Palladium-Catalyzed Cyclization Reactions of Acetylene-Containing Amino Acids

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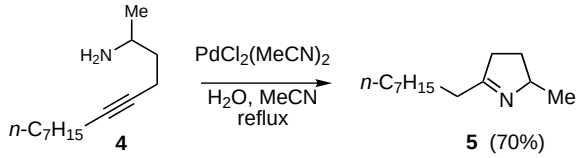
Abstract: Enantiomerically pure acetylene-containing α-amino acids were used as versatile starting materials for the synthesis of a variety of heterocycles via Pd-mediated cyclization reactions. Depending on the protecting group strategy, both the carboxylate and the amine function of the amino acids could participate in the cyclizations, thus giving rise to oxygen heterocycles (α-aminolactones) and nitrogen heterocycles (cyclic α-amino acid derivatives), respectively. Beside the straightforward cyclization, cyclization/cross-coupling reactions were also successfully carried out to provide the corresponding substituted cyclic amino acid derivatives.

Keywords: cross-coupling reactions; cyclic amino acids; palladium catalysis; unsaturated amino acids.

Introduction

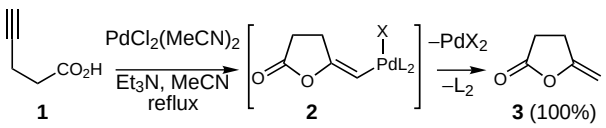
Small functionalized heterocycles are important intermediates in the synthesis of pharmaceuticals and natural products[1] and may serve as ideal scaffolds for further functionalization via combinatorial techniques.[2] Amongst a wide variety of existing approaches, intramolecular palladium-catalyzed cyclizations of heteronucleophiles onto alkynes provide a convenient method for preparing such heterocycles.[3] Successful examples of the latter include oxygen nucleophiles – in the form of carboxylic acids or alcohols – which cyclize onto the triple bond to give five- or six-membered lactones or cyclic ethers, respectively, when treated with palladium catalysts.[4] As an example, 4-pentynoic acid (**1**) cyclized to the unsaturated lactone **3** upon exposure to $PdCl_2(MeCN)_2$ in the presence of a catalytic amount of base (Scheme 1).[4d] The catalytic cycle presumably involves electrophilic activation of the triple bond by Pd(II), followed by nucleophilic attack of the carboxylate function. The resulting vinylpalladium(II) intermediate **2** cannot – in contrast with analogous cyclizations of olefins – undergo β-hydride elimination, but instead undergoes protonolysis of the Pd-C bond which leads to the formation of lactone **3** and regeneration of the Pd(II)-catalyst.

Nitrogen nucleophiles such as amines and amides have also been successfully applied in Pd-catalyzed cyclizations of acetylenes. Representative for these types of reactions is the intramolecular aminopalladation of alkyne **4**, which upon treatment with a Pd(II)-catalyst leads to the five-membered cyclic imine **5** in good yield (Scheme 2).[5] In a similar fashion, the corresponding six-membered imines can also be obtained.

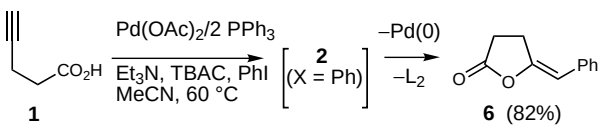


Scheme 2.

In the presence of vinyl or aryl halides it is possible to perform Pd(0)-catalyzed cyclization/cross-coupling reactions in a single step.[6] Under these circumstances, the first step involves the *in situ* formation of an organopalladium(II) species [oxidative addition of the aryl halide onto the Pd(0) species], which then activates the triple bond towards nucleophilic attack. After ring closure (*viz.* **1**), the resulting vinylpalladium(II) species **2** (X = Ph) can undergo a reductive elimination to form a new C-C bond – the aryl group is transferred *trans* with respect to the oxygen nucleophile giving rise to **6** – and regenerate the Pd(0)-catalyst (Scheme 3).[6e] In



Scheme 1.

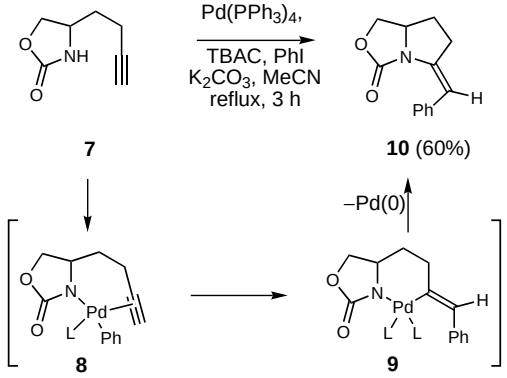


Scheme 3.

the literature, several other successful examples of this type of reaction involving oxygen nucleophiles are known.[6]

Analogously, these types of Pd-catalyzed coupling/cyclization reactions can also be carried out with nitrogen nucleophiles.[7] For example, tosylated carbamates,[8] tosylated amides[9] and sulfonamides[10] are known to react with aryl halides and vinyl triflates to give the corresponding cross-coupled tosylated oxazolidinones**,** tosylated lactams and sulfonylated piperidines, respectively, all containing an (*E*)-configured double bond.

Inversely, in the group of Hiemstra acetylene-substituted lactams and oxazolidinones (*viz.* **7**) were cyclized under similar conditions to afford the corresponding bicyclic (*Z*)-substituted enamides (Scheme 4).[11] A plausible reaction mechanism that explains these contradictary results involves the intermediate **8**, in which palladium(II) coordinates to the carbamate nitrogen atom *before* the nitrogen-carbon bond is formed. This intramolecular activation of the triple bond is then followed by nucleophilic attack of the nitrogen from within the coordination sphere of palladium to initially give the bicyclic species **9.** Reductive elimination of Pd(0) finally gives rise to the (*Z*)-configured olefin **10.**

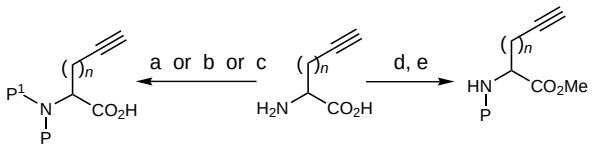


Scheme 4.

The precedence of these literature examples, combined with the relatively facile biocatalytic access to enantiomerically pure acetylene-containing amino acids developed in our group in collaboration with DSM (Geleen, The Netherlands)[12] inspired us to use these trifunctional amino acids[13] in similar Pd-catalyzed reactions. Logically, these amino acids – containing both an oxygen and a nitrogen nucleophile – might upon suitable protection give access to a variety of enantiomerically pure substituted lactones, as well as to the corresponding nitrogen heterocycles.[14]

Results and Discussion

In order to obtain the cyclization precursors, the enantiomerically pure amino acids **11** and **12**[12] were protected with different protecting groups. In case of the oxypalladation precursors, the nitrogen atom was protected according to literature procedures[15] involving either tosylation or acylation in an aqueous medium or irradiation in a microwave in the presence of phthalic anhydride.[16] In all cases, the *N*-protected amino acids **13 – 16** were obtained in good yields without loss of



(*R*)-**13**: (83%)
n = 1, P = Ts, P[1] = H
(*S*)-**14**: (73%)
n = 2, P = Ts, P[1] = H
(*R*)-**15**: (83%)
n = 1, P = Boc, P[1] = H
(*S*)-**16**: (91%)
n = 1, P = P[1] = Phth
rac-**17**: (91%)
n = 2, P = P[1] = Phth

(*S*/*R*)-**11**: *n* = 1
(*S*/*R*)-**12**: *n* = 2

(*S*)-**18**: (94%)
n = 1, P = Ts
(*R*)-**19**: (72%)
n = 2, P = Ts
(*R*)-**20**: (59%)
n = 2, P = Ns

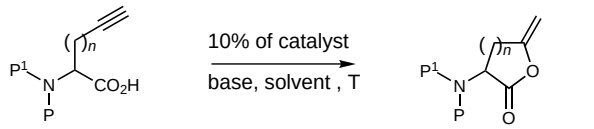
Scheme 5. *Reagents and conditions*: **13**, **14** → **15**, **16** (a) TsCl (1.4 equiv), 1 M NaOH (1.1 equiv), rt, 16 h; **13** → **17** (b) di-*tert*-butyl dicarbonate (1.1 equiv), $NaHCO_3$ (2 equiv), dioxane/H_2O, reflux, 4 h; **13**, **14** → **18**, **19** (c) phthalic anhydride (1 equiv), H_2O, microwave (600 W, 5 min); (d) $SOCl_2$ (2 equiv), MeOH, reflux; (e) TsCl or NsCl (2 equiv), Et_3N (5 equiv), CH_2Cl_2, rt, 16 h.

enantiopurity according to chiral HPLC analysis (Scheme 5). Additionally, *rac*-**12** was converted to racemic phthalimide **17.**

Conversely, the enantiomerically pure amidopalladation precursors **18 – 20** were obtained by esterification using thionyl chloride (2 equiv) in MeOH at reflux temperature and subjection of the crude residue to Et_3N (5 equiv) and *p*-toluenesulfonyl chloride (TsCl, 2 equiv) or *p*-nitrobenzenesulfonyl chloride (NsCl, 2 equiv) in CH_2Cl_2. Alternatively, the crude esterified residue was dissolved in pyridine and treated with TsCl or NsCl to give the same products in similar yields.

The palladium-catalyzed cyclizations with the carboxylic acid as the nucleophile are shown in Table 1. Subjection of the *N*-protected amino acids **13 – 17** to a mixture of 10 mol % of a Pd(II) catalyst and 15 mol % of Et_3N in various solvents at different temperatures led to five- and six-membered lactones. The tosylamide (*R*)-**13** was cyclized in a satisfactory yield of 66% at 70 °C (entry 1). Changing the catalyst to $Pd(OAc)_2$ led to a much faster reaction at room temperature in the same yield (66%, entry 2). A single attempt to use an inorganic base (K_2CO_3) appeared fatal to the reaction (entry 3). Subjection of

Table 1.



13-17 **21-25**

entry	substrate	catalyst	base	solvent	T (°C)	time (h)	product	yield (%)[a]
1	(*R*)-**13**	$Pd(MeCN)_2Cl_2$	Et_3N	THF	70	16	(*R*)-**21**	66
2	(*R*)-**13**	$Pd(OAc)_2$	Et_3N	THF	rt	1	(*R*)-**21**	66[b]
3	(*R*)-**13**	$Pd(MeCN)_2Cl_2$	K_2CO_3	DMF	80	6		0
4	(*R*)-**15**	$Pd(OAc)_2$	Et_3N	THF	rt	2	(*R*)-**22**	63
5	(*S*)-**16**	$Pd(OAc)_2$	Et_3N	THF	rt	1.5	(*S*)-**23**	42[b]
6	*rac*-**14**	$Pd(MeCN)_2Cl_2$	Et_3N	MeCN	60	16	*rac*-**24**	32
7	*rac*-**17**	$Pd(OAc)_2$	Et_3N	THF	60	5	*rac*-**25**	24

[a] Isolated yields after column chromatography.
[b] ee >97% according to ^1H NMR using $Eu(hfc)_3$ as the shift reagent in $CDCl_3$.

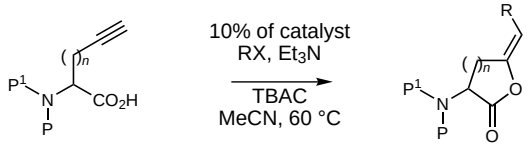
the Boc-protected acid **15** to similar conditions resulted at room temperature in **22** in 63% (entry 4). Likewise, the phthalimide-protected amino acid **16** cyclized in a lower yield. In contrast with the five-membered rings, the six-membered lactones **24** and **25** were obtained in somewhat disappointing yields (entries 6 and 7), which is probably due to the lower tendency of Pd to react in a 6-*exo*-fashion.[4d,6f] The ee of **21** and **23** was determined via ^{1}H NMR experiments using a chiral shift reagent [Eu(hfc)$_3$ in $CDCl_3$] showing an ee higher than 97%, which led us to conclude that virtually no racemization occurred in these cyclization reactions.

In addition to these reactions, other cyclization reactions were carried out in the presence of various aryl halides or a vinyl triflate to introduce an organic substituent in the cyclization step, which are summarized in Table 2. The general reaction conditions involved 10 mol % of a Pd(0) catalyst, Et_3N (5 equiv), tetrabutylammonium chloride (TBAC, 2 equiv) and the aryl halide (2 equiv) in MeCN at 60 °C. When tosylamide (*R*)-**13** was reacted under these conditions neither cyclization nor introduction of the aryl group was observed. Although the starting material had disappeared, amidopalladation could be excluded on the basis of NMR analysis. More gratifyingly, the Boc-protected amino acid (*R*)-**15** reacted under similar conditions to the cross-coupled lactone (*R*)-**27** in a moderate yield of 44%, without detectable racemization. The phthalimide-protected amino acid (*S*)-**16** was treated with iodobenzene and *p*-iodoanisole to afford the lactams **28** and **29**, respectively, in similar yields (entries 3–6). Unfortunately, in all these cases complete racemization occurred at the temperature required for cyclization. Apparently, the phthalimide protecting group renders the α-proton of the amino acid sufficiently acidic to be prone to racemization under the slightly basic reaction conditions. No cyclization occurred with *p*-nitroiodobenzene (entry 7), which was probably due to the decreased reactivity of the organopalladium intermediate. Treatment of (*S*)-**16** with vinyl triflate **26**[17] afforded **30**, albeit in only 23% (entry 8). Furthermore, in analogy with the aforementioned oxypalladation reactions, formation of a six-membered lactone appeared difficult as indicated by the relatively low yield of **31** (31%, entry 9).

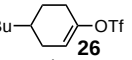
In summary, the yields of the cross-coupling reactions turned out to be somewhat disappointing; this could either be due to a lower reactivity of the amino acids towards oxypalladation reactions compared to 'regular' carboxylic acids, but on the other hand also to the relative instability of the enol esters that are formed. The fact that analysis by TLC always showed complete conversion and no starting material was recovered in these reactions seems to support the latter hypothesis.

The Pd-catalyzed cyclizations with the enantiopure propargylglycine-derived precursor (*S*)-**18** are shown in Table 3. The anticipated five-membered endocyclic enamide (*S*)-**32** was formed in 76% yield using 10 mol % of $Pd(PPh_3)_4$ and 5 equiv of K_2CO_3 in DMF at 80 °C (entry 1). Unfortunately, partial racemization occurred under these conditions leading to an enantiopurity of the product of only 33%. To circumvent the undesired racemization, catalyst, solvent, reaction temperature and the base were varied. By changing the solvent from DMF to THF and the catalyst from $Pd(PPh_3)_4$ to $Pd(OAc)_2$/$2PPh_3$, the ee increased from 91% at 60 °C (entry 2) to > 99% at 40 °C (entry 3), albeit that the yield dropped to 48%. Adding a smaller amount of base, i.e., one equiv instead of five equiv, resulted in a dramatic lowering of the yield (18%), while still partial racemization was observed (entry 5). Changing the base to the less basic salt $NaHCO_3$ did not improve the yield either (entry 6). When using the organic base Et_3N, no cyclization product was observed at all (entry 7). In addition, the influence of different ligands was studied. Several combinations of catalysts and ligands with different bite angles[18] were screened, but none of these combinations had a dramatic influence on the yield or the reaction time. The chloride sources were also varied to study their effect on the yield and the reaction rate at 40 °C. The use of TBAC led to an

Table 2.

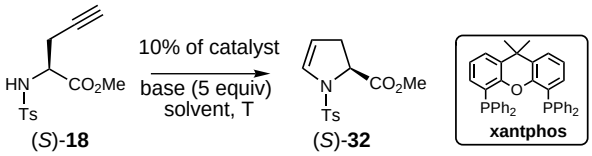


13, **15-17** **27-31**

entry	substrate	catalyst	RX	time (h)	product	yield (%)[a]
1	(*R*)-**13**	$Pd(PPh_3)_4$	PhI	2		0
2	(*R*)-**15**	$Pd(OAc)_2$/$2PPh_3$	PhI	6	(*R*)-**27**	44[b]
3	(*S*)-**16**	$Pd(PPh_3)_4$	PhI	5	**28**	43
4	(*S*)-**16**	$Pd(OAc)_2$/$2PPh_3$	PhI	5	**28**	41
5	(*S*)-**16**	$Pd(PPh_3)_2Cl_2$	PhI	5	**28**	18
6	(*S*)-**16**	$Pd(PPh_3)_4$	*p*-$MeOC_6H_4I$	24	**29**	41
7	(*S*)-**16**	$Pd(PPh_3)_4$	*p*-$NO_2C_6H_4I$	16		0
8	(*S*)-**16**	$Pd(PPh_3)_4$	 **26**	16	**30**	23
9	*rac*-**17**	$Pd(OAc)_2$/$2PPh_3$	PhI	5	**31**	31

[a] Isolated yields after column chromatography.
[b] The geometry of the (*E*)-double bond was proven via ^{1}H NMR NOE experiments.

Table 3.



(*S*)-**18** (*S*)-**32**

entry	catalyst	base	solvent	T (°C)	time (h)	yield (%)[a]	ee (%)[b]
1	$Pd(PPh_3)_4$	K_2CO_3	DMF	80	3.5	76	33
2	$Pd(OAc)_2$/$2PPh_3$	K_2CO_3	THF	60	4	65	91
3	$Pd(OAc)_2$/$2PPh_3$	K_2CO_3	THF	40	48	48	>99
4	$Pd(PPh_3)_4$	K_2CO_3	THF	40	48	36	
5	$Pd(OAc)_2$/$2PPh_3$	K_2CO_3[c]	THF	60	24	18	84
6	$Pd(OAc)_2$/$2PPh_3$	$NaHCO_3$	THF	60	24	18	61
7	$Pd(OAc)_2$/$2PPh_3$	Et_3N	THF	60	24	0	
8	$Pd(OAc)_2$/xantphos	K_2CO_3	THF	60	3	66	
9	$Pd_2(dba)_3$/xantphos	K_2CO_3	THF	60	25	64	
10	$Pd(OAc)_2$/dppe	K_2CO_3	THF	60	4	44	
11	$Pd(OAc)_2$/dppb	K_2CO_3	THF	60	21	40	
12	$Pd(OAc)_2$/$2PPh_3$/TBAC	K_2CO_3	THF	40	24	64	89
13	$Pd(OAc)_2$/$2PPh_3$/LiCl	K_2CO_3	THF	40	48	26	
14	$Pd(OAc)_2$	K_2CO_3	DMF	60	5	12	
15		K_2CO_3	THF	80	5.5	25	

[a] Isolated yields after column chromatography.
[b] The ee was determined by chiral HPLC (Chiralpak OD; eluent: 20% IPA/heptane).
[c] One instead of five equiv of base was added.

improvement of the yield to 64%, but again significant racemization occurred (entry 12). Inversely, the use of LiCl did not result in any improvement (entry 13). Conducting the reaction under ligandless conditions with only $Pd(OAc)_2$ present resulted in a disappointing yield of only 12%.

Finally, without a Pd-catalyst present, the cyclization also proceeded to afford product **32** in a yield of 25% (entry 15). In the literature, several examples of such types of cyclizations without using a transition metal catalyst have been published. Examples include the cyclization of acetylenic amines (neat at 180–200 °C),[19] the cyclization of acetylenic amides using TBAF as the base at 80 °C[20] and the cyclization of amides using NaOEt in refluxing EtOH[21] to provide the corresponding cyclic enamides. Presumably, the base acts to generate a more nucleophilic nitrogen anion, and then gives rise to a cycloisomerization. However, in order to obtain acceptable yields in our reactions the cyclizations have to be enhanced through palladium(II) activation of the triple bond.

Not shown in Table 3 are cyclizations that were carried out with several other protecting groups at the nitrogen atom under the standard conditions. Precursors activated as an amide (e.g., acetyl) or a carbamate (Boc, CO_2Me) were subjected to these conditions, but all of them failed to give the desired cyclized product. Apart from the tosyl group, only a nosyl-protected compound gave cyclized material under the optimized conditions albeit in the very low yield of 8%.

A similar set of reactions was carried out using the enantiopure homologous precursors (*R*)-**19** and (*R*)-**20** of which the results are summarized in Table 4. A satisfactory yield of the five-membered ring (*R*)-**33** containing an exocyclic double bond was obtained upon subjection of (*R*)-**19** to the standard conditions in THF at 60 °C (entries 1 and 2). In both cases, no (partial) racemization was observed during the reaction, the products were shown to have completely retained their enantiopurity with the aid of chiral HPLC. When 5 equiv of iodobenzene were added during the reaction, the yield improved to 90% (entry 3). A possible explanation is that the iodobenzene reacts with the Pd(0)-catalyst to *in situ* generate an organopalladium(II) catalyst that is more reactive towards the triple bond. As long as there is no TBAC present, reductive elimination to form the corresponding phenyl-substituted cross-coupled product does not occur (see also the mechanistic discussion).

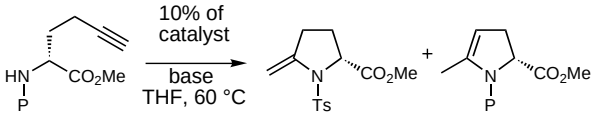
By changing the catalyst or the ligands, comparable yields were obtained; remarkably, when dppb, xantphos and $P(o\text{-tol})_3$ were used as the ligands, the isomerized enamide (*R*)-**34** was obtained after column chromatography (entries 5–7). However, from ^1H NMR data of the crude product it was apparent that the isomerization took place during column chromatography.

Analogous to previous examples, the combination of a Pd(II) catalyst with Et_3N as a base did not give any product (entry 9). With Cs_2CO_3 as the base, (*R*)-**33** was formed in a small amount (entry 11). Without a metal catalyst, the cyclized product was found in 12% (entry 12), which is in line with the results described in Table 3. Finally, the homopropargylglycine derivative (*R*)-**20** containing the more easily removable Ns-protecting group cyclized in satisfactory yields to (*R*)-**35** (entries 13 and 14). As before, the addition of iodobenzene resulted in an improved yield (difference between entries 13 and 14).

Similar Pd-catalyzed cyclizations were also carried out in the presence of aryl halides and vinyl triflates to introduce an organic substituent in the cyclization step (Table 5). The enantiomerically pure Ts- and Ns-protected amino acids (*R*)-**19** and (*R*)-**20**, respectively, were subjected to 10 mol % of a Pd(0) catalyst, TBAC (1 equiv), an aryl halide or a vinyl triflate (5 equiv) and K_2CO_3 (5 equiv). When the reaction was carried out in DMF and iodobenzene was added as the aryl halide, beside (*R*)-**37**, a small amount of the undesired non-arylated cyclized product (*R*)-**33** was found. In MeCN, however, the cross-coupled product (*R*)-**37** was selectively formed in 74% (entry 2) without detectable racemization. Coupling with *p*-nitroiodobenzene and *p*-iodoanisole resulted in the cross-coupled products (*R*)-**38** and (*R*)-**39** in reasonable yields. Reaction with the less reactive *p*-bromoanisole resulted in the same product albeit in a significantly lower yield of 22% (entry 5). The range of coupling reagents was extended to vinyl triflates (*viz*. **26** and **36**),[22] which resulted in the coupled products (*R*)-**40** and (*R*)-**41** (entries 6 and 7). Changing from the Ts to the Ns-protecting/activating group resulted in a high yield and excellent selectivity using standard conditions in MeCN at a lower temperature (entry 8). On the other hand, poor selectivity was observed when the solvent or the ligands were changed. Apparently, the CC-bond formation through reductive elimination is slower with these ligands.

The double bond geometry of (*R*)-**37** was unambiguously proven by ^1H NMR NOE studies which clearly showed the (*E*)-configuration. Figure 1 summarizes the NOE-enhancements of the different protons. Especially the enhancement of the aromatic protons upon irradiation of the vinylic proton was diagnostic for proving the (*E*)-geometry.

Table 4.



(*R*)-**19**
(*R*)-**20**

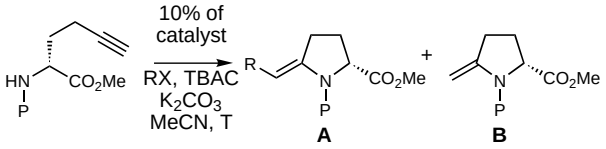
(*R*)-**33**: P = Ts
(*R*)-**35**: P = Ns

(*R*)-**34**: P = Ts

entry	reactant	catalyst	base	time (h)	product	yield (%)[a]
1	**19**	$Pd(PPh_3)_4$	K_2CO_3	1	**33**	64[c]
2	**19**	$Pd(OAc)_2/2PPh_3$	K_2CO_3	1	**33**	74[c]
3	**19**	$Pd(OAc)_2/2PPh_3$/5PhI	K_2CO_3	1	**33**	90
4	**19**	$Pd(OAc)_2$/dppe	K_2CO_3	1	**33**	74
5	**19**	$Pd(OAc)_2$/dppb	K_2CO_3	1	**34**	70[d]
6	**19**	$Pd(OAc)_2$/xantphos	K_2CO_3	1.5	**34**	60[d]
7	**19**	$Pd(OAc)_2/2P(o\text{-tol})_3$	K_2CO_3	1	**34**	43
8	**19**	$Pd_2(dba)_3/2PPh_3$	K_2CO_3	1	**33**	54
9	**19**	$PdCl_2(MeCN)_2$	Et_3N[b]	5		0
10	**19**	$Pd(PPh_3)_4$	Et_3N[b]	7	**33**	<5
11	**19**	$Pd(OAc)_2/2PPh_3$	Cs_2CO_3	1	**34**	4
12	**19**		K_2CO_3	5	**33**	12
13	**20**	$Pd(OAc)_2/2PPh_3$	K_2CO_3	1	**35**	48
14	**20**	$Pd(OAc)_2/2PPh_3$/5PhI	K_2CO_3	0.5	**35**	75

[a] Isolated yield after column chromatography.
[b] One instead of five equiv of base was added.
[c] The enantiopurity (>98%) was determined by chiral HPLC (Chiralpak OD; eluent: 20% IPA/heptane).
[d] Isolated as a mixture of **33**:**34**; 1:8 (entry 5), **33**:**34**; 1:10 (entry 6).

Table 5.

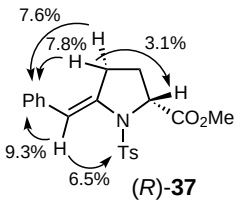


(*R*)-**19**
(*R*)-**20**

(*R*)-**37**-**41**: P = Ts (*R*)-**33**: P = Ts
(*R*)-**42**: P = Ns (*R*)-**35**: P = Ns

entry	reactant	RX	catalyst	T (°C)	time (h)	ratio[a] **A**:**B**	prod- uct	yield[b] (%)	ee[c] (%)
1	**19**	PhI	$Pd(PPh_3)_4$	80[d]	1	83:17	**37**	53	>99
2	**19**	PhI	$Pd(PPh_3)_4$	82	2.5	100:0	**37**	74	
3	**19**	*p*-$NO_2C_6H_4I$	$Pd(PPh_3)_4$	82	0.6	100:0	**38**	59	95
4	**19**	*p*-$MeOC_6H_4I$	$Pd(PPh_3)_4$	82	2	100:0	**39**	58	97
5	**19**	*p*-$MeOC_6H_4Br$	$Pd(PPh_3)_4$	82	2	100:0	**39**	22	
6	**19**	**26**	$Pd(PPh_3)_4$	82	1	100:0	**40**	55	>99
7	**19**	Bu, **36**, OTf	$Pd(PPh_3)_4$	82	1	100:0	**41**	13	
8	**20**	PhI	$Pd(PPh_3)_4$	60	1.5	100:0	**42**	80	>99
9	**20**	PhI	$Pd(OAc)_2/2PPh_3$	60	1	100:0	**42**	62	
10	**20**	PhI	$Pd(OAc)_2/2PPh_3$	60[e]	3.5	91:9	**42**	57	
11	**20**	PhI	$Pd(OAc)_2$/dppe	60[e]	0.5	66:33	**42**	17	
12	**20**	PhI	$Pd(OAc)_2$/dppb	60	4	93:7	**42**	59	
13	**20**	PhI	$Pd(OAc)_2$/xantphos	60	2	25:75	**42**	19	

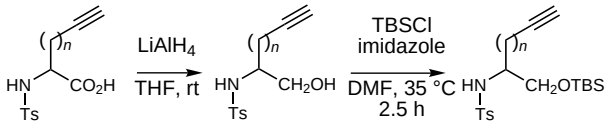
[a] In entries 1 and 10-13, the products were isolated as mixtures of which the ratio was determined on the basis of ^1H NMR spectra of the crude mixtures.
[b] Isolated yield after column chromatography.
[c] The ee was determined by chiral HPLC (Chiralpak OD; eluent: 20% IPA/heptane)
[d] The reaction was carried out in DMF.
[e] The reaction was carried out in THF.



(*R*)-**37**

Figure 1. ^1H NMR NOE data of enamide (*R*)-**37**.

In order to study the influence of the ester group on the amidopalladation reactions, the enantiopure amino acids were converted into the corresponding (protected) amino alcohols (Scheme 6). The Ts-protected amino acids (*R*)-**13** and (*S*)-**14** were reduced with $LiAlH_4$ (4 equiv) following a literature procedure.[23] The resulting alcohols (*R*)-**43** and (*S*)-**44** were without further purification protected using TBSCl (1.2 equiv) and imidazole (2.5 equiv) in DMF[24] to give (*R*)-**45** and (*S*)-**46** in good overall yields without loss of enantiopurity.



(*R*)-**13**: *n* = 1 (*R*)-**43**: *n* = 1 (*R*)-**45**: *n* = 1 (80%)
(*S*)-**14**: *n* = 2 (*S*)-**44**: *n* = 2 (*S*)-**46**: *n* = 2 (90%)

Scheme 6.

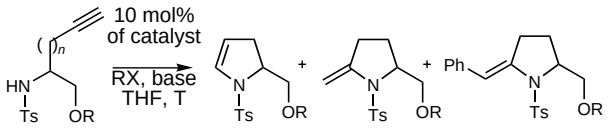
Both the TBS-protected and the unprotected amino alcohols were subjected to the aforementioned amidopalladation conditions of which the results are summarized in Table 6. Amino alcohol (*R*)-**43** cyclized in a 5-*endo* fashion to the five-membered enamide in a low yield (entry 1). When the homologous alcohol (*S*)-**44** was subjected to similar conditions, the yield of the cyclized product improved to 55% (entry 2). A possible explanation for the increase of yield is the stability of the product; the endocyclic enamide readily decomposed under the reaction conditions and during work-up. Under ligandless conditions [$Pd_2(dba)_3$] even higher yields were obtained (entry 3). Furthermore, using the TBS-protected amino alcohols (*R*)-**45** and (*S*)-**46** (entries 4 and 5) somewhat higher yields were obtained. Surprisingly, the best result was obtained at room temperature (entry 6); although the reaction was rather slow, the yield (90%) was excellent. This might be a result of the fact that the formed enamide is more stable at room temperature than at 60 °C.

The cyclization/coupling reaction of the unprotected alcohol (*S*)-**44** with iodobenzene did only result in trace amounts of the cyclized product. In contrast, the TBS-protected alcohol (*S*)-**46** reacted in high yield (82%) to the desired product (*S*)-**52** (entry 8). When this reaction was carried out at room temperature under the same conditions, cyclization did occur, but no CC-coupling took place and the only product that was isolated was the cyclic product (*S*)-**50** (entry 9). Apparently, at this temperature protonolysis of the intermediate organopalladium intermediate is faster than reductive elimination.

At first sight, there is no significant difference between the cyclizations of the amino esters and the amino alcohols. It is clear that the reactions with the protected alcohols proceed in higher yields than the unprotected ones. Furthermore, from the latter cyclizations it is apparent that the alcohol itself is not sufficiently nucleophilic to effect cyclization. This might be due to the fact that the alcohol is not deprotonated under the mildly basic conditions, which is the case for the corresponding carboxylic acids.

The mechanism of the oxypalladation reactions follows what is known from literature experiments and is already mentioned

Table 6.

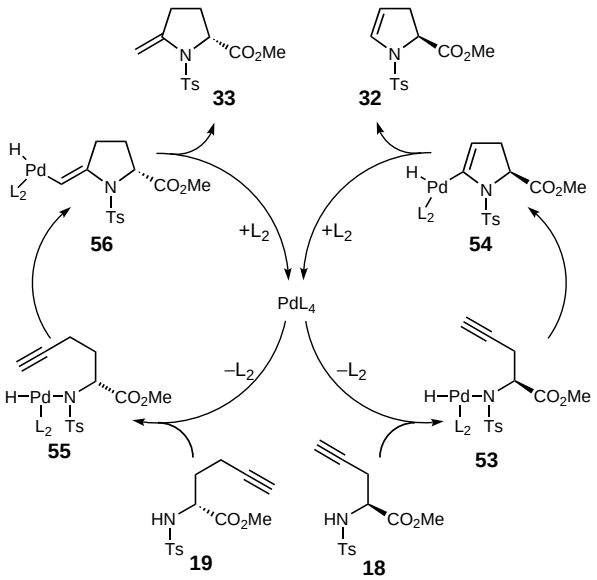


43-**46**

47: R = H **49**: R = H **51**: R = H
48: R = TBS **50**: R = TBS **52**: R = TBS

entry	reactant	RX	catalyst	base	T (°C)	time (h)	prod- uct	yield (%)[a]
1	(*R*)-**43**		$Pd_2(dba)_3$	K_2CO_3	60	7	(*R*)-**47**	16
2	(*S*)-**44**		$Pd(OAc)_2/2PPh_3$	K_2CO_3	60[b]	3.5	(*S*)-**49**	55
3	(*S*)-**44**		$Pd_2(dba)_3$	K_2CO_3	60	1.5	(*S*)-**49**	78
4	(*R*)-**45**		$Pd(PPh_3)_4$	K_2CO_3	80[b]	4.5	(*R*)-**48**	28
5	(*S*)-**46**		$Pd(PPh_3)_4$	K_2CO_3	60	25	(*S*)-**50**	74
6	(*S*)-**46**		$Pd(PPh_3)_4$	K_2CO_3	rt	48	(*S*)-**50**	90
7	(*S*)-**44**	PhI	$Pd_2(dba)_3$	K_2CO_3/TBAC	60	16	(*S*)-**51**	<5
8	(*S*)-**46**	PhI	$Pd(PPh_3)_4$	K_2CO_3/TBAC	60	5.5	(*S*)-**52**	82
9	(*S*)-**46**	PhI	$Pd(PPh_3)_4$	K_2CO_3/TBAC	rt	48	(*S*)-**50**	67

[a] Isolated yield after column chromatography.
[b] The reaction was carried out in DMF.

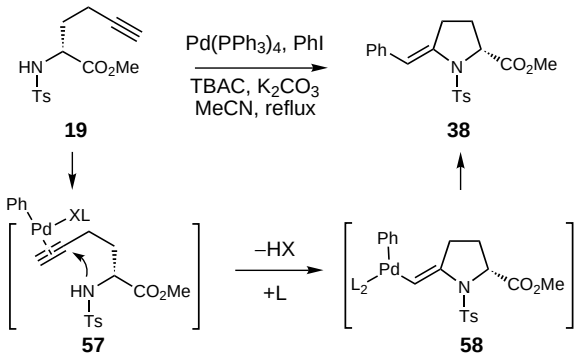


Scheme 7.

in the introduction. Therefore, we will mainly focus on the mechanism of the amidopalladation reactions, which showed some remarkable features. The most striking observation was that the use of Pd(0) catalysts resulted in the formation of the cyclization products, while Pd(II) is required as an intermediate. It is our hypothesis that the reaction starts with oxidative addition of Pd(0) into the NH-bond to form a Pd-H species (*viz*. structures **53** and **55** in Scheme 7). Then, intramolecular insertion of the triple bond can take place, which depending on the chain length can result in a vinylpalladium species that either contains an endocyclic (**54**) or an exocyclic (**56**) double bond. Eventually, reductive elimination of the Pd-H intermediate will provide the unsubstituted enamides. To the best of our knowledge, the activation of Pd(0) via oxidative addition into the sulfonamide NH has not been reported previously in the literature. On the other hand, weak acids have been used to react in such a manner with Pd(0) (e.g., HCO_2H and CH_3CO_2H),[25] and more recently even malonitriles have been reported to undergo oxidative addition of Pd(0) into the acidic CH-bond.[26] We assume that a similar reaction is also possible with the relatively acidic NH bond, which then also explains that the reaction does not proceed with the less acidic carbamates and amides. Furthermore, we believe that the latter observation favors the proposed mechanism over the previously reported mechanism,[27] involving insertion in the acetylenic CH-bond, which does not account satisfactorily for the difference in reactivity between the carbamates and the sulfonamides.

It is possible, however, that more than one mechanism is operating at the same time. For instance, the reaction also proceeds in the presence of Pd(II) salts, although in lower yields. This might be due to the difference in reactivity between the Pd-H intermediate (**53** and **55**) and an intermediate that contains an acetate as the counterion.

Similarly, in the presence of an *in situ* generated phenylpalladium(II) species, the reaction results in a higher yield which might be due to the presence of the aryl group on the palladium.



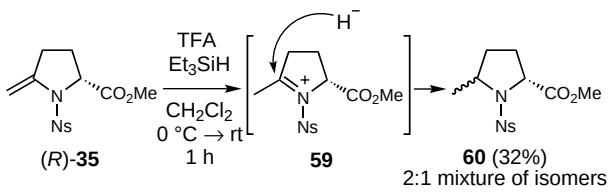
Scheme 8.

In case of the coupling/cyclization reactions, the latter mechanism also operates and is shown in Scheme 8. Again, phenylpalladium(II) is generated *in situ* via oxidative addition of palladium(0) into the aryl halide bond and complexes to the triple bond to give the π-complex (**57**). The acetylene is now electrophilic enough for nucleophilic attack of the (deprotonated) nitrogen atom to give the corresponding vinylpalladium intermediate (**58**). This intermediate undergoes reductive elimination to regenerate Pd(0) and give the cross-coupled products.

The addition of TBAC to the reaction mixture appeared essential to effect the reductive elimination process. Without TBAC no cross-coupled product was observed, but instead only the cyclized product **33.** The beneficial influence of quaternary ammonium chlorides on Pd-catalyzed reactions has been investigated by Arcadi[6e] and Jeffery.[28] A possible effect is a halogen exchange between the *in situ* formed $PhPdI(PPh_3)_2$ species and TBAC to generate the more reactive intermediate $PhPdCl(PPh_3)_2$. On the other hand, it cannot be ruled out that TBAC simply might serve as a phase-transfer catalyst, increasing the amount of base in the reaction.

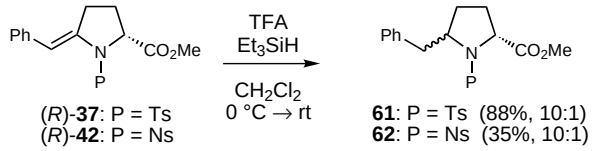
In order to further explore the possibilities of the cyclic enamides, different methods to functionalize the double bond were investigated. A first method involved reduction of the enamide (*R*)-**35** to the saturated proline derivative **60** via the intermediate *N*-sulfonyliminium ion **59** (Scheme 9).[29] This was achieved using a mixture of trifluoroacetic acid and triethylsilane to give the proline derivative **60** in 32% as a 2:1 mixture of diastereoisomers. Unfortunately, we were unable to identify the relative configuration of the major isomer.

The enamides (*R*)-**37** and (*R*)-**42** were subjected to identical conditions affording (*R*)-**61** in good yield (88%, 10:1 mixture of diastereoisomers) and (*R*)-**62** in a somewhat lower yield (35%, 10:1 mixture of isomers). The increased selectivity



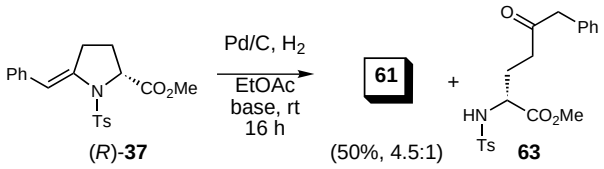
Scheme 9.

compared to the reduction of **35** was probably a result of the steric bulk of the larger phenyl group. The reaction with the Ns-protecting group took significantly longer due to its stronger electron-withdrawing properties and therefore more difficult formation of the *N*-sulfonyliminium ion. The long reaction time was probably also the main reason for the lower yield. Despite the fact that extensive NOE-experiments were carried out with product (*R*)-**62,** the configuration of the major isomer could not be unambiguously determined (Scheme 10).



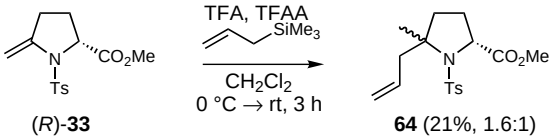
Scheme 10.

Straightforward hydrogenation of the enamide function using Pd on carbon under a hydrogen atmosphere in the presence of a catalytic amount of base led to **61** (major isomer appeared identical to the major isomer in the previous reactions on the basis of NMR data), albeit in a lower yield and significantly lower selectivity (Scheme 11). In this reaction a small amount of ketone **63** was also isolated, but the yield was not determined. Without the base, the hydrolysis product **63** was the only isolated product.



Scheme 11.

Instead of the small hydride nucleophile, it was also attempted to introduce a larger nucleophile *via* the tertiary *N*-sulfonyliminium ion using a cocktail of allyltrimethylsilane (10 equiv), trifluoroacetic acid (TFA, 5 equiv) and trifluoroacetic anhydride (TFAA, 5 equiv). The latter compound was added to trap traces of water that might be present in the reaction mixture. The allylated product **64** was obtained in a moderate yield and slightly contaminated with the hydrolysis product and the isomerized product **34.** The formation of side products is understandable, considering the difficulty of nucleophilic attack on the tertiary iminium ion.[30] Unfortunately, the stereochemistry of both isomers could not be assigned.



Scheme 12.

The enamide (*R*)-**37** was subjected to the same conditions, but in this case only the product resulting from hydrolysis was found. Due to the lability of the enamides and the reluctancy of the tertiary iminium ions to undergo nucleophilic attack, further investigations were not carried out.

Conclusions

In this article, several types of palladium-catalyzed cyclization reactions with different acetylene-containing amino acids are detailed. Depending on the protection of the amine or the carboxylic acid function, either the nitrogen or the oxygen could act as a nucleophile to form nitrogen- or oxygen-heterocycles, respectively. In most cases, the yield of the cyclization(/coupling) reactions was satisfactory and the enantiopurity of the starting material was retained in the product. The nitrogen appeared a more useful and efficient nucleophile than the oxygen atom, leading to a larger variety of cyclization products. The cyclic enamides and enol ethers that were formed in these reactions were generally not very stable and therefore partially responsible for the moderate yields. A few methods to derivatize these products were investigated, but were abandoned due to the reluctance of the resulting cations to undergo further substitution.

Experimental Section

General Information

All reactions were carried out under an inert atmosphere of dry nitrogen, unless stated otherwise. Standard syringe techniques were applied for transfer of Lewis acids and dry solvents. Infrared (IR) spectra were obtained from KBr pellets or neat, using a Bruker IFS 28FT spectrometer and wavelengths (ν) are reported in cm^{-1}. Proton nuclear magnetic resonance (^1H NMR) spectra were determined in $CDCl_3$ (unless stated otherwise) using a Bruker AC 200 (200 MHz) and a Bruker ARX 400 (400 MHz) spectrometer. The machines were also used for ^{13}C NMR (APT) spectra (50 MHz and 100 MHz) in $CDCl_3$ (unless stated otherwise). Chemical shifts (δ) are given in ppm downfield from tetramethylsilane. Mass spectra and accurate mass measurements were carried out using a JEOL JMS-SX/SX 102A Tandem Mass Spectrometer, a Varian NIAT 711 or a VG Micromass ZAB-HFQQ instrument. Elemental analysis were performed by Dornis u. Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. R_f values were obtained by using thin layer chromatography (TLC) on silica gel-coated plastic sheets (Merck silica gel 60 F_{254}) with the indicated solvent (mixture). Chromatographic purification refers to flash column chromatography[31] using the indicated solvent (mixture) and Acros Organics silica gel (0.035 – 0.070 mm). Melting and boiling points are uncorrected. Melting points were determined with Büchi melting point B-545. Dry THF and Et_2O were distilled from sodium benzophenone ketyl prior to use. Dry DMF, CH_2Cl_2 and MeCN were distilled from CaH_2 and stored over MS 4 Å under a dry nitrogen atmosphere. Triethylamine was dried from KOH pellets. Et_2O, EtOAc, PE (60 – 80 °C) were distilled prior to use. All commercially available reagents were used as received, unless indicated otherwise.

(*R*)-2-(Toluene-4-sulfonylamino)pent-4-ynoic Acid (13)

To a solution of (*R*)-**11** (200 mg, 1.77 mmol) in H_2O (15.0 mL), 1 M NaOH (1.80 mL, 1.80 mmol) and *p*-toluenesulfonyl chloride (47.2 mg, 2.47 mmol) were added. The reaction mixture was stirred at ambient temperature for 16 h. The reaction mixture was kept at a basic pH by slowly adding 1 M aqueous NaOH. After the conversion was complete, the reaction mixture was extracted with ether (3 × 10 mL), acidified with 1 M aqueous HCl and extracted with EtOAc (3 × 15 mL). The combined EtOAc layers were dried ($MgSO_4$) and concentrated. Purification of the crude product by flash chromatography (EtOAc, 5% AcOH) afforded (*R*)-**13** as an amorphous solid; yield: 390 mg (1.46 mmol, 83%); (*R*)-**13**: $[\alpha]_D$: = – 36.0 (*c* 1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 10.27 (s, 1H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 5.75 (d, *J* = 8.8 Hz, 1H), 4.16 – 4.11 (m, 1H), 2.69 – 2.63

(m, 2H), 2.39 (s, 3H), 1.23 (t, $J = 7.1$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 173.8, 143.9, 136.5, 129.6, 127.0, 80.0, 72.5, 53.7, 23.5, 21.4$; IR (film): $\nu =$ 3500 – 2750, 3288, 2125, 1732, 1598, 1335, 1161, 1092 cm^{-1}; HRMS (FAB): calcd. for $C_{12}H_{14}NO_4S$ (MH^+) 268.0644, found 268.0654.

(*S*)-2-(Toluene-4-sulfonylamino)hex-5-ynoic Acid (14)

To a solution of (*S*)-**12** (100 mg, 0.79 mmol) in H_2O (2.0 mL), 1 M NaOH (0.90 mL, 0.90 mmol) and *p*-toluenesulfonyl chloride (180 mg, 0.95 mmol) were added and the reaction mixture was stirred for 16 h at ambient temperature. The reaction mixture was kept basic during the reaction time. The reaction mixture was washed with ether (3× 50 mL), acidified with 1 M HCl and extracted with EtOAc (3 × 50 mL). The combined EtOAc layers were dried ($MgSO_4$) and concentrated. After purification of the crude product by flash chromatography (ether, 5% AcOH), (*S*)-**14** was obtained as an amorphous solid; yield: 162 mg (0.58 mmol, 73%). (*R*)-**14**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.74$ (d, $J = 8.3$ Hz, 2H), 7.29 (d, $J = 7.7$ Hz, 2H), 5.35 (d, $J = 8.8$ Hz, 1H), 4.07 – 4.02 (m, 1H), 2.41 (s, 3H), 2.30 – 2.26 (m, 2H), 2.09 – 2.00 (m, 1H), 1.94 (t, $J = 2.6$ Hz, 1H), 1.87 – 1.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$); $\delta = 175.6, 143.9, 136.2, 129.6, 127.1, 81.8, 69.8, 54.2, 31.6, 21.4, 14.5$; IR (film): $\nu = 3292, 3250$-$2750, 1750, 1410, 1334$ cm^{-1}; HRMS (EI): calcd. for $C_{13}H_{15}NO_4S$ 281.0722, found 281.0707.

(*R*)-2-*tert*-Butoxycarbonylaminopent-4-ynoic Acid (15)

To a solution of (*R*)-**11** (100 mg, 0.88 mmol) in dioxane/water (2.0 mL/ 2.0 mL), sodium bicarbonate (148 mg, 1.76 mmol) and di-*tert*-butyl dicarbonate (203 mg, 0.92 mmol) were added. After refluxing for 4 h, the dioxane was evaporated and aqueous saturated sodium bicarbonate (5 mL) was added to the reaction mixture. The reaction mixture was washed with ether (3 × 10 mL), acidified with 1 M HCl and extracted with EtOAc (3 × 10 mL). The combined EtOAc layers were dried ($MgSO_4$) and concentrated. Purification of the crude product by flash chromatography (ether, 5% AcOH) afforded (*R*)-**15** as a colorless oil; yield: 114 mg (0.73 mmol, 83%). (*R*)-**15**: $[\alpha]_D$: − 33.6 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.34$ (d, $J = 7.8$ Hz, 1H), 4.52 – 4.51 (m, 1H), 2.80 – 2.74 (m, 2H), 2.08 (t, $J = 2.6$ Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 174.5, 155.2, 80.4, 78.1, 71.6, 51.5, 28.0, 22.3$; IR (film): $\nu = 3500 - 2800, 3298, 2980, 1716, 1668, 1514, 1161$ cm^{-1}; HRMS (EI): calcd. for $C_{10}H_{15}NO_4$ 213.1001, found 213.0994.

(*S*)-2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)pent-4-ynoic Acid (16)

To a solution of (*S*)-**11** (500 mg, 3.76 mmol) in H_2O (10 mL) phthalic anhydride (560 mg, 3.76 mmol) was added. The reaction mixture was irradiated in a microwave until the water was evaporated. Then, again H_2O (10 mL) was added and this procedure was repeated three times. After purification of the crude product by flash chromatography (ether, 5% AcOH), (*S*)-**16** was obtained as a colorless oil; yield: 830 mg (3.42 mmol, 91%). (*S*)-**16**: $[\alpha]_D$: − 40.4 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 9.20 – 8.80 (bs, 1H), 7.92 – 7.85 (m, 2H), 7.78 – 7.72 (m, 2H), 5.14 (dd, $J =$ 4.8 Hz, 11.3 Hz), 3.30 – 3.22 (m, 1H), 3.12 – 3.06 (m, 1H), 1.90 (t, $J = 2.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.3, 168.8, 135.7, 134.1, 132.9, 132.0, 130.0, 124.4, 80.3, 71.7, 51.9, 20.04$; IR (film): $\nu = 3290, 1775, 1713, 1393$ cm^{-1}; HRMS (EI): calcd. for $C_{13}H_9NO_4$ 243.0532, found 243.0537.

2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)hex-5-ynoic Acid (17)

To a solution of *rac*-**12** (200 mg, 1.57 mmol) in H_2O (10 mL) phthalic anhydride (233 mg, 1.57 mmol) was added. The reaction mixture was irradiated in a microwave until the water was evaporated. Then, again H_2O (10 mL) was added and the procedure was repeated three times. After purification of the crude product by flash chromatography (ether, 5% AcOH), **17** was obtained as a colorless oil; yield: 369 mg (1.44 mmol, 91%). **17**: ^{1}H NMR (400 MHz, CD_3OD): $\delta = 7.90 - 7.81$ (m, 4H), 4.98 – 4.94 (m, 1H), 2.46 – 2.40 (m, 2H), 2.32 – 2.22 (m, 2H), 2.10 (t, $J = 2.6$ Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 169.4, 135.5, 133.2, 132.0, 131.7, 124.3, 83.5, 70.4, 53.0, 28.8, 16.6$; IR (film): $\nu = 3288 - 2750, 1715, 1393$ cm^{-1}; HRMS (EI): calcd. for $C_{14}H_{11}NO_4$ 257.0688, found 257.0671.

(*S*)-2-(4-Toluenesulfonylamino)pent-4-ynoic Acid Methyl Ester (18)

To a solution of (*S*)-**11** (3.00 g, 0.020 mol) in MeOH (100 mL) thionyl chloride (2.9 mL, 0.040 mol) was added. After refluxing at 70 °C for 3 h, the reaction mixture was concentrated under vacuum. The crude reaction mixture was dissolved in pyridine (50 mL), *p*-toluenesulfonyl chloride (4.60 g, 0.020 mol) was added and the reaction mixture was stirred for 16 h at ambient temperature. The pyridine was evaporated and aqueous saturated $CuSO_4$ (50 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were washed with aqueous saturated sodium bicarbonate (25 mL), then with brine, dried ($MgSO_4$) and concentrated. After purification by flash chromatography (70% ether/ petroleum ether) and crystallization (EtOAc/petroleum ether), (*S*)-**18** was obtained as a white solid; 5.30 g (18.0 mmol, 94%). (*S*)-**18**: mp 82 – 84 °C; $[\alpha]_D$: + 19.4 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.73$ (d, $J = 1.5$ Hz, 2H), 7.71 (d, $J = 7.7$ Hz, 2H), 5.71 (d, $J = 8.8$ Hz, 1H), 4.12 – 4.07 (m, 1H), 3.59 (s, 3H), 2.67 – 2.63 (m, 2H), 2..39 (s, 3H), 2.01 (t, $J = 2.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 169.9, 143.7, 136.7, 126.6, 127.1, 77.4, 72.2, 53.9, 52.7, 23.9, 21.4$; IR (film): $\nu = 3273, 2953, 1712$ cm^{-1}; HRMS: (FAB) calcd. for $C_{13}H_{16}NO_4S$ (MH^+) 282.0800, found 282.0791.

(*R*)-2-(4-Toluenesulfonylamino)hex-5-ynoic Acid Methyl Ester (19)

To a solution of (*R*)-**12** (1.00 g, 7.87 mmol) in MeOH (250 mL) thionyl chloride (1.12 mL, 15.7 mmol) was added. After refluxing at 70 °C for 5 h the reaction mixture was concentrated under vacuum. The crude reaction mixture was dissolved in CH_2Cl_2 (50 mL), Et_3N (5.46 mL, 29.4 mmol) and *p*-toluenesulfonyl chloride (3.0 g, 15.7 mmol) were added and the reaction mixture was stirred for 16 h at ambient temperature. An aqueous solution of NH_4Cl (50 mL) was added to the reaction mixture. After separation, the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were stirred with aqueous saturated sodium bicarbonate (25 mL) for 1 h. After separation the organic layer was dried ($MgSO_4$) and concentrated. Purification of the crude product by flash chromatography (70% ether/petroleum ether) and crystallization (EtOAc/petroleum ether) afforded (*R*)-**19** as a white solid; yield: 1.68 g (5.69 mmol, 72%). (*R*)-**19**: mp 75 – 77 °C; $[\alpha]_D$: − 35.7 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) $\delta = 7.73$ (dd, $J = 1.6$ Hz, 6.6 Hz, 2H), 7.29 (d, $J = 7.9$ Hz, 2H), 5.22 (d, $J = 8.9$ Hz, 1H), 4.02 – 3.99 (m, 1H), 3.52 (s, 3H), 2.41 (s, 3H) 2.32 – 2.27 (m, 2H), 1.98 – 1.94 (m, 2H), 1.86 – 1.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.6, 143.6, 136.4, 129.5, 127.1, 82.1, 69.4, 54.6, 52.4, 31.9, 21.3, 14.4$; IR (film): $\nu = 3280, 2954, 2119, 1922, 1732, 1598$ cm^{-1}; HRMS (EI): calcd. for $C_{14}H_{17}NO_4S$ 295.0878, found 295.0858.

(*R*)-2-(4-Nitrobenzenesulfonylamino)hex-5-ynoic Acid Methyl Ester (20)

To a solution of (*R*)-**12** (400 mg, 3.15 mmol) in MeOH (250 mL) thionyl chloride (0.45 mL, 6.30 mmol) was added. After refluxing at 70 °C for 5 h the reaction mixture was concentrated under vacuum. The crude residue was dissolved in CH_2Cl_2 (25 mL), Et_3N (2.15 mL, 15.7 mmol) and *p*-nitrophenylsulfonyl chloride (1.05 g, 4.72 mmol) was added and the reaction mixture was stirred for 16 h at ambient temperature. An aqueous solution of NH_4Cl (50 mL) was added to the reaction mixture. After separation the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were stirred with aqueous saturated sodium bicarbonate (25 mL) for 1 h. After separation the organic layer was dried ($MgSO_4$) and

concentrated. Purification by flash chromatography (70% ether/petroleum ether) and crystallization (EtOAc/petroleum ether) afforded (*R*)-**20** as a yellow solid; yield: 604 mg (1.85 mmol, 59%). (*R*)-**20**: mp 87–89 °C; $[\alpha]_D$: −33.9 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (d, *J* = 8.6 Hz, 2H), 8.05 (d, *J* = 8.6 Hz, 2H), 5.40 (d, *J* = 8.8 Hz, 1H), 4.13–4.11 (m, 1H), 3.60 (s, 3H), 2.34–2.29 (m, 2H), 2.05–2.01 (m, 1H), 1.98 (t, *J* = 2.6 Hz, 1H), 1.90–1.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 149.9, 145.2, 128.2, 124.0, 81.6, 69.7, 54.6, 52.6, 31.6, 14.3; IR (film): ν = 3284, 1742, 1532, 1351, 1166 cm^{-1}; HRMS (EI): calcd. for $C_{13}H_{14}N_2O_6S$ 326.0573, found 326.0583.

General Procedure A for the Oxypalladation Reactions

To a solution of the cyclization precursor in THF, Et_3N and the Pd-catalyst were added. The reaction mixture was stirred at ambient temperature or at 60 °C. After the reaction was finished (TLC), the solvent was evaporated and the product was purified by flash chromatography (gradient: 20 → 70% ether/petroleum ether, 1% Et_3N).

(*R*)-4-Methyl-*N*-(5-methylene-2-oxotetrahydrofuran-3-yl)benzenesulfonamide (21)

Following the general procedure A, to a solution of (*R*)-**13** (100 mg, 0.37 mmol) in THF (3.0 mL), Et_3N (8.0 μL, 0.06 mmol) and $Pd(OAc)_2$ (8.0 mg, 0.04 mmol) were added. The reaction mixture was stirred for 1 h at ambient temperature. Purification afforded (*R*)-**21** as a colorless oil; yield: 66.0 mg (0.25 mmol, 66%). (*R*)-**21**: $[\alpha]_D$: −27.2 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.3 Hz, 2H), 7.74 (d, *J* = 8.1 Hz, 2H), 5.19 (d, *J* = 3.4 Hz, 1H), 4.82–4.81 (m, 1H), 4.46–4.45 (m, 1H), 4.12–4.06 (m, 1H), 3.27 (dd, *J* = 15.9 Hz, 9.1 Hz, 1H), 2.92–2.85 (m, 1H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9, 151.6, 144.1, 136.1, 129.8, 127.1, 90.9, 51.9, 33.8, 21.4; IR (film): ν = 3270, 2922, 2258, 1811, 1681, 1598, 1340 cm^{-1}; HRMS (FAB): calcd. for $C_{12}H_{13}NO_4S$ (MH^+) 267.0565, found 267.0554.

(*R*)-(5-Methylene-2-oxotetrahydrofuran-3-yl)carbamic Acid *tert*-Butyl Ester (22)

Following the general procedure A, to a solution of (*R*)-**15** (40 mg, 0.19 mmol) in THF (2.0 mL) Et_3N (4.0 μL, 0.03 mmol) and $Pd(OAc)_2$ (4.0 mg, 0.02 mmol) were added. Work-up and purification afforded (*R*)-**22** as an amorphous solid; yield: 25 mg (0.12 mmol, 63%). (*R*)-**22**: $[\alpha]_D$: +64.1 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.13 (s, 1H), 4.80 (d, *J* = 1.8 Hz, 1H), 4.41–4.40 (m, 2H), 3.29–3.23 (m, 1H), 2.89-2.83 (m, 1H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 152.11, 90.26, 80.1, 50.4, 33.3, 28.0 (the quaternary olefinic carbon was not observed); IR (film): ν = 3360, 2980, 1816, 1682, 1520, 1255, 1138 cm^{-1}; HRMS (EI): calcd. for $C_{10}H_{15}NO_4$ 213.1001, found 213.1003.

(*S*)-2-(5-Methylene-2-oxotetrahydrofuran-3-yl)isoindole-1,3-dione (23)

Following the general procedure A, to a solution of (*S*)-**16** (50 mg, 0.21 mmol) in THF (2.0 mL), Et_3N (4.0 μL, 0.03 mmol) and $Pd(OAc)_2$ (4.0 mg, 0.02 mmol) were added. The reaction mixture was stirred for 24 h at ambient temperature. Purification afforded (*S*)-**23** as a white amorphous solid; yield: 21 mg (0.09 mmol, 42%). (*S*)-**23**: $[\alpha]_D$: −58.4 (*c* 0.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91–7.86 (m, 2H), 7.80–7.76 (m, 2H), 5.24 (t, *J* = 10.1 Hz, 1H), 4.91 (d, *J* = 1.2 Hz, 1H), 4.47 (s, 1H), 3.32–3.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.0, 166.5, 151.5, 134.5, 131.4, 123.7, 90.7, 47.0, 30.3; IR (film): ν = 2900, 1809, 1775, 1716, 1676, 1397 cm^{-1}; HRMS (EI): calcd. for $C_{13}H_9NO_4$ 243.0532, found 243.0531.

4-Methyl-*N*-(6-methylene-2-oxotetrahydropyran-3-yl)benzenesulfonamide (24)

Following the general procedure A, to a solution of *rac*-**14** (50 mg, 0.18 mmol) in MeCN (2.0 mL), Et_3N (4.0 μL, 0.03 mmol) and $PdCl_2(MeCN)_2$ (2.3 mg, 0.01 mmol) were added. The reaction mixture was stirred for 16 h at reflux temperature. Purification afforded **24** as a white amorphous solid; yield: 16.0 mg (0.06 mmol, 32%). **24**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 5.10 (d, *J* = 4.1 Hz, 1H), 4.72 (s, 1H), 4.41 (d, *J* = 1.5 Hz, 1H), 3.84–3.78 (m, 1H), 3.05–2.98 (m, 1H), 2.73–2.66 (m, 1H), 2.63–2.57 (m, 1H), 2.55-2.44 (m, 1H), 2.43 (s, 3H).

1-(6-Methylene-2-oxotetrahydropyran-3-yl)isosindole-1,3-dione (25)

Following the general procedure A, to a solution of **17** (50 mg, 0.19 mmol) in THF (2.0 mL) Et_3N (4.0 μL, 0.03 mmol) and $Pd(OAc)_2$ (4.0 mg, 0.02 mmol) were added. The reaction mixture was refluxed for 6 h. Purification afforded **25** as a colorless oil; yield: 12 mg (0.05 mmol, 24%). **25**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90–7.86 (m, 2H), 7.77–7.73 (m, 2H), 5.00–4.95 (m, 1H), 4.79 (t, *J* = 1.5 Hz, 1H), 4.43 (t, *J* = 1.4 Hz, 1H), 2.86–2.80 (m, 1H) 2.72-2.52 (m, 2H), 2.16–2.09 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 164.5, 153.8, 134.5, 131.4, 123.7, 95.2, 48.0, 26.5, 23.6; IR (film): ν = 2923, 1759, 1716, 1666, 1392 cm^{-1}.

General Procedure B for the Oxypalladation Reactions

To a solution of the cyclization precursor in MeCN, Et_3N, TBAC, the aryl halide and finally the Pd(0) catalyst were added. The reaction was heated at reflux and monitored with TLC. Upon completion, the reaction mixture was poured into saturated aqueous ammonium chloride, extracted with EtOAc (3 ×), dried ($MgSO_4$) and concentrated. The product was purified by flash chromatography (gradient: 20 → 70% ether/petroleum ether, 1% Et_3N).

(*R*)-(5-Benzylidene-2-oxotetrahydrofuran-3-yl)-carbamic Acid *tert*-Butyl Ester (27)

Following the general procedure B, to a solution of (*R*)-**15** (52 mg, 0.27 mmol) in MeCN (2.0 mL), Et_3N (186 μL, 1.34 mmol), TBAC (148 mg, 0.53 mmol), PhI (60 μl, 0.53 mmol), PPh_3 (15 mg, 0.05 mmol) and $Pd(OAc)_2$ (6.0 mg, 0.03 mmol) were added. Work-up and purification afforded (*R*)-**27** as a yellow amorphous solid; yield: 34 mg (0.12 mmol, 44%). (*R*)-**27**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.20 (m, 5H), 6.37 (s, 1H), 5.22 (d, *J* = 6.2 Hz, 1H), 4.44 (m, 1H), 3.63–3.57 (m, 1H), 3.17–3.12 (m, 1H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 147.5, 133.6, 128.5, 127.7, 126.8, 108.4, 82.3, 50.2, 33.1, 28.1, (the quaternary olefinic carbon was not observed); IR (film): ν = 2978, 1810, 1681, 1507, 1156 cm^{-1}.

2-(5-Benzylidene-2-oxotetrahydrofuran-3-yl)-isoindole-1,3-dione (28)

Following the general procedure B, to a solution of (*S*)-**16** (50 mg, 0.21 mmol) in MeCN (2.0 mL), Et_3N (142 μL, 1.03 mmol), TBAC (114 mg, 0.41 mmol), PhI (46 mg, 0.41 mmol) and $Pd(PPh_3)_4$ (24 mg, 0.03 mmol) were added. Purification afforded **28** as a white amorphous solid; yield: 28 mg (0.09 mmol, 43%). **28**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91–7.88 (m, 2H), 7.80–7.76 (m, 2H), 7.36–7.32 (m, 2H), 7.24–7.21 (m, 3H), 6.49 (t, *J* = 2.0 Hz, 1H), 5.28 (t, *J* = 9.9 Hz, 1H), 3.55–3.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3, 166.5, 146.9, 134.5, 133.5, 131.4, 128.5, 127.8, 126.9, 123.8, 108.7, 46.8, 30.4; IR (film): ν = 2926, 1815, 1778, 1721, 1682, 1397 cm^{-1}; HRMS (EI): calcd. for $C_{19}H_{13}NO_4$ 319.0845, found 319.0840.

2-[5-(4-Methoxybenzylidene)-2-oxo-tetrahydrofuran-3-yl]isoindole-1,3-dione (29)

Following the general procedure B, to a solution of (*S*)-**16** (50 mg, 0.21 mmol) in MeCN (2.0 mL), Et_3N (142 μL, 1.03 mmol), TBAC (114 mg, 0.41 mmol), 4-iodoanisole (96 mg, 0.41 mmol) and $Pd(PPh_3)_4$ (24 mg, 0.03 mmol) were added. Work-up and purification afforded **29** as a yellow oil; yield: 29 mg (0.08 mmol, 45%). **29**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 – 7.87 (m, 2H), 7.80 – 7.76 (m, 2H), 7.16 – 7.12 (m, 2H), 6.88 – 6.85 (m, 2H), 6.41 (t, *J* = 1.9 Hz, 1H), 5.27 (t, *J* = 9.9 Hz, 1H), 3.70 (s, 3H), 3.51 – 3.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 166.5, 158.5, 145.4, 134.5, 131.4, 128.9, 125.9, 123.7, 114.0, 114.0, 55.1, 46.9, 30.3; IR (film): ν = 1807, 1778, 1716, 1683, 1397 cm^{-1}; HRMS (EI): calcd. for $C_{20}H_{15}NO_5$ 349.0950, found 349.0924.

2-[5-(4-*tert*-Butylcyclohex-1-enylmethylene)-2-oxotetrahydrofuran-3-yl]isoindole-1,3-dione (30)

Following the general procedure B, to a solution of (*S*)-**16** (50 mg, 0.21 mmol) in THF (2.0 mL) were added Et_3N (142 μl, 1.03 mmol), TBAC (114 mg, 0.41 mmol), **26** (46 mg, 0.41 mmol) and $Pd(PPh_3)_4$ (24 mg, 0.03 mmol). Purification afforded **30** as a white amorphous solid; yield: 18 mg (0.05 mmol, 23%). **30**: ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.89 – 7.84 (m, 2H), 7.77 – 7.74 (m, 2H), 5.92 (d, *J* = 12.7 Hz, 1H) 5.68 – 5.66 (m, 1H), 5.37 – 5.16 (m, 1H), 3.96 – 3.21 (m, 2H), 2.71 – 2.09 (m, 2H), 1.84 – 1.52 (m, 2H), 1.40 – 1.09 (m, 3H), 0.85 (s, 9H).

2-(6-Benzylidene-2-oxotetrahydropyran-3-yl)isoindole-1,3-dione (31)

Following the general procedure B, to a solution of **17** (50 mg, 0.19 mmol) in MeCN (2.0 mL) were added Et_3N (135 μL, 0.94 mmol), TBAC (107 mg, 0.39 mmol), PhI (43 μL, 0.39 mmol) PPh_3 (10 mg, 0.04 mmol) and $Pd(OAc)_2$ (4.3 mg, 0.02 mmol). Purification afforded **31** as a white amorphous solid; yield: 20 mg (0.06 mmol, 31%). **31**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 – 7.85 (m, 2H), 7.77 – 7.74 (m, 2H), 7.56 – 7.53 (m, 2H), 7.39 – 7.35 (m, 2H), 7.28 – 7.26 (m, 1H), 6.45 (s, 1H), 5.04 (dd, *J* = 6.4 Hz, 12.3 Hz, 1H), 3.23 – 3.17 (dt, *J* = 15.8 Hz, 4.4 Hz, 1H), 2.88 – 2.79 (m, 1H), 2.69 – 2.58 (dt, *J* = 12.4 Hz, 4.4 Hz, 1H), 2.15 – 2.08 (m, 1H).

General Procedure C for the Amidopalladation Reactions

To a solution of the cyclization precursor in DMF or THF were added K_2CO_3 (5 equiv) and the Pd catalyst (10 mol %). The solution was refluxed and monitored with TLC. Upon completion, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with ether (3 ×). The combined organic layers were dried ($MgSO_4$), concentrated and purified by flash chromatography (70% ether/petroleum ether, 1% Et_3N) to afford the pure product.

(*S*)-1-(4-Toluenesulfonyl)pyrrolidine-2-carboxylic Acid Methyl Ester (32)

Following the general procedure C, to a solution of (*S*)-**18** (50 mg, 0.18 mmol) in THF (2.0 mL) were added K_2CO_3 (123 mg, 0.90 mmol) and $Pd(PPh_3)_4$ (21 mg, 0.02 mmol). Work-up and purification afforded (*S*)-**32** as a colorless oil; yield: 38 mg (0.14 mmol, 76%). (*S*)-**32**: $[\alpha]_D$: – 102.9 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$); δ = 7.69 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 6.38 – 6.36 (m, 1H), 5.08 – 5.06 (m, 1H), 4.25 (dd, *J* = 7.2 Hz, 11 Hz, 1H), 3.79 (s, 3H), 2.80 – 2.63 (m, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 144.21, 133.3, 133.0, 130.3, 129.7, 127.7, 109.6, 60.0, 52.7, 35.2, 21.5; IR (film): ν = 1742, 1355, 1167 cm^{-1}; HRMS (EI): calcd. for $C_{13}H_{15}NO_4S$ 281.0722, found 281.0722.

(*R*)-5-Methylene-1-(4-toluenesulfonyl)pyrrolidine-2-carboxylic Acid Methyl Ester (33)

Following the general procedure C, to a solution of (*R*)-**19** (50 mg, 0.17 mmol) in THF (2.0 mL) were added K_2CO_3 (117 mg, 0.85 mmol), $Pd(OAc)_2$ (4.0 mg, 0.02 mmol) and PPh_3 (19 mg, 0.07 mmol). Work-up and purification afforded (*R*)-**33** as a yellow oil; yield: 37 mg (0.125 mmol, 74%). (*R*)-**33**: $[\alpha]_D$: – 50.5 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6): δ = 7.93 (d, *J* = 8.3 Hz, 2H), 6.79 (d, *J* = 8.1 Hz, 2H), 5.52 (d, *J* = 1.2 Hz, 1H), 4.71 (dd, *J* = 4.7 Hz, 8.2 Hz, 1H), 4.23 (d, *J* = 1.3 Hz, 1H), 3.39 (s, 3H), 2.22 – 2.13 (m, 1H), 1.88 (s, 3H), 1.80 – 1.69 (m, 1H), 1.51 – 1.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.6, 145.2, 144.4, 137.2, 130.2, 128.9, 91.0, 64.5, 52.6, 32.0, 30.8, 21.7; IR (film): ν = 2921, 2849, 1734, 1162 cm^{-1}; HRMS (EI): calcd. for $C_{14}H_{19}NO_4S$ 295.0878, found 295.0881.

(*R*)-5-Methyl-1-(4-toluenesulfonyl)-2,3-dihydro-1*H*-pyrrole-2-carboxylic Acid Methyl Ester (34)

Following the general procedure C, to a solution of (*R*)-**19** (50 mg, 0.17 mmol) in THF (2.0 mL) were added K_2CO_3 (117 mg, 0.85 mmol), $Pd(OAc)_2$ (4.0 mg, 0.02 mmol) and dppb (7.2 mg, 0.02 mmol). Work-up and purification afforded a 1 : 8 mixture of (*R*)-**33** and (*R*)-**34** as a yellow oil; yield: 35 mg (0.12 mmol, 70%). (*R*)-**34**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 4.82 (s, 1H), 4.69 (dd, *J* = 4.9 Hz, 10.9 Hz, 1H), 3.79 (s, 3H), 2.63 – 2.58 (m, 1H), 2.56 – 2.55 (m, 1H), 2.43 (s, 3H), 2.02 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.7, 143.8, 139.5, 138.2, 129.6, 127.5, 108.9, 62.1, 52.5, 32.1, 21.7, 15.0; IR (film): ν = 2953, 1743, 1346, 1163 cm^{-1}.

(*R*)-5-Methylene-1-(4-nitrobenzenesulfonyl)pyrrolidine-2-carboxylic Acid Methyl Ester (35)

Following the general procedure C, to a solution of (*R*)-**20** (48 mg, 0.15 mmol) in THF (2.0 mL) were added K_2CO_3 (104 mg, 0.74 mmol), $Pd(OAc)_2$ (4.0 mg, 0.015 mmol) and PPh_3 (8.0 mg, 0.03 mmol). Work-up and purification afforded (*R*)-**35** as a yellow oil; yield: 23 mg (0.07 mmol, 48%). (*R*)-**35**: $[\alpha]_D$: – 41.9 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6): δ = 8.36 (d, *J* = 8.9 Hz, 2H), 8.15 (d, *J* = 8.9 Hz, 2H), 5.52 (d, *J* = 1.2 Hz, 1H), 4.75 – 4.72 (m, 1H), 4.39 (dd, *J* = 1.6 Hz, 3.2 Hz, 1H), 3.79 (s, 3H), 2.67 – 2.59 (m, 1H), 2.44 – 2.40 (m, 1H), 2.40 – 2.36 (m, 1H), 2.21 – 1.97 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 150.3, 143.8, 143.3, 128.9, 123.9, 91.2, 63.4, 52.6, 31.0, 26.9; IR (film): ν = 2956, 1747, 1531, 1351 cm^{-1}; HRMS (EI): calcd. for $C_{13}H_{14}N_2O_6S$ 326.0573, found 326.0579.

General Procedure D for the Amidopalladation Reactions

To a solution of the cyclization precursor in MeCN were added K_2CO_3 (5 equiv), anhydrous TBAC (1 equiv), an aryl halide (5 equiv) and finally a Pd(0) catalyst (10 mol %). The solution was heated at reflux and monitored by TLC. Upon completion, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with ether (3 ×). The combined organic layers were dried ($MgSO_4$), concentrated and purified by flash chromatography (gradient: 20 → 70% ether/petroleum ether, 1% Et_3N) to afford the pure product.

(*R*)-5-Benzylidene-1-(4-toluenesulfonyl)pyrrolidine-2-carboxylic Acid Methyl Ester (37)

Following the general procedure D, to a solution of (*R*)-**19** (80 mg, 0.27 mmol) in MeCN (2.0 mL) were added K_2CO_3 (187 mg, 1.36 mmol), TBAC (79 mg, 0.27 mmol), PhI (84 μL, 1.36 mmol) and $Pd(PPh_3)_4$ (31 mg, 0.03 mmol). Work-up and purification afforded (*R*)-**37** as an amorphous solid; yield: 74 mg (0.20 mmol, 74%). (*R*)-**37**: $[\alpha]_D$: – 73.6 (*c* 0.5, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.3 Hz, 2H), 7.32 – 7.26 (m, 5H), 7.18 – 7.12 (m, 3H), 6.74 (s, 1H), 4.57 (dd, *J* = 6.6 Hz, 7.8 Hz, 1H), 3.82 (s, 3H), 2.79 – 2.75 (m, 1H), 2.42 (s, 3H), 2.35-2.30 (m, 1H), 2.15 – 2.10 (m, 1H), 1.94 – 1.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.9, 144.2, 139.8, 136.9, 134.7, 129.5, 128.1, 128.0, 126.0, 111.3, 62.4, 52.5, 28.8, 27.3, 21.4; IR (film): ν = 2951, 1750, 1653, 1349, 1163 cm^{-1}; HRMS (EI): calcd. for $C_{20}H_{21}NO_4S$ 371.1191, found 371.1178.

(*R*)-5-(4-Nitrobenzylidene)-1-(4-toluenesulfonyl)pyrrolidine-2-carboxylic Acid Methyl Ester (38)

Following the general procedure D, to a solution of (*R*)-**19** (50 mg, 0.17 mmol) in MeCN (2.0 mL) were added K_2CO_3 (117 mg, 0.85 mmol), TBAC (49 mg, 0.17 mmol), 1-iodo-4-nitrobenzene (210 mg, 0.85 mmol) and $Pd(PPh_3)_4$ (20 mg, 0.02 mmol). Work-up and purification afforded (*R*)-**38** as a yellow oil; yield: 42 mg (0.10 mmol, 59%). (*R*)-**38**: $[\alpha]_D$: − 152.2 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 – 8.09 (m, 3H), 7.83 – 7.80 (m, 3H), 7.60 – 7.22 (m, 4H), 6.68 (s, 1H), 4.71 (dd, *J* = 5.2 Hz, 8.2 Hz, 1H), 3.82 (s, 3H), 2.87 – 2.83 (m, 1H), 2.52-2.51 (m, 1H), 2.42 (s, 3H), 2.22 – 2.14 (m, 1H), 2.04 – 1.97 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 144.7, 144.0, 143.1, 141.1, 134.7, 129.6, 129.2, 128.1, 127.1, 123.5, 123.1, 107.7, 62.6, 52.6, 29.4, 27.0, 22.1; IR (film): ν = 2953, 2925, 2851, 1748, 1641, 1593, 1513, 1340 cm^{-1}; HRMS (EI): calcd. for $C_{20}H_{20}N_2O_6S$ 416.1042, found 416.1037.

(*R*)-5-(4-Methoxybenzylidene)-1-(4-toluenesulfonyl)-pyrrolidine-2-carboxylic Acid Methyl Ester (39)

Following the general procedure D, to a solution of (*R*)-**19** (50 mg, 0.17 mmol) in MeCN (2.0 mL) were added K_2CO_3 (117 mg, 0.85 mmol), TBAC (49 mg, 0.17 mmol), 4-iodoanisole (198 mg, 0.85 mmol) and $Pd(PPh_3)_4$ (20 mg, 0.02 mmol). Work-up and purification afforded (*R*)-**39** as an amorphous solid; yield: 39 mg (0.10 mmol, 58%). (*R*)-**39**: $[\alpha]_D$: − 78.2 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.83 (dd, *J* = 2.0 Hz, 6.8 Hz, 2H), 6.72 (s, 1H), 4.54 (dd, *J* = 7.0 Hz, 7.6 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 2.80 – 2.65 (m, 1H), 2.42 (s, 3H) 2.33 – 2.26 (m, 1H), 2.23 – 2.05 (m, 1H), 1.95 – 1.82 (m, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 171.9, 157.9, 144.1, 137.6, 134.7, 129.4, 129.2, 127.6, 113.6, 111.5, 62.3, 55.1, 52.5, 28.6, 27.3, 21.4; IR (film): ν = 2952, 2838, 1740, 1654, 1606, 1511, 1163 cm^{-1}; HRMS (EI): calcd. for $C_{21}H_{23}NO_5S$ 401.1297, found 401.1303.

(*R*)-5-(4-*tert*-Butylcyclohex-1-enylmethylene)-1-(4-toluenesulfonyl)pyrrolidine-2-carboxylic Acid Methyl Ester (40)

Following the general procedure D, to a solution of (*R*)-**19** (50 mg, 0.17 mmol) in MeCN (2.0 mL) were added K_2CO_3 (117 mg, 0.85 mmol), TBAC (49 mg, 0.17 mmol), **26** (242 mg, 0.85 mmol) and $Pd(PPh_3)_4$ (20 mg, 0.02 mmol). Work-up and purification afforded (*R*)-**40** as an amorphous solid; yield: 40 mg (0.09 mmol, 55%). (*R*)-**40**: $[\alpha]_D$: − 30.4 (*c* 1, CH_2Cl_2); ^{1}H NMR [400 MHz, $CDCl_3$, several signals are double due to the *s*(*cis, trans*) rotamers]: δ = 7.73 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 6.17 (s, 0.5H), 6.15 (s, 0.5H), 5.52 (s, 0.5H), 5.41 (s, 0.5H), 4.46 – 4.42 (m, 1H), 3.79 (s, 3H), 2.52 – 2.41 (m, 1H), 2.15 – 2.02 (m, 5H), 1.88 – 1.80 (m, 3H), 1.22 – 1.13 (m, 2H), 0.86 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8, 143.6, 136.3, 133.8, 131.1, 129.3, 127.2, 115.4, 115.0, 62.1, 52.4, 43.5, 36.4, 30.3, 30.0, 28.8, 27.2, 27.0, 27.0, 21.4; IR (film): ν = 2950, 2390, 2380, 1745, 1700 cm^{-1}; HRMS (EI): calcd. for $C_{24}H_{33}NO_4S$ 431.2130, found 431.2119.

(*R*)-5-(2-Butylallylidene)-1-(4-toluenesulfonyl)pyrrolidine-2-carboxylic Acid Methyl Ester (41)

Following the general procedure D, to a solution of (*R*)-**19** (50 mg, 0.17 mmol) in MeCN (2.0 mL) were added K_2CO_3 (117 mg, 0.85 mmol), TBAC (49 mg, 0.17 mmol), **36** (196 mg, 0.85 mmol) and $Pd(PPh_3)_4$ (20 mg, 0.02 mmol). Work-up and purification afforded (*R*)-**41** as an amorphous solid; yield: 9 mg (0.02 mmol, 13%). (*R*)-**41**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 6.00 (d, *J* = 15.8 Hz, 1H), 5.57 (td, *J* = 7.0 Hz, 15.8 Hz, 1H), 5.10 (d, *J* = 9.2 Hz, 1H), 3.94 – 3.88 (m, 1H), 3.50 (s, 3H), 2.41 (s, 3H), 2.17-2.13 (m, 4H), 1.87 – 1.68 (m, 2H), 1.47 – 1.40 (m, 2H), 1.37 – 1.28 (m, 2H), 0.93 – 091 (m, 3H).

(*R*)-5-Benzylidene-1-(4-nitrobenzenesulfonyl)pyrrolidine-2-carboxylic Acid Methyl Ester (42)

Following the general procedure D, to a solution of (*R*)-**20** (50 mg, 0.15 mmol) in MeCN (2.0 mL) were added K_2CO_3 (106 mg, 0.77 mmol), TBAC (43 mg, 0.15 mmol), PhI (34 μL, 0.31 mmol) and $Pd(PPh_3)_4$ (18 mg, 0.015 mmol). Work-up and purification afforded (*R*)-**42** as a yellow solid; yield: 50 mg (0.12 mmol, 80%). (*R*)-**42**: mp 149 – 150 °C; $[\alpha]_D$: − 129.3 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.35 (d, *J* = 8.9 Hz, 2H), 8.16 (d, *J* = 8.9 Hz, 2H), 7.32 – 7.12 (m, 5H), 6.69 (s, 1H), 4.67 (dd, *J* = 5.6 Hz, 8.2 Hz, 1H), 3.83 (s, 3H), 2.85 – 2.77 (m, 1H), 2.49 – 2.41 (m, 1H), 2.25 – 2.15 (m, 1H), 2.04 – 1.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.4, 150.4, 143.5, 138.5, 136.1, 128.9, 128.3, 128.1, 126.5, 124.0, 111.4, 62.4, 52.7, 28.7, 27.3; IR (film): ν = 1717, 1652, 1532, 1350 cm^{-1}; HRMS (EI): calcd. for $C_{19}H_{18}N_2O_6S$ 402.0886, found 402.0894.

(*R*)-*N*-(1-Hydroxymethylbut-3-ynyl)-4-methylbenzenesulfonamide (43)

To a solution of $LiAlH_4$ (531 mg, 3.76 mmol) in dry THF (20 mL) (*R*)-**13** (250 mg, 0.94 mmol) was added in portions. After stirring for 16 h, the $LiAlH_4$ was carefully quenched by dropwise adding 1 M HCl at 0 °C. The reaction mixture was extracted with ether (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. Without further purification (*R*)-**43** was obtained as white solid; yield: 249 mg (0.98 mmol, 100%). (*R*)-**43**: $[\alpha]_D$: + 51.0 (*c* 1.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.94 (d, *J* = 7.9 Hz, 1H), 3.72 – 3.86 (m, 1H), 3.64 – 3.59 (m, 1H), 3.45 – 3.40 (m, 1H), 2.46 – 2.39 (m, 1H), 2.44 (s, 3H), 2.36 – 2.33 (dd, *J* = 2.7 Hz, 6.8 Hz, 1H), 1.98 (t, *J* = 2.7 Hz, 1H), 1.81 (bs, 1H); IR (film): ν = 3503, 3280, 2925, 1328 cm^{-1}; HRMS (FAB): calcd. for $C_{12}H_{16}NO_3S$ (MH^+) 254.0851, found 254.0845.

(*S*)-*N*-(1-Hydroxymethylpent-4-ynyl)-4-methylbenzenesulfonamide (44)

To a solution of $LiAlH_4$ (750 mg, 19.8 mmol) in dry THF (25 mL) (*S*)-**14** (1.40 g, 4.90 mmol) was added in portions. After stirring for 16 h, the $LiAlH_4$ was carefully quenched by dropwise adding 1 M HCl at 0 °C. The reaction mixture was extracted with ether (3 × 20 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. Without further purification (*S*)-**44** was obtained as white solid; yield: 1.41 mg (5.26 mmol, 100%). (*S*)-**44**: $[\alpha]_D$: − 19.5 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.92 (d, *J* = 8.2 Hz, 1H), 3.61 – 3.39 (m, 3H), 2.43 (s, 3H), 2.17 – 2.09 (m, 2H), 1.92 (t, *J* = 2.6 Hz, 1H), 1.73 – 1.60 (m, 2H); ^{13}C NMR (400 MHz, $CDCl_3$): δ = 143.5, 137.3, 129.6, 127.0, 81.9, 69.2, 64.2, 54.5, 30.3, 21.4, 14.8; IR (film): ν = 3470, 3283, 1433, 1308, 1155 cm^{-1}; HRMS (FAB): calcd. for $C_{13}H_{18}NO_3S$ (MH^+) 268.1007, found 268.1004.

(*R*)-*N*-[1-(*tert*-Butyldimethylsiloxymethyl)but-3-ynyl]-4-methylbenzenesulfonamide (45)

To a solution of (*R*)-**43** (255 mg, 1.01 mmol) in DMF (1.0 mL), imidazole (172 mg, 2.53 mmol) and *tert*-butyldimethylsilyl chloride (181 mg, 1.21 mmol) were added. After stirring for 2.5 h at 35 °C aqueous saturated $NaHCO_3$ was added and the organic layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (20 → 70% ether/petroleum ether, 5% Et_3N) to afford (*R*)-**45** as a colorless oil; yield: 298 mg (0.81 mmol, 80%). (*R*)-**45**: $[\alpha]_D$: −12.6 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.88 (d, *J* = 8.2 Hz, 1H), 3.66 (dd, *J* = 3.8 Hz, 9.9 Hz, 1H), 3.48–3.44 (m, 1H), 3.40–3.37 (m, 1H), 2.51–2.44 (m, 1H), 2.43 (s, 3H), 2.35–2.28 (ddd, *J* = 2.7 Hz, 7.9 Hz, 16.8 Hz, 1H), 1.93 (t, *J* = 2.6 Hz, 1H), 0.84 (s, 9H), 0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.3, 137.3, 129.6, 126.9, 79.5, 70.8, 62.6, 53.0, 25.6, 21.3, 20.8, 18.0, −5.7; IR (film): ν = 3280, 2954, 2928, 2857, 1333, 1163 cm^{-1}; HRMS (FAB): calcd. for $C_{18}H_{30}NO_3Si$ (MH^+) 368.1716, found 368.1706.

(*S*)-(*N*-[1-(*tert*-Butyldimethylsiloxymethyl)pent-4-ynyl]-4-methylbenzenesulfonamide) (46)

To a solution of (*S*)-**44** (934 mg, 3.50 mmol) in DMF (7.5 mL), imidazole (595 mg, 8.75 mmol) and *tert*-butyldimethylsilyl chloride (633 mg, 4.20 mmol) were added. After stirring for 2.5 h at 35 °C, aqueous saturated $NaHCO_3$ was added and the organic layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography with (20 → 70% ether/petroleum ether, 5% Et_3N) to afford (*R*)-**46** as a colorless oil; yield: 1.20 g (3.16 mmol, 90%). (*S*)-**46**: ee 96.5% (HPLC); $[\alpha]_D$: +10.9 (*c* 1, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 4.81 (d, *J* = 8.2 Hz, 1H), 3.49–3.37 (m, 3H), 2.42 (s, 3H), 2.20–2.15 (m, 1H), 1.91 (t, *J* = 2.6 Hz, 1H), 1.72–1.65 (m, 1H), 0.84 (s, 9H), −0.02 (s, 3H), −0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.2, 129.5, 126.9, 73.3, 68.8, 63.9, 53.9, 30.9, 25.6, 21.3, 18.0, 14.9, −5.7; IR (film): ν = 3280, 2957, 2927, 2855, 2119, 1327, 1259 cm^{-1}; HRMS (FAB): calcd. for $C_{19}H_{32}NO_3Si$ (MH^+) 382.1872, found 382.1875.

(*R*)-[1-(4-Toluenesulfonyl)-3,4-dihydro-2*H*-pyrrol-2-yl]methanol (47)

Following the general procedure C, to a solution of (*R*)-**43** (44 mg, 0.12 mmol) in THF (3.0 mL) were added K_2CO_3 (83 mg, 0.66 mmol) and $Pd_2(dba)_3$. After work-up and purification (*R*)-**47** was obtained as a colorless oil; yield: 7 mg (0.02 mmol, 16%). (*R*)-**47**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, *J* = 8.2 Hz, 2H), 6.72 (d, *J* = 8.0 Hz, 2H), 6.26–6.24 (m, 1H), 4.54–4.52 (m, 1H), 3.63–3.55 (m, 3H), 1.88-1.83 (m, 2H), 1.83 (s, 3H).

(*R*)-2-(*tert*-Butyldimethylsiloxymethyl)-1-(4-toluenesulfonyl)-3,4-dihydro-2*H*-pyrrole (48)

Following the general procedure C, to a solution of (*R*)-**45** (90 mg, 0.25 mmol) in DMF (2.0 mL) were added K_2CO_3 (173 mg, 1.25 mmol) and $Pd(PPh_3)_4$ (33 mg, 0.03 mmol). After work-up and purification (*R*)-**48** was obtained as a colorless oil; yield: 24 mg (0.07 mmol, 28%). (*R*)-**48**: $[\alpha]_D$: −39.9 (*c* 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 6.29–6.27 (m, 1H), 5.10–5.08 (m, 1H), 3.86 (dd, *J* = 3.9 Hz, 9.7 Hz, 1H), 3.77–3.72 (m, 1H), 3.64 (dd, *J* = 9.7 Hz, 7.9 Hz, 1H), 2.49–2.35 (m, 2H), 2.43 (s, 3H), 0.88 (s, 9H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ = 143.9, 131.6, 130.3, 128.9, 128.70, 112.2, 66.6, 61.6, 34.1, 26.7, 21.7, 19.1, −4.52; IR (film): ν = 2951, 2929, 2857, 1345, 1161 cm^{-1}; HRMS (EI): calcd. for $C_{19}H_{29}SNO_3Si$ 379.1637, found 367.1636.

(*S*)-[5-Methyl-1-(4-toluenesulfonyl)pyrrolidin-2-yl]methanol (49)

Following the general procedure C, to a solution of (*S*)-**44** (37 mg, 0.14 mmol) in THF (2.0 mL) were added K_2CO_3 (96 mg, 0.70 mmol) and $Pd_2(dba)_3$ (2 mg). After work-up and purification (*S*)-**49** was obtained as a yellow oil; yield: 29 mg (0.11 mmol, 78%). (*S*)-**49**: $[\alpha]_D$: −19.3 (*c* 0.9, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3OD): δ = 7.74 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 2H), 5.01 (s, 1H), 4.36 (s, 1H), 4.11–4.08 (m, 1H), 3.80 (dd, *J* = 3.9 Hz, 11.0 Hz, 1H), 3.65–3.60 (m, 1H), 2.56–2.50 (m, 1H), 2.49 (s, 3H) 2.16–2.09 (m, 1H), 1.82–1.76 (m, 1H), 1.67–1.60 (m, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ = 146.9, 145.4, 137.2, 130.3, 128.3, 92.7, 65.9, 65.2, 31.4, 25.5, 21.2; IR (film): ν = 3560–3250, 2923, 1312, 1163 cm^{-1}; HRMS (EI): calcd. for $C_{13}H_{17}NO_3S$ 267.0929, found 267.0930.

(*S*)-(2-*tert*-Butyldimethylsiloxymethyl)-5-methylene-1-(4-toluenesulfonyl)pyrrolidine (50)

Following the general procedure C, to a solution of (*S*)-**46** (49 mg, 0.13 mmol) in THF (3.0 mL) were added K_2CO_3 (91 mg, 0.70 mmol) and $Pd(PPh_3)_4$ (2 mg). After work-up and purification (*R*)-**50** was obtained as a colorless oil; yield: 37 mg (0.10 mmol, 74%). (*S*)-**50**: $[\alpha]_D$: +73.2 (*c* 0.25, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6): δ = 7.77 (d, *J* = 8.2 Hz, 2H), 6.73 (d, *J* = 8.0 Hz, 2H), 5.47 (s, 1H), 4.29 (s, 1H), 4.18–4.14 (m, 1H), 4.00 (dd, *J* = 3.5 Hz, 10.1 Hz, 1H), 3.75–3.71 (m, 1H), 2.32–2.28 (m, 1H), 1.85 (s, 3H), 1.83–1.77 (m, 1H), 1.65–1.61 (m, 1H), 1.38–1.27 (m, 1H), 0.96 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ = 143.5, 91.0, 65.6, 64.4, 30.5, 25.6, 24.5, 20.5, −5.8; IR (film): ν = 2954, 2928, 2856, 1352, 1166 cm^{-1}; HRMS (FAB): calcd. for $C_{19}H_{32}SNO_3Si$ (MH^+) 382.1872, found 382.1878.

(*S*)-2-Benzylidene-5-(*tert*-butyldimethylsiloxymethyl)-1-(4-toluenesulfonyl)pyrrolidine (52)

Following the general procedure D, to a solution of (*S*)-**46** (35 mg, 0.09 mmol) in THF (2.0 mL) were added K_2CO_3 (60 mg, 0.43 mmol), TBAC (10 mg), PhI (48 μL, 0.43 mmol) and $Pd(PPh_3)_4$ (2 mg). After work-up and purification (*S*)-**52** was obtained as a colorless oil; yield: 34 mg (0.07 mmol, 82%). (*S*)-**52**: $[\alpha]_D$: +17.4 (*c* 1.5, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6): δ = 7.76 (d, *J* = 8.3 Hz, 2H), 7.28 (s, 1H), 7.16–7.05 (m, 5H), 6.69 (d, *J* = 8.0 Hz, 2H), 4.16–4.10 (m, 2H), 3.79–3.75 (m, 1H), 2.46–2.38 (m, 1H), 1.89–1.78 (m, 1H), 1.84 (s, 3H), 1.62–1.54 (m, 1H), 1.45–1.36 (m, 1H), 0.96 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ = 144.1, 142.0, 136.3, 137.2, 130.2, 129.3, 129.2, 126.9, 114.0, 67.4, 64.2, 29.7, 26.7, 26.4, 21.7, 19.1, −4.53, −4.56; IR (film): ν = 2954, 2929, 2857, 1651, 1350, 1165 cm^{-1}; HRMS (FAB): calcd. for $C_{25}H_{36}SNO_3Si$ (MH^+) 458.2185, found 458.2191.

5-Methyl-1-(4-nitrobenzenesulfonyl)pyrrolidine-2-carboxylic Acid Methyl Ester (60)

To a solution of (*R*)-**35** (37 mg, 0.11 mmol) in CH_2Cl_2 (3.0 mL) was added triethylsilane (90 μL, 0.56 mmol). At 0 °C trifluoroacetic acid (43 μL, 0.11 mmol) was added to the reaction mixture. It was allowed to reach ambient temperature, stirred for 1 h and concentrated under vacuum. Purification of the crude product by flash chromatography (20 → 70% ether/petroleum ether) afforded **60** (2:1 mixture of *cis*/*trans*-isomers) as a yellow oil; yield: 12 mg (0.04 mmol, 32%). **60** (data of both isomers): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 8.8 Hz, 2H), 8.11 (d, *J* = 8.9 Hz, 1.3H), 8.07 (d, *J* = 8.9 Hz, 0.67H), 4.53–4.51 (m, 0.33H), 4.21–4.39 (m, 0.67H), 4.09–4.07 (m, 0.33H), 3.98–3.93 (m, 0.67H), 3.75 (s, 2H), 3.67 (s, 1H), 2.08–2.01 (m, 2H), 1.99–1.89 (m, 1H), 1.70–1.61 (m, 1H), 1.30 (d, *J* = 6.4 Hz, 3H).

5-Benzyl-1-(4-toluenesulfonyl)pyrrolidine-2-carboxylic Acid Methyl Ester (61)

Method 1: To a solution of (*R*)-**37** (78 mg, 0.23 mmol) and triethylsilane (179 μL, 1.12 mmol) in CH_2Cl_2 (4.0 mL) was added trifluoroacetic acid (86 μL, 1.12 mmol) at 0 °C. It was allowed to reach ambient temperature, stirred for 16 h and concentrated. Purification of the crude product by flash chromatography (20 → 70% ether/petroleum ether) afforded **61** (10:1 mixture of *trans*/*cis*-isomers) as a yellow oil; yield: 69 mg (0.20 mmol, 88%). **61** (data of the major isomer): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.2 Hz, 2H), 7.33 – 7.22 (m, 5H), 7.20 – 7.18 (m, 2H), 4.28 – 4.25 (m, 1H), 3.94 – 3.87 (m, 1H), 3.77 (s, 3H), 3.33 (dd, *J* = 4.0 Hz, 13.4 Hz, 1H), 2.75 (dd, *J* = 10.5 Hz, 13.4 Hz, 1H), 2.42 (s, 3H), 2.03 – 1.90 (m, 1H), 1.89 – 1.82 (m, 1H), 1.74 – 1.66 (m, 1H), 1.53 – 1.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.4, 143.6, 138.2, 135.0, 129.6, 129.5, 129.2, 128.3, 127.4, 127.3, 126.3, 63.0, 61.8, 52.3, 42.1, 29.4, 29.0, 21.4; IR (film): ν = 3027, 2952, 1754, 1454, 1349, 1161 cm^{-1}; HRMS (EI): calcd for $C_{20}H_{23}NO_4S$ 373.1348, found 373.1332.

Method 2: To a suspension of 10% Pd/C (5 mg) in EtOAc (3.0 mL) were added K_2CO_3 (5 mg) and (*R*)-**37** (28 mg, 0.11 mmol). The flask was evaporated with a water aspirator and filled with H_2 gas (3 ×). After stirring for 16 h under an H_2 atmosphere, the reaction mixture was filtered over Celite. The filtrate was concentrated and the residue was purified by flash chromatography (20 → 70% ether/petroleum ether) to afford **61** (4.5:1 ,mixture of *trans*/*cis*-isomers) as a yellow oil; yield: 19 mg (0.05 mmol, 50%).

5-Benzyl-1-(4-nitrobenzenesulfonyl)pyrrolidine-2-carboxylic Acid Methyl Ester (62)

To a solution of (*R*)-**42** (34 mg, 0.10 mmol) and triethylsilane (78 μL, 0.48 mmol) in CH_2Cl_2 (4.0 mL) was added trifluoroacetic acid (37 μL, 0.48 mmol) at 0 °C. It was allowed to reach ambient temperature, stirred for 24 h and concentrated. Purification by flash chromatography (20 → 70% ether/petroleum ether) afforded **62** (10:1 mixture of *trans*/*cis*-isomers) as a yellow oil; yield: 13 mg (0.03 mmol, 35%). **62** (data of the major isomer): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 8.8 Hz, 2H), 8.06 (d, *J* = 8.9 Hz, 2H), 7.28 – 7.20 (m, 3H), 7.18 – 7.14 (m, 2H), 4.42 (t, *J* = 7.2 Hz, 1H), 4.11 – 4.07 (m, 1H), 3.77 (s, 3H), 3.20 (dd, *J* = 4.8 Hz, 13.4 Hz, 1H), 2.71 (dd, *J* = 9.9 Hz, 13.4 Hz, 1H), 2.10 – 2.04 (m, 2H), 1.77 – 175 (m, 1H), 1.66 – 1.62 (m, 1H).

5-Oxo-6-phenyl-2-(4-toluenesulfonylamino)hexanoic Acid Methyl Ester (63)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.3 Hz, 2H), 7.36 – 7.20 (m, 7H), 5.16 (d, *J* = 9.1 Hz, 1H), 3.91 – 3.85 (m, 1H), 3.72 (s, 2H), 3.46 (s, 3H), 2.76 – 2.69 (m, 1H), 2.61 – 2.55 (m, 1H), 2.41 (s, 3H), 2.08 – 2.05 (m, 1H), 1.77 – 1.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.9, 171.6, 143.5, 136.1, 133.8, 129.4, 129.3, 128.5, 127.0, 126.8, 54.5, 52.3, 49.8, 36.9, 26.7, 21.3; IR (film): ν = 3265, 1742, 1716, 1339, 1162 cm^{-1}.

5-Allyl-5-methyl-1-(4-toluenesulfonyl)pyrrolidine-2-carboxylic Acid Methyl Ester (64)

To a solution of (*R*)-**33** (40 mg, 0.14 mmol) and allyltrimethylsilane (217 μL, 1.37 mmol) in CH_2Cl_2 (2.0 mL) was added trifluoroacetic acid anhydride (96.5 μL, 0.68 mmol) at 0 °C. After stirring for 15 min at 0 °C, trifluoroacetic acid (53 μL, 0.68 mmol) was added. After stirring for 3 h at 0 °C, the reaction mixture was concentrated and purified by flash chromatography (20 → 70% ether/petroleum ether) to afford **64** (1.6:1 mixture of isomers) as a yellow oil; yield: 10 mg (0.03 mmol, 21%). **64** (data of mixture of isomers): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.3 Hz, 2H), 7.26 (d, *J* = 7.0 Hz, 2H), 5.87 – 5.83 (m, 1H), 5.14 – 4.99 (m, 2H), 4.41 – 4.39 (m, 1H), 3.57 (s, 3H), 2.47 (d, *J* = 8.9 Hz, 2H), 2.41 (s, 3H), 2.18 – 2.11 (m, 2H), 1.96 – 1.85 (m, 2H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 145.56, 143.0, 134.5, 129.2, 127.7, 117.9, 69.5, 61.8, 51.9, 45.8, 37.5, 27.5, 24.7, 21.3; IR (film): ν = 2951, 1753, 1344, 1156 cm^{-1}; HRMS (FAB): calcd. for $C_{17}H_{24}NO_4S$ (MH^+) 338.1426, found 338.1428.

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