Tetrahedron 66 (2010) 6133–6137

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

On the scope of Pd-catalyzed carboamination reactions—synthesis of 2,4-disubstituted pyrrolidines and 2-substituted piperidines and morpholines

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ARTICLE INFO

Article history:
Received 15 February 2010
Received in revised form 7 May 2010
Accepted 1 June 2010
Available online 9 June 2010

Keywords:
Carboamination
Diastereoselectivity
Morpholine
Piperidine
Pyrrolidine

ABSTRACT

The scope of the palladium-catalyzed carboamination reaction for the synthesis of 2-substituted pyrrolidines, piperidines, and morpholines was investigated. Formation of a 2,4-disubstituted pyrrolidine proceeded in high yield but with a diastereoisomeric ratio of only 2:5, favoring the *cis*-isomer. The diastereoselectivity is hence significantly smaller than that observed previously in the formation of 2,3- and 2,5-disubstituted pyrrolidines. The yields of substituted piperidines and morpholines were lowered by competing Heck arylation reactions. Both the *N*-substituent and the choice of phosphine ligand for the palladium-catalyzed reaction were determining for the outcome.

1. Introduction

Numerous biologically active molecules incorporate a framework of substituted pyrrolidines, piperidines, and morpholines.[1] These heterocyclic compounds are often used as drug targets, and development of new ways for their synthesis and functionalization is therefore of significant interest. There are two general methods of functionalizing these aliphatic heterocycles. The first method is direct functionalization of the parent heterocycle. This approach is neither very easy nor very stereoselective, and a more convenient method is the intramolecular cyclization of a suitably functionalized aliphatic chain. Several methods for C–N forming intramolecular reactions are found in literature,[2] but often they require harsh reaction conditions or lack the opportunity for further functionalization of the molecule. Few methods exist that allow a simultaneous intramolecular C–N bond formation and an intermolecular C–C bond formation in the 2-position of the heterocycle.[3]

Wolfe and co-workers have developed an efficient method of synthesizing 2-substituted pyrrolidines,[4] piperazines,[5] and morpholines[6] via palladium-catalyzed carboamination. This reaction is particularly attractive because it proceeds under relatively mild reaction conditions and because biologically active molecules often contain substituents in the 2-position of the heterocycle. *N*-Protected 2,3- and 2,5-disubstituted pyrrolidines were prepared with excellent diastereoselectivities of dr >1:20 corresponding to *trans*-2,3-pyrrolidines and *cis*-2,5-pyrrolidines as the favored products.[4a] In addition, Wolfe and Bertrand[4a] have reported one example of formation of a 2,4-disubstituted pyrrolidine, for which an unspecified (in regard to cis/trans isomers) diastereoselectivity of dr=1:3 was observed. Michael and Cochran[7] have prepared 2,4-disubstituted pyrrolidines in cis/trans ratios of 7:3, but the exact carboamination conditions were different from those of Wolfe and co-workers.

We became interested in further investigating the diastereoselective synthesis of *N*-protected 2,4-disubstituted pyrrolidines by carboamination of suitable γ-aminoalkenes.[8] Further, we present here the synthesis of *N*-substituted 2-benzylpiperidines and 2-benzylmorpholines via the carboamination protocol. It should be noted that an alternative palladium-catalyzed carboamination reaction between aminoalkenes and unactivated arenes (i.e., without a halide group) promoted by *N*-fluorobenzenesulfonimide was recently reported by Michael and co-workers.[9] In fact, halobenzenes were also subjected to this method without breaking the aryl–halide bond.

2. Results and discussion

2.1. Synthesis of pyrrolidines

Using the method of Wolfe, a Pd-catalyzed carboamination reaction between *p*-bromoanisole and (pent-4-enyl) carbamic acid

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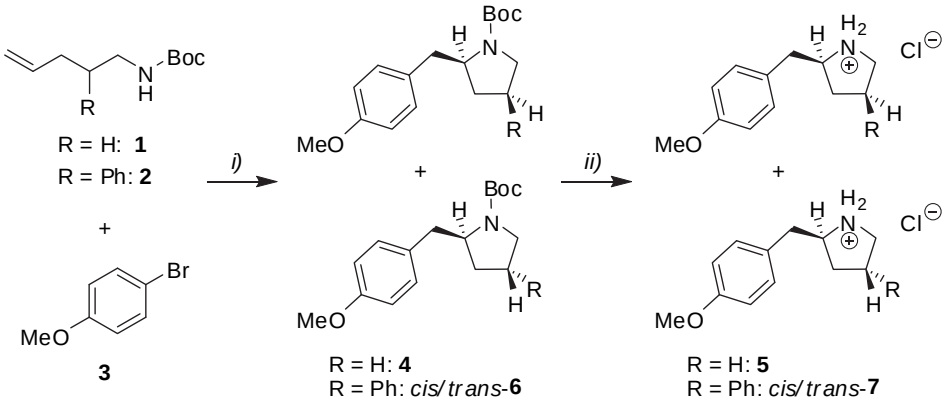
0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.06.004

tert-butyl ester (**1**[4a]) in the presence of the phosphine bis(2-diphenylphosphinophenyl) ether (dpe-phos) furnished quantitatively 2-(*p*-methoxybenzyl)pyrrolidine-1-yl-carboxylic acid *tert*-butyl ester (**4**) (Scheme 1, Table 1—entry 1). The Boc-protected compound **4** was subsequently deprotected using HCl in methanol, generating the ammonium salt **5** in a yield of 70% (Scheme 1). Changing the phosphine ligand to the racemic 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP, entry 2) provided a significantly lower yield of **4**. The chiral nature of BINAP was found to play no role for the stereochemical outcome; thus, with (*R*)-BINAP the same 1:1 racemic mixture of **4** was obtained (entry 3).



Scheme 1. Conditions: (i) $Pd_2(dba)_3$, NaO*t*-Bu, phosphine ligand (Table 1), toluene, 105 °C, 15 h; (ii) HCl, MeOH. dba=dibenzylidene acetone.

Table 1
Products from carboamination of precursors **1** and **2**

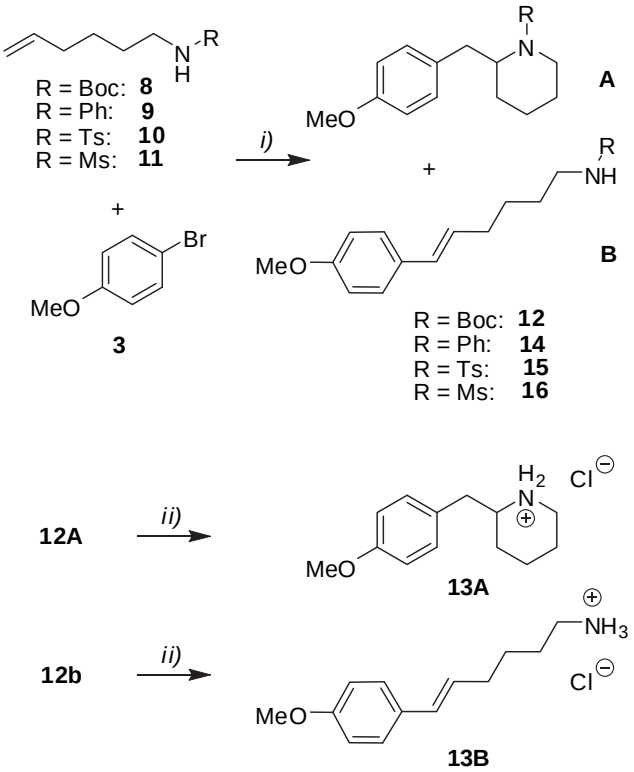
Entry	R	Ligand[a]	Conversion[b] (%)	Product	Yield[b] (Isolated)
1	H	dpe-phos	100	**4**	100% (99%)
2	H	BINAP	70	**4**	70% (45%[c])
3	H	(*R*)-BINAP	69	**4**	69% (45%[c])
4	Ph	dpe-phos	100	*cis*/*trans*-**6**	100% (93%) 71%[d] 29%[d]
				cis-**6** *trans*-**6**	

[a] dpe-phos (2 mol %)=bis(2-diphenylphosphinophenyl) ether, 2 mol % BINAP=2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.
[b] According to LC-MS.
[c] Racemic mixture (1:1).
[d] The ratio between *cis*-**6** and *trans*-**6** was evaluated after Boc deprotection and isolation of pure *cis*-**7** and *trans*-**7**.

The next objective was to elucidate the stereochemistry in the formation of *N*-protected 2,4-disubstituted pyrrolidines. Subjecting (2-phenylpent-4-enyl) carbamic acid *tert*-butyl ester (**2**[7]) to the carboamination reaction provided *cis*/*trans*-2-(*p*-methoxybenzyl)-4-phenylpyrrolidine-1-yl-carboxylic acid *tert*-butyl ester (*cis*/*trans*-**6**) (Scheme 1, Table 1—entry 4). A 100% conversion was observed by LC-MS, and a total yield of 93% of the two diastereoisomers was isolated. Deprotection of the mixture of *cis*/*trans*-**6** using HCl in methanol gave the two diastereoisomeric ammonium salts *cis*-**7** and *trans*-**7** in an overall yield of 83% (Scheme 1). According to ^{1}H NMR spectroscopy as well as analytical HPLC using a chiral column, the two isomers were present in a ratio of 29:71 ≈2:5. Fortunately, these salts could be separated by preparative Supercritical Fluid Chromatography (SFC) using a chiral column (eluent: 0.5% diethylamine in ethanol), and the stereochemistry was determined by 2D NOESY NMR. The isomer *trans*-**7** was isolated in a yield of 14%, while *cis*-**7** was isolated in a yield of 29%. Thus, the *cis*-isomer was isolated in majority, and the carboamination reaction forming *cis*/*trans*-**6** can now be characterized by a dr of 2:5 in favor of the cis-isomer. The diastereoisomer selectivity for formation of 2,4-disubstituted pyrrolidines is therefore significantly smaller than that for formation of 2,3- and the 2,5-disubstituted pyrrolidines. The ratio obtained is similar to the one reported by Wolfe and Bertrand[4a] for the formation of 2-benzyl-4-allylpyrrolidine (dr=1:3). Yet, the preferred stereoisomer (cis or trans) was not determined in this previous work.

2.2. Synthesis of piperidines

In order to develop a method for synthesizing *N*-protected 2-substituted piperidines, the reaction conditions were screened and different N-protective groups were used, such as Boc, phenyl, tosyl, and mesyl according to the reactants **8**,[7] **9**,[10] **10**,[11] and **11** (prepared by treating **10** with $MsNH_2$ and NaH in DMSO) (Scheme 2, Table 2). Generally the piperidine synthesis was complicated on account of a competing Heck reaction.[12] The monodentate phosphine ligand P(2-furyl)$_3$ was the best choice of ligand for accomplishing the piperidine. It was not possible to convert the Boc-protected precursor **8** by using the bidentate ligand dpe-phos (entry 1), but with use of



Scheme 2. Conditions: (i) $Pd_2(dba)_3$, NaO*t*-Bu, phosphine ligand (Table 2), toluene, 105 °C, 15 h; (ii) HCl, MeOH. dba=dibenzylidene acetone.

Table 2
Products from carboamination of precursors **8**-**11**

Entry	R	Ligand[a]	Conversion (%)	Product	Yield[b] (Isolated)	
					A	B
1	Boc	dpe-phos	0	**12**	—	—
2	Boc	P(2-furyl)$_3$	50	**12**	24% (13%)	26% (9%)
3	Boc	P(2-furyl)$_3$	6[c]	**12**	35% (17%)	30%
4	Ph	P(2-furyl)$_3$	80	**14**	75% (51%)	0%
5	Ts	dpe-phos[d]	10	**15**	0%	100%
6	Ts	P(2-furyl)$_3$	70	**15**	0%	70% (41%)
7	Ms	dpe-phos or P(2-furyl)$_3$	0%	**16**	—	—

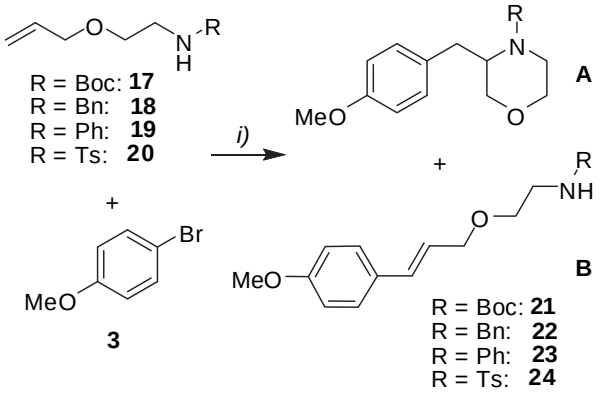
[a] dpe-phos (2 mol %)=bis(2-diphenylphosphinophenyl) ether, 8 mol % P(2-furyl)$_3$=tris(2-furyl)phosphine.
[b] According to LC-MS.
[c] $Pd(OAc)_2$ was used instead of $Pd_2(dba)_3$.
[d] dpe-phos (4 mol %) was used instead of 2 mol %.

P(2-furyl)$_3$ (entries 2 and 3) it was possible to obtain 35% of the piperidine **12A** according to LC-MS. The *N*-Boc-protected compounds **12A** and **12B** (Heck product) were deprotected using HCl in methanol, and the products **13A** and **13B** were isolated in yields of 78% and 81%, respectively (Scheme 2).

Carboamination of the *N*-phenyl-substituted substrate **9** gave an LC-MS based yield of 75% of the *N*-phenyl-substituted piperidine **14A** (entry 4). When the N-protecting group was changed to a tosyl group (compound **10**), a 70–100% conversion of the starting material was observed (entries 5 and 6). Yet, only the Heck product **15B** was now obtained. Subjecting instead the *N*-mesyl precursor **11** to the reaction conditions resulted in no conversion; neither **16A** nor **16B** was formed no matter the choice of phosphine ligand (entry 7).

2.3. Synthesis of morpholines

Finally, we turned to the synthesis of *N*-protected 2-substituted morpholines from precursors **17**,[13] **18**,[14] **19** (prepared from 2-anilinoethanol, allylbromide, NaH, and Bu_4NI in THF), and **20** (prepared by tosylation of the corresponding amine[13]) (Scheme 3, Table 3). Attempts of synthesizing the *N*-Boc-protected morpholine **21** (entry 1) and *N*-benzyl-protected morpholine **22** (entry 2) failed, with no conversion of the starting material. In contrast, the *N*-phenyl-



Scheme 3. Conditions: (i) $Pd_2(dba)_3$, NaO*t*-Bu, phosphine ligand (Table 3), toluene, 105 °C, 15 h. dba=dibenzylidene acetone.

substituted morpholine **23A** was successfully obtained in almost quantitative yield (entry 3). Conversion of *N*-aryl precursors to morpholines by the carboamination reaction was also very recently reported in parallel work by Wolfe and co-workers.[6] In the same paper, efforts to couple an *N*-Boc-protected substrate with 1-bromo-4-*tert*-butylbenzene are mentioned to afford only Heck

Table 3
Products from carboamination of precursors **17**–**20**

Entry	R	Ligand[a]	Conversion (%)	Product	Yield[b] (Isolated)	
					A	B
1	Boc	dpe-phos[c] or P(2-furyl)$_3$	0	**21**	—	—
2	Bn	P(2-furyl)$_3$	0	**22**	—	—
3	Ph	P(2-furyl)$_3$	100	**23**	100% (69%)	0%
4	Ts	P(2-furyl)$_3$	100	**24**	0%	95% (39%)

[a] dpe-phos (2 mol %)=bis(2-diphenylphosphinophenyl) ether, 8 mol % P(2-furyl)$_3$=tris(2-furyl)phosphine.
[b] According to LC-MS.
[c] Using either 2 or 4 mol % dpe-phos.

arylation. We also attempted to prepare the *N*-tosyl-protected morpholine **24A**, but the conditions gave instead 95% of the Heck product **24B** (entry 4) according to LC-MS analysis. In addition, 5% of a product corresponding to two subsequent Heck reactions was observed. Changing the solvent from toluene to dioxane resulted in an increase of two-fold Heck arylation products to 31% (using dpe-phos). Using Cs_2CO_3 instead of NaO*t*-Bu as base still only gave Heck coupling products.

3. Conclusions

In conclusion, we have found that 2,4-disubstituted pyrrolidines are formed from an *N*-Boc-protected precursor in a diastereoisomeric *trans/cis* ratio of 2:5 via the palladium-catalyzed carboamination route. The diastereoselectivity is hence significantly smaller than that observed previously[4a] in the formation of 2,3- and 2,5-disubstituted pyrrolidines (Fig. 1). The phosphine ligand dpe-phos was superior to BINAP in the pyrrolidine synthesis. The carboamination reaction was successfully extended to the synthesis of 2-substituted *N*-phenylpiperidines and *N*-phenylmorpholines. In contrast, it was not possible to obtain 2-substituted *N*-Boc-morpholines, while we managed to prepare 2-substituted *N*-Boc-piperidines by changing the phosphine ligand from dpe-phos to P(2-furyl)$_3$, the yields were only moderate owing to competing Heck arylation. The Heck arylation products completely dominated in efforts to prepare *N*-tosyl-substituted piperidines and morpholines.

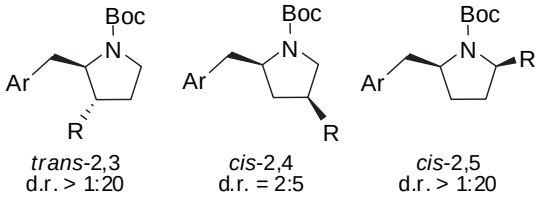


Figure 1. Summary of the diastereoselectivity in pyrrolidine formation by palladium-catalyzed carboamination (favored products are shown), including the work of Wolfe[4a]

4. Experimental

4.1. General experimental procedures

Chemicals were purchased from Aldrich, Across, Merck, or Fluka and used without further purification. Carboamination reactions were carried out under an argon atmosphere in dried glassware and using dry HPLC grade solvent. NMR spectra were recorded at either a 500 MHz Bruker Spectrospin instrument or a 600 MHz Bruker Ultrashield 600 Plus instrument, and deuterated solvents from Cambridge Isotope Labs and Aldrich were used. Proton chemical shifts are reported in parts per million with TMS as an

internal reference, and carbon chemical shifts are reported in parts per million relative to chemical shifts for the deuterated solvents ($CDCl_3$: 77.16 ppm, DMSO-d_6: 39.52 ppm). Stereochemistry was assigned on the basis of ^{1}H NMR and 2D COSY experiments, as well as APT, HSQC/HMBC, and 2D NOESY experiments. All reactions were analyzed by LC-MS and TLC (Merck 5554), and the ratios of the regioisomers, enantiomers and diastereoisomers were determined by LC-MS with either a reversed phase column or a chiral column. LC-MS data were obtained from a UPLC equipped with an ESI mass spectrometer and UV- and ELSD-detectors. The system consists of an API300ex instrument with a Waters Acuity UPLC system and an APPI ion source (ESI). Column chromatography was used for purification of the products, using Merck silica gel (0.040–0.063 mm) as the stationary phase. Diastereoisomers were separated by Supercritical Fluid Chromatography (SFC) using a chiral column. Melting points were determined on a Büchi apparatus and are uncorrected. Elemental analyses were performed at the Department of Chemistry, University of Copenhagen.

4.2. General procedure for carboamination reactions

A Schlenk tube was dried with a heat gun under an argon atmosphere. Dry solvent (usually toluene) was added and degassed under an argon atmosphere. The Pd-source ($Pd(OAc)_2$ (2 mol %) or $Pd_2(dba)_3$ (1 mol % complex, 2 mol % Pd)) was added along with either a monodentate phosphine ligand (4 mol % or 8 mol %) or a bidentate phosphine ligand (2 mol % or 4 mol %). Then *p*-bromoanisole (1.2 M equiv), an aminoalkene (1.0 M equiv), and a base consisting of NaO*t*-Bu (1.2 M equiv) or Cs_2CO_3 (2.3 M equiv) were added. The mixture was degassed under an argon atmosphere, whereafter the tube was sealed and stirred at 105 °C for 15 h. The reaction mixture was analyzed by LC-MS and TLC, and then quenched with a saturated aqueous solution of NH_4Cl (50 mL). The toluene layer was separated, and the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered through a short column of silica gel. The solution was concentrated in vacuo to a brownish oil that was purified further using column chromatography on silica gel.

4.3. 2-(*p*-Methoxybenzyl)pyrrolidinium chloride (5)

4.3.1. Carboamination. Pd-source: 1% $Pd_2(dba)_3$; Phosphine ligand: 2% dpe-phos. According to the general procedure, *p*-bromoanisole (2.24 g, 12.0 mmol) was treated with **1** (1.85 g, 10.0 mmol), $Pd_2(dba)_3$ (92.0 mg, 0.100 mmol), dpe-phos (108 mg, 0.200 mmol), and NaO*t*-Bu (1.15 g, 12.0 mmol) in toluene (50 mL). LC-MS of the mixture indicated quantitative conversion to the product **4** that was isolated as a yellow oil (R_f=0.53; 30% EtOAc/heptane). Yield: 2.87 g (99%); LC-MS yield: 100%. LC-MS: RT (UV-detector): 3.14 min, *m*/*z*=191.7 [MH^+-Boc]. *Boc deprotection*: MeOH (50 mL) was poured into a flask and HCl was bubbled through with cooling, generating a saturated solution of HCl in MeOH. Compound **4** (2.87 g, 9.85 mmol) was dissolved in the solution. After stirring for 60 min at rt, the mixture was concentrated in vacuo to a yellow oil. Recrystallization from acetone/diethyl ether gave the salt **5** as a white solid (R_f=0.31; NEt_3/MeOH/EtOAc 5:10:85). Yield: 1.56 g (70%). Mp 50–53 °C. LC-MS: RT (UV-detector): 1.37 min, *m*/*z*=191.9 [M−Cl]$^+$. ^{1}H NMR (600 MHz, DMSO-d_6): δ=9.43 (s, 1H), 9.34 (s, 1H), 7.24 (d, *J*=8.6 Hz, 2H), 6.90 (d, *J*=8.6 Hz, 2H), 3.73 (s, 3H), 3.63–3.51 (m, 1H), 3.20 (m, 1H), 3.12–3.07 (m, 1H), 3.08–3.02 (m, 1H), 2.85 (m, 1H), 2.00–1.93 (m, 1H), 1.94–1.88 (m, 1H), 1.87–1.77 (m, 1H), 1.63–1.54 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ=158.6, 130.5, 129.7, 114.5, 61.2, 55.5, 44.5, 36.6, 29.9, 23.2. Anal. Calcd for $C_{12}H_{18}ClNO$: C, 63.29; H, 7.97; N, 6.15. Found: 62.94; H, 7.96; N, 6.15.

4.4. *cis*/*trans*-2-(*p*-Methoxybenzyl)-4-phenylpyrrolidinium chloride (*cis*/*trans*-7)

4.4.1. Carboamination. Pd-source: 1% $Pd_2(dba)_3$, Phosphine ligand: 2% dpe-phos. According to the general procedure, *p*-bromoanisole (1.12 g, 6.00 mmol) was treated with **2** (1.31 g, 5.00 mmol), $Pd_2(dba)_3$ (45.8 mg, 0.0500 mmol), dpe-phos (53.8 mg, 0.100 mmol), and NaO*t*-Bu (0.56 g, 6.00 mmol) in toluene (30 mL). Yield of *cis*/*trans*-**6** (R_f=0.58; 30% EtOAc/heptane): 1.71 g (93%); LC-MS yield: 100%. LC-MS: RT (UV-detector): 1.02 min, *m*/*z*=268.1 [MH^+−Boc]. *Boc deprotection*: According to the procedure described above, *cis*/*trans*-**6** (1.18 g, 3.21 mmol) was dissolved in a saturated solution of HCl in MeOH. The product precipitated as white flakes as a mixture of the two diastereoisomers in the ratio (cis/trans)=5:2, judged by LC-MS and NMR. Yield: 0.80 g (83%). The two diastereoisomers were separated by preparative Supercritical Fluid Chromatography (SFC) using a chiral column (eluent: 0.5% diethylamine in ethanol, flow: 3 mL/min, UV: 230 nm, temp 40 °C).

Compound *trans*-**7** (R_f=0.38; NEt_3/MeOH/EtOAc 5:10:85): Yield: 130 mg (14%). Mp 49–51 °C. LC-MS: RT (UV-detector): 1.95 min, *m*/*z*=268.2 [M−Cl]$^+$. ^{1}H NMR (600 MHz, DMSO-d_6): δ=9.75 (s, 2H), 7.35 (m, 4H), 7.30 (d, *J*=8.1 Hz, 2H), 7.25 (m, 1H), 6.91 (d, *J*=8.1 Hz, 2H), 3.93 (m, 1H), 3.73 (s, 3H), 3.71 (m, 1H), 3.67 (m, 1H), 3.14 (m, 1H), 3.11 (m, 1H), 2.93 (m, 1H), 2.15 (m, 1H), 2.01 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ=158.6, 141.3, 130.6, 129.6, 129.1, 127.8, 127.4, 114.5, 60.7, 55.5, 50.7, 41.3, 37.2, 36.9. Anal. Calcd for $C_{18}H_{22}ClNO$: C, 71.16; H, 7.30; N, 4.61. Found: C, 71.09; H, 7.35; N, 4.60.

Compound *cis*-**7** (R_f=0.38; NEt_3/MeOH/EtOAc 5:10:85) Yield: 280 mg (29%). Mp 50–52 °C. LC-MS: RT (UV-detector): 1.93 min, *m*/*z*=268.1 [M−Cl]$^+$. ^{1}H NMR (600 MHz, DMSO-d_6) δ=9.87 (s, 1H), 9.64 (s, 1H), 7.39 (m, 2H), 7.35 (m, 2H), 7.28 (d, *J*=8.2 Hz, 2H), 7.26 (m, 1H), 6.91 (d, *J*=8.2 Hz, 2H), 3.77 (m, 1H), 3.74 (s, 3H), 3.59 (m, 1H), 3.49 (m, 1H), 3.24 (m, 1H), 3.19 (m, 1H), 3.02 (m, 1H), 2.30 (m, 1H), 1.83 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6) δ=158.6, 140.7, 130.5, 129.6, 129.1, 127.8, 127.5, 114.5, 61.9, 55.5, 50.1, 42.6, 39.4, 36.6. Anal. Calcd for $C_{18}H_{22}ClNO$: C, 71.16; H, 7.30; N, 4.61. Found: C, 71.11; H, 7.36; N, 4.59.

4.5. 2-(*p*-Methoxybenzyl)piperidinium chloride (13A) and 6-(*p*-Methoxyphenyl)-hex-5-en-1-ammonium chloride (13B)

4.5.1. Carboamination. Pd-source: 1% $Pd_2(dba)_3$, Phosphine ligand: 8% P(2-furyl)$_3$. According to the general procedure, *p*-bromoanisole (1.12 g, 6.00 mmol) was treated with **8** (1.00 g, 5.00 mmol), $Pd_2(dba)_3$ (45.8 mg, 0.0500 mmol), P(2-furyl)$_3$ (92.9 mg, 0.400 mmol), and NaO*t*-Bu (1.15 g, 12.0 mmol) in toluene (30 mL). After column chromatography (SiO_2, EtOAc/heptane 1:10), compounds **12A** and **12B** were isolated as yellow oils containing minor impurities. Compound **12A** (R_f=0.51; 30% EtOAc/heptane): Yield: 0.21 g (ca. 13%), LC-MS yield: 24%. **12B** (R_f=0.58; EtOAc/heptane): Yield: 0.15 g (ca. 9%), LC-MS yield: 26%. LC-MS: **12A**: RT (UV-detector): 3.24 min, *m*/*z*=205.7 [MH^+−Boc]. LC-MS: **12B**: RT (UV-detector): 3.12 min, *m*/*z*=205.8 [MH^+−Boc]. Using $Pd(OAc)_2$ (22.45 mg, 0.100 mmol) instead of $Pd_2(dba)_3$, but otherwise identical conditions, **12A** was isolated in a yield of 026 g (17%).

*4.5.2. Boc deprotection of **12A**.* According to the procedure described above, compound **12A** (0.26 g, 0.85 mmol) was dissolved in a saturated solution of HCl in MeOH. The product **13A** precipitated as white flakes (R_f=0.32; NEt_3/MeOH/EtOAc 5:10:85). Yield: 0.16 g (78%). Mp 91–92 °C; litt.[2c] 92 °C. LC-MS: RT (UV-detector): 1.45 min, *m*/*z*=205.9 [M−Cl]$^+$. ^{1}H NMR (600 MHz, DMSO-d_6): δ=9.11 (s, 1H), 9.05 (s, 1H), 7.16 (d, *J*=8.6 Hz, 2H), 6.90 (d, *J*=8.6 Hz, 2H), 3.74 (s, 3H), 3.21 (m, 1H), 3.15 (m, 1H), 3.04 (m, 1H), 2.82 (m, 1H), 2.68 (m, 1H), 1.70 (m, 2H), 1.62 (m, 2H), 1.38 (m, 2H). ^{13}C NMR

(151 MHz, DMSO-d_6): δ=158.6, 130.8, 128.5, 114.5, 57.4, 55.5, 44.3, 38.4, 27.7, 22.2, 22.0. Anal. Calcd for $C_{13}H_{20}ClNO$: C, 64.59; H, 8.34; N, 5.79. Found: C, 64.34; H, 8.34; N, 5.81.

4.5.3. Boc deprotection of ***12B****.* According to the procedure described above, **12B** (0.15 g, 0.49 mmol) was dissolved in a saturated solution of HCl in MeOH. The product **13B** precipitated as white flakes (R_f=0.35; NEt_3/MeOH/EtOAc 5:10:85). Yield: 94 mg (81%). Mp 83–84 °C. LC-MS: RT (UV-detector): 1.76 min, m/z=205.8 $[M-Cl]^+$. ^{1}H NMR (600 MHz, DMSO-d_6): δ=8.15 (s, 3H), 7.32 (d, J=7.8 Hz, 2H), 6.87 (d, J=7.8 Hz, 2H), 6.35 (d, J=15.8 Hz, 1H), 6.11 (dt, J=15.8, 6.7 Hz, 1H), 3.74 (s, 3H), 2.77 (m, 2H), 2.17 (m, 2H), 1.61 (m, 2H), 1.47 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6): δ=158.8, 130.4, 129.9, 128.1, 127.5, 114.4, 55.5, 39.0, 32.3, 27.0, 26.2. Anal. Calcd for $C_{13}H_{20}ClNO$: C, 64.59; H, 8.34; N, 5.79. Found: C, 64.61; H, 8.45; N, 5.86.

4.6. *N*-Phenyl-2-(*p*-methoxybenzyl)piperidine (14A)

4.6.1. Carboamination. Pd-source: 1% $Pd_2(dba)_3$, Phosphine ligand: 8% P(2-furyl)$_3$. According to the general procedure, *p*-bromoanisole (2.24 g, 12.0 mmol) was treated with **9** (1.75 g, 10.0 mmol), $Pd_2(dba)_3$ (91.6 mg, 0.100 mmol), P(2-furyl)$_3$ (186 mg, 0.800 mmol), and NaO*t*-Bu (1.15 g, 12.0 mmol) in toluene (50 mL). The product was recrystallized from MeOH, affording the product **14A** as a white solid (R_f=0.54; 30% EtOAc/heptane). Yield: 1.44 g (51%); LC-MS yield: 75%. Mp 57–60 °C. LC-MS: RT (UV-detector): 1.91 min, m/z=282.0 $[MH^+]$. ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.31 (m, 2H), 7.06 (m, 2H), 7.01 (m, 2H), 6.84 (m, 3H), 3.99 (m, 1H), 3.80 (s, 3H), 3.40 (m, 1H), 3.07 (m, 1H), 2.78 (m, 1H), 2.64 (m, 1H), 1.74 (m, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ=157.8, 147.2, 132.2, 130.0, 129.2, 121.7, 116.7, 113.8, 58.3, 55.3, 43.9, 32.1, 26.3, 25.7, 19.1. Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.03; H, 8.33; N, 4.95.

4.7. *N*-[6-(*p*-Methoxyphenyl)hex-5-enyl]tosylamide (15B)

4.7.1. Carboamination. Pd-source 1% $Pd_2(dba)_3$, Phosphine ligand: 8% P(2-furyl)$_3$. According to the general procedure, *p*-bromoanisole (1.12 g, 6.00 mmol) was treated with **10** (1.27 g, 5.00 mmol), $Pd_2(dba)_3$ (45.8 mg, 0.0500 mmol), P(2-furyl)$_3$ (92.9 mg, 0.400 mmol), and NaO*t*-Bu (1.15 g, 12.0 mmol) in toluene (30 mL). Yield of **15B** (colorless oil, R_f=0.45; 30% EtOAc/heptane): 0.73 g (41%); LC-MS yield: 70%. LC-MS: RT (UV-detector): 0.87 min, m/z=360.2 $[MH^+]$. ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.77 (d, J=8.0 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H), 7.26 (d, J=7.7 Hz, 2H), 6.86 (d, J=7.7 Hz, 2H), 6.29 (d, J=15.8 Hz, 1H), 5.99 (dt, J=15.8, 7.0 Hz, 1H), 4.64 (t, J=13.4, 1H), 3.82 (s, 3H), 2.98 (dt, J=13.4, 6.7 Hz, 2H), 2.43 (s, 3H), 2.15 (m, 2H), 1.53 (m, 2H), 1.46 (m, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ=158.7, 143.4, 136.9, 130.4, 129.9, 129.7, 127.8, 127.1, 127.0, 113.9, 55.3, 43.1, 32.3, 29.0, 26.3, 21.5. Anal. Calcd for $C_{20}H_{25}NO_3S$: C, 66.82; H, 7.01; N, 3.90. Found: C, 66.77; H, 7.05; N, 3.88.

4.8. *N*-Phenyl-2-(*p*-methoxybenzyl)morpholine (23A)

4.8.1. Carboamination. Pd-source: 1% $Pd_2(dba)_3$, Phosphine ligand: 8% P(2-furyl)$_3$. According to the general procedure, *p*-bromoanisol (2.24 g, 12.0 mmol) was treated with **19** (1.77 g, 10.0 mmol), $Pd_2(dba)_3$ (91.6 mg, 0.100 mmol), P(2-furyl)$_3$ (186 mg, 0.800 mmol), and NaO*t*-Bu (1.15 g, 12.0 mmol) in toluene (50 mL). Recrystallization from MeOH afforded the product **23A** as white needles (R_f=0.43; 30% EtOAc/heptane). Yield: 1.96 g (69%); LC-MS yield: 100%. Mp 102–103 °C. LC-MS: RT (UV-detector): 2.61 min, m/z=283.8 $[MH^+]$. ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.37 (dd, J=8.7, 7.3 Hz, 2H), 7.13 (d, J=8.5 Hz, 2H), 6.99 (d, J=8.7 Hz, 2H), 6.91 (t, J=7.3 Hz, 1H), 6.87 (d, J=8.5 Hz, 2H), 4.09 (m, 1H), 3.84 (m, 1H), 3.82 (s, 3H), 3.77 (m, 2H), 3.65 (m, 1H), 3.30 (m, 1H), 3.23 (m, 1H), 3.04 (m, 1H), 2.59 (m, 1H). ^{13}C NMR (151 MHz, $CDCl_3$): δ=158.0, 149.6, 131.3, 130.3, 129.5, 119.3, 115.4, 114.0, 67.2, 67.0, 57.9, 55.3, 43.0, 30.1. Anal. Calcd for $C_{18}H_{21}NO_2$: C, 76.29; H, 7.47; N, 4.94. Found: C, 76.27; H, 7.51; N, 4.93.

4.9. *N*-{2-[3-(*p*-Methoxyphenyl)prop-2-enyl-oxy]ethyl} tosylamide (24B)

4.9.1. Carboamination. Pd-source: 1% $Pd_2(dba)_3$, Phosphine ligand: 8% P(2-furyl)$_3$. According to the general procedure, *p*-bromoanisole (1.12 g, 6.00 mmol) was treated with **20** (1.28 g, 5.00 mmol), $Pd_2(dba)_3$ (45.8 mg, 0.0500 mmol), P(2-furyl)$_3$ (92.9 mg, 0.400 mmol), and NaO*t*-Bu (1.15 g, 12.0 mmol) in toluene (50 mL). Yield of **24B** (yellow oil, R_f=0.47; 30% EtOAc/heptane): 0.69 g (39%); LC-MS yields: 95% (**24B**), 5% (product from two Heck coupling reactions). LC-MS: **24B**: RT (UV-detector): 2.76 min, m/z=384.0 $[MNa^+]$; product from two Heck coupling reactions: RT (UV-detector): 3.01 min, m/z=468.4 $[MH^+]$, m/z=490.0 $[MNa^+]$. Compound **24B**: ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.77 (d, J=8.0 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H), 7.29 (d, J=7.7 Hz, 2H), 6.86 (d, J=7.7 Hz, 2H), 6.47 (d, J=15.8 Hz, 1H), 6.05 (dt, J=15.8, 7.0 Hz, 1H), 4.87 (t, J=13.4, 1H), 4.02 (d, J=7.0 Hz, 2H), 3.82 (s, 3H), 3.49 (t, J=6.7 Hz, 2H), 3.13 (dt, J=13.4, 6.7 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ=159.4, 143.6, 136.9, 132.9, 130.0, 129.0, 127.8, 127.1, 122.8, 113.9, 71.9, 67.8, 55.2, 42.8, 21.5. Anal. Calcd for $C_{19}H_{23}NO_4S$: C, 63.14; H, 6.41; N, 3.87. Found: C, 63.01; H, 6.25; N, 3.67.

Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.06.004.

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