5.07 (2H, m), 5.76−5.90 (1H, m), 6.28 (1H, br s), 6.92−7.26 (10H, m). ^{13}C NMR (DMSO-d_6) (only the signals of the two highly prevailing rotamers are reported): δ 9.2 (CH_3), 20.9 (m) and 23.0 (M) (CH_2), 26.3 (M) and 26.5 (m) (CH_2), 29.4 (M) and 32.0 (m) (CH_2), 45.8 (M) and 46.2 (m) (CH_2), 47.9 (M) and 48.4 (m) (CH_2), 57.9 (M) and 60.3 (m) (CH), 58.2 (m) and 59.6 (M) (CH), 113.6 (M) and 115.4 (m) (CH_2), 125.5, 126.1, 126.2, 127.8, 127.9, 128.18, 128.25, 128.4, 128.7, 128.9, 129.6, 129.9 (10C, CH), 134.1 (m) and 134.2 (M) (C), 137.4 (m) and 137.8 (M) (CH), 138.6 (M) and 138.8 (m) (C), 168.0 (M) and 168.6 (m) (C), 174.3 (M) and 174.4 (m) (C).

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Supporting Information Available: Full experimental procedures (including additional data for the Pd(II)-catalyzed protocol) and characterization data for all compounds not already described (compounds **1**−**4**, **5b**−**h**, **6a**−**h**, **7b**−**g**). This material is available free of charge via the Internet at http://pubs.acs.org.

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