RSC Advances

ROYAL SOCIETY OF CHEMISTRY

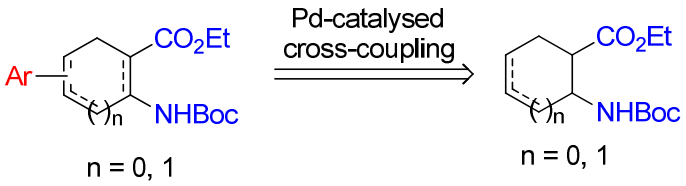
www.rsc.org/advances

An insight into the synthesis of novel aryl-substituted alicyclic β-amino acid derivatives through substrate-directed palladium-catalysed regio- and stereoselective cross-coupling

Melinda Nonn,[1,2] Loránd Kiss,[1] Mikko M. Hänninen,[3] Ferenc Fülöp[1,2]*

[1]Institute of Pharmaceutical Chemistry and [2]Stereochemistry Research Group of the Hungarian Academy of Sciences, University of Szeged, H-6720 Szeged, Eötvös u. 6, Hungary

[3]Department of Chemistry, University of Jyväskylä, FIN-40014, Jyväskylä, Finland



Abstract: Novel aryl-substituted alicyclic β-amino acid derivatives were synthetized through substrate-determined palladium-catalysed cross-coupling of aryl iodides with five- or six-membered cycloalkene β-amino esters. The arylations were investigated with different catalysts, solvents, bases and aryl halides, and with some cyclohexene 2-aminocarboxylate isomers. The stereochemistry and the position of the ring olefinic bond of the starting 2-aminocycloalkanecarboxylate influenced the coupling reaction, and predetermined the structure of the arylated product.

Introduction

Palladium-catalysed cross-couplings are among the most common and practical methods for the creation of a carbon-carbon bond, and are widely used for the synthesis of a large variety of organic substances, bioactive compounds or natural products. These coupling reactions have become, almost indispensable techniques for the synthesis of a large family of pharmaceuticals. Besides carbon-carbon bond-forming transformations, they are important for the functionalization of a large number of biomolecules, including the important arylation of different substrates.[1]

The natural and unnatural β-amino acids are an expanding area of research in synthetic organic and medicinal chemistry. They are elements of a series of complex pharmacons (e.g. enzyme inhibitors, antibiotics and antitumoural agents) or natural products.[2] Due to π-π or CH-π interactions, a carbon-carbon π-electronic system in the framework of conformationally rigid amino acids or oligopeptides may have a significant role in their structural stabilization, influencing their secondary structures; this may be manifested in improved stability towards enzymes or metabolic degradation. The incorporation of such monomers into oligopeptides may lead to improved pharmacokinetic characteristics and tuned biological properties, and may therefore be of significance in drug discovery research.[3] Some small molecular entities in this class of products, such as cispentacin or icofungipen, themselves exhibit interesting biological properties.[2] Moreover, thanks to the pharmacological potential of their functionalized derivatives, such as the antifungal methylenated icofungipen (**1**), the antibacterial hydroxylated oryzoxymicin (**2**), or the analgetic phenyl-substituted tilidin (**3**) (Figure 1), this type of molecule has received considerable attention in recent years.[2a,b, 4]

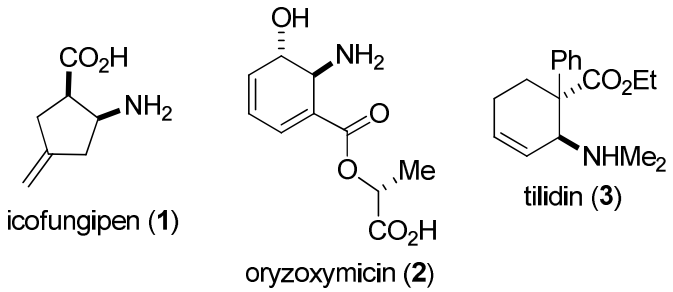


Figure 1. Structures of some bioactive functionalized cyclic β-amino acid derivatives.

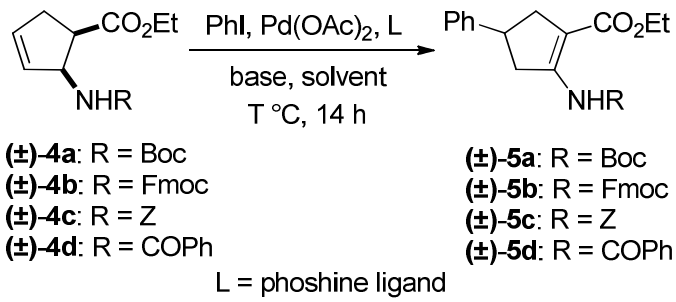
The aryl- or heteroaryl-substituted amino acids may be regarded as interesting pharmacophores and building elements for oligopetides,[3a-i] while cyclic β-amino acid scaffolds linked via amides to aryl- or heteroaryl systems are known to exhibit interesting pharmacological properties.[2a] Moreover, the combination of an aryl or heteroaryl framework with a saturated ring system with multiple chiral centres has aroused increasing interest in drug development in recent years.[3j-l] Despite to the potential tremendous benefits in medicinal and drug discovery research, only a very few approaches to aryl-substituted cycloalkane β-amino acid derivatives have been reported so far. One synthetic access route to aryl-substituted cyclic β-amino acids is based on the intramolecular dipolar cycloaddition of a nitrone (derived from a phenyl-substituted unsaturated aldehyde) to an olefinic function, followed by isoxazolidine ring opening and hydroxymethyl group oxidation.[5] The rhodium-catalysed conjugate addition of organoborons to unsaturated cyanoesters followed by ring closure is another method for the construction of arylated cycloalkane β-amino acids,[6] while cerium(IV)-catalysed sequential three-component reactions of alkylamines, β-oxoesters and aryl ketones (chalcones) lead to polysubstituted β-amino acids with a phenyl substituent attached to the cyclohexane ring.[7] Lithium amide conjugate addition to five- or six-membered phenyl-substituted α,β-unsaturated esters furnishes the corresponding phenyl-substituted β-amino acids.[8]

Among the various palladium-coupling arylation methods, the Heck, Heck-Mizoroki, Heck-Matsuda, and reductive Heck reactions are widely available routes for the creation of a carbon-carbon bond for the preparation of arylated substances, pharmaceuticals or biomolecules through the palladium-catalysed reaction of aryl halides and olefin-containing molecules in the presence of a ligand and a base.[1f-l, 9]

Since extremely few arylated alicyclic β-amino acids are available in this class of derivatives, and as a consequence of the high potential of aryl-substituted cyclic amino acids, our present aim was to synthetize carbocyclic β-amino acid derivatives bearing different aryl functions on the cycloalkane skeleton. For this purpose, palladium-catalysed arylations involving different aryl halides and cyclopentene or cyclohexene 2-aminocarboxylates as non-activated alkenes were investigated.

Results and Discussion

Our investigations of the preparation of arylated cycloalkane β-amino acid derivatives began with the reaction of the five-membered unsaturated derivative ethyl *cis*-2-*tert*-butoxycarbonylaminocyclopentane carboxylate (**(±)-4a**)[10] with iodobenzene (PhI) as aryl source compound, different palladium compounds, phosphine ligands and bases (Heck coupling reaction conditions). When stirred with PhI, palladium acetate ($Pd(OAc)_2$), triphenylphosphine (PPh_3) and Et_3N as non-nucleophilic amine as common base at 40 °C in acetone **(±)-4a** afforded under standard Heck reaction conditions, a phenylated product in 34% isolated yield after purification by column chromatography. This was identified by 2D NMR and X-ray analyses as **(±)-5a**, with the phenyl ring attached at C-4 of the ring, and a C-C double bond between the ester and the carbamate functions (Scheme 1, Table 1, entry 1, Figure 2).

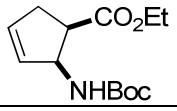
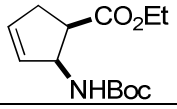
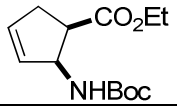
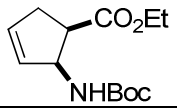
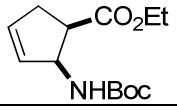
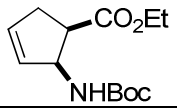
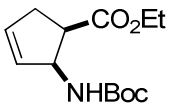
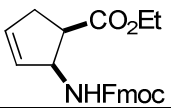


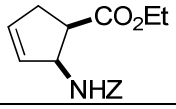
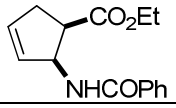
Scheme 1. Arylation of *N*-protected ethyl *cis*-2-aminocyclopent-3-enecarboxylates with PhI.

In the continuation, instead of Et_3N, some inorganic bases (K_2CO_3, NaOAc or $NaHCO_3$) were systematically used, but after 14 h only starting material was recovered, and no arylated product. Silver salts such as AgOAc, Ag_3PO_4 or Ag_2CO_3 were next used as bases in the transformation (Table 1, entries 2-4); the reaction led to **(±)-5a**, the highest yield (42% after purification by column chromatography) being attained with Ag_2CO_3. The most suitable palladium catalyst in this reaction affording **(±)-5a** seemed to be $Pd(OAc)_2$. Only traces of product were detected with several commercially available Pd(0) or Pd(II) catalysts such as *bis*(triphenylphosphine)palladium(II) dichloride ($Pd(PPh_3)_2Cl_2$), *bis*(benzonitrile)palladium(II) chloride, *bis*(dibenzylideneacetone)palladium(0) ($Pd(dba)_2$) or $PdCl_2$. Experiments were further conducted by changing the solvent from acetone to MeCN, PhMe, THF, 1,4-dioxane or DMF at 40 °C. However, the corresponding **(±)-5a** could be isolated only in MeCN and in a yield of only 24% (Table 1, entry 5). No transformation was detected in the other solvents. When the transformation was attempted at temperatures higher than 40 °C, palladium black precipitated from the reaction mixture. Interestingly, when **(±)-4a** was stirred for 14 h under similar conditions ($Pd(OAc)_2$, PPh_3, Ag_2CO_3 and acetone) at 25 °C, the yield was slightly higher (65%, Table 1, entry 6), but the effect of modification of the temperature on the yield in other situations was insignificant. Replacement of PPh_3 with *bis*(diphenylphosphino)ethane (dppe) did not lead to

any drastic modification in the yield; the target compound **(±)-5a** was isolated in 51% by column chromatography (Table 1, entry 7). During the following experiments, several other cyclopentene β-amino esters with different *N*-protecting groups were investigated in the phenylation reaction. On modification of the Boc group to Fmoc, Cbz or PhCO, the arylation of **(±)-4b-d** resulted in the corresponding phenyl-substituted five-membered β-amino esters (**(±)-5b-d**) in moderate yields (Table 1, entries 8-10).

Table 1. Various arylation conditions applied in the preparation of *N*-protected ethyl β-aminocyclopentenecarboxylates

Entry	Starting compound	Catalyst (10 mol%)	Ligand (20 mol%)	Base (2.5 equiv)	T	Solvent	Yield
1		$Pd(OAc)_2$	Ph_3P	Et_3N	40 °C	acetone	34%
2		$Pd(OAc)_2$	Ph_3P	AgOAc	40 °C	acetone	5%
3		$Pd(OAc)_2$	Ph_3P	Ag_3PO_4	40 °C	acetone	37%
4		$Pd(OAc)_2$	Ph_3P	Ag_2CO_3	40 °C	acetone	42%
5		$Pd(OAc)_2$	Ph_3P	Ag_2CO_3	40 °C	acetonitrile	24%
6		$Pd(OAc)_2$	Ph_3P	Ag_2CO_3	25 °C	acetone	65%
7		$Pd(OAc)_2$	dppe	Ag_2CO_3	40 °C	acetone	51%
8		$Pd(OAc)_2$	Ph_3P	Ag_2CO_3	40 °C	acetone	53%

9		$Pd(OAc)_2$	Ph_3P	Ag_2CO_3	40 °C	acetone	50%
10		$Pd(OAc)_2$	Ph_3P	Ag_2CO_3	40 °C	acetone	36%

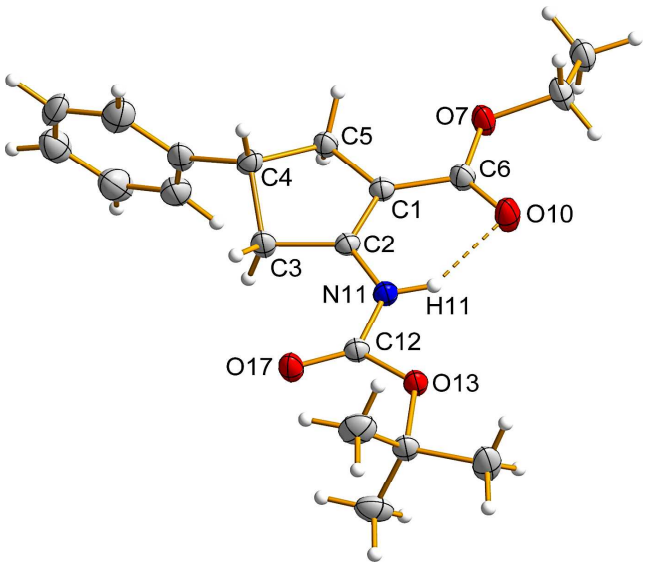
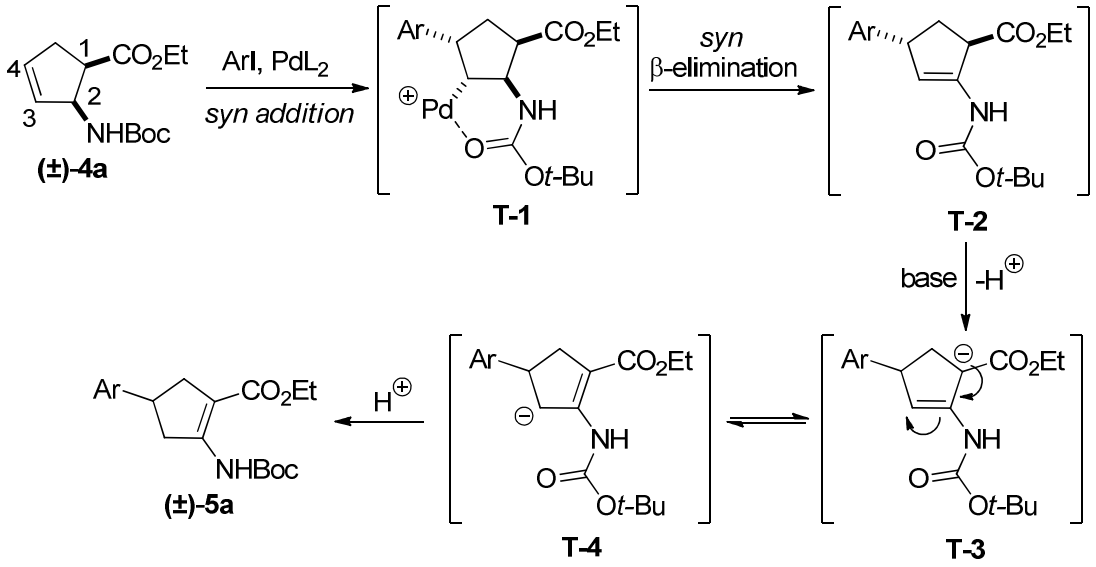


Figure 2. Molecular structure of compound **(±)-5a**. Thermal ellipsoids are drawn at the 30% probability level. Second part of the disordered groups (methine carbon, phenyl and ethyl) is omitted for clarity. Selected bond distances (Å): C1–C2 = 1.351(3), C2–C3 = 1.497(3), C3–C4 = 1.594(4), C4–C5 = 1.575(4), C5–C1 = 1.504(3).

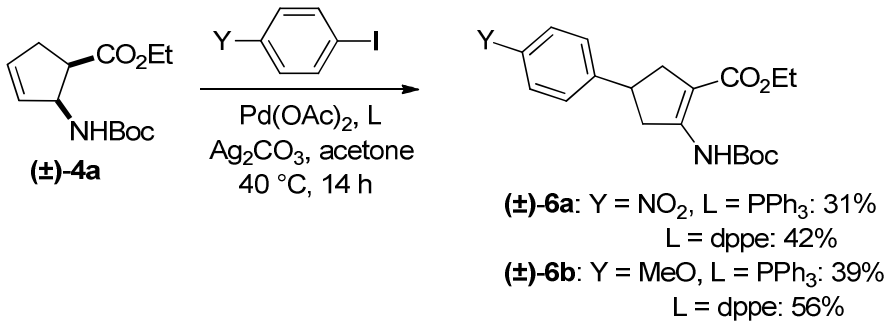
Although a common Heck arylation proceeds by *syn* addition to the olefinic bond, followed by β-elimination, to afford an α,β-unsaturated aryl-substituted product, the phenylation of ethyl *cis*-2-aminocyclopent-3-enecarboxylate took place by substrate control with the assistance of the carbamate group to result in a somewhat unexpected compound (**(±)-5**). In the first step, after Pd insertion into the aromatic C-I bond, *syn* addition gives intermediate **T-1** both stereo- and regioselectively. The stereo- and regioselectivity of this step are probably a result of the stabilizing effect of the carbamate *O*-atom on the

Pd. Next, the β-elimination process gives **T-2**. In turn under basic conditions, the active hydrogen at C-1 leads to deprotonation-reprotonation and hence double bond migration (**T-3** and **T-4**), to furnish compound **(±)-5a**, in which the phenyl ring is attached to C-4, while the olefinic bond is situated between the ester and the carbamate functions (C-1-C-2) (Scheme 2). Besides the above presented route, an alternative mechanism which relies in an addition/β-elimination/reinsertion/ β-elimination it is also plausible for the formation of arylated compound **(±)-5a.**



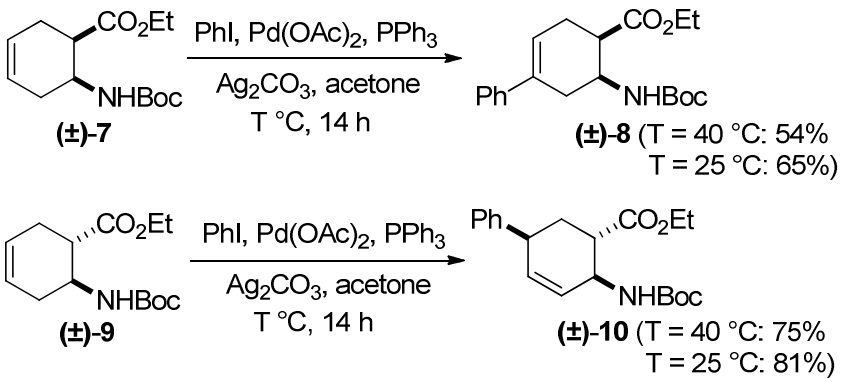
Scheme 2. A possible route to the arylated ethyl *cis*-2-aminocyclopent-3-encarboxylate with PhI.

Further experiments were carried out with aryl iodide containing an electron-withdrawing or an electron-donating group. Thus, the Pd-catalysed cross-coupling reactions of **(±)-4a** with 4-nitroiodobenzene (electron-withdrawing) and 4-methoxyiodobenzene (electron-donating) in the presence of $Pd(OAc)_2$, Ag_2CO_3 and PPh_3 in acetone resulted in the C-4 aryl group-substituted five-membered β-amino ester **(±)-6a** or **(±)-6b** (31% and 39%, respectively) (Scheme 3). The yields in this case could be increased somewhat (42% and 56%) by changing the phosphine ligand from PPh_3 to dppe (Scheme 3).



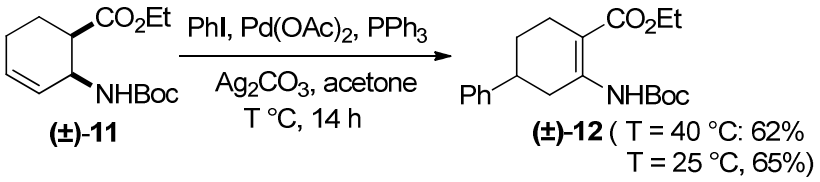
Scheme 3. Arylation of *N*-Boc-protected ethyl *cis*-2-aminocyclopent-3-enecarboxylates with *p*-substituted iodobenzenes.

Interestingly, in contrast with the arylation of ethyl *cis*-2-aminocyclopent-3-enecarboxylate (**(±)-4a**), its six-membered analogue **(±)-7**[11] underwent phenylation under similar conditions ($Pd(OAc)_2$, PPh_3, Ag_2CO_3, acetone, 40 °C) to provide a different type of arylated product from that obtained in the earlier case **(±)-5a**. Structure elucidation by means of 2D NMR analysis showed that the product (**(±)-8**) contained an α,β-unsaturated phenyl moiety in its structure, with the phenyl group attached to C-4 of the six-membered cycloalkane ring (Scheme 4). With a similar reaction protocol, the *trans* counterpart of **(±)-7**, amino ester **(±)-9**,[11] surprisingly gave phenylated compound **(±)-10**, containing the phenyl group at C-5, with the olefinic bond located between C-3 and C-4. At 25 °C, both reactions gave slightly better yields (65% and 81%, respectively) (Scheme 4).



Scheme 4. Arylation of *N*-Boc-protected ethyl *cis*- and *trans*-2-aminocyclohex-4-enecarboxylates with PhI.

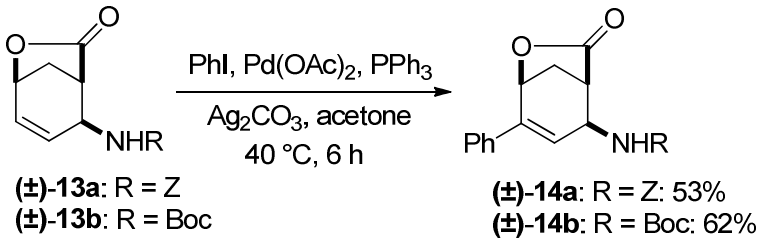
The substrate ethyl *cis*-2-aminocyclohex-3-enecarboxylate **(±)-11**,[11] a regioisomer of **(±)-7**, was next subjected to phenylation under Heck reaction conditions. Analogously to its five-membered homologue **(±)-4a**, this allylamine afforded the corresponding six-membered arylated β-amino ester **(±)-12** (Scheme 5), in which the phenyl ring is on C-4, and the C-C double bond is between the ester and carbamate functions (see also the transformation of **(±)-4**, Scheme 1).



Scheme 5. Arylation of *N*-Boc-protected ethyl *cis*-2-aminocyclohex-3-enecarboxylate with PhI.

For investigation of the influence of the position of the ring olefinic bond on the reaction, amino lactone **(±)-13**,[12] was reacted analogously to **(±)-11** with PhI in the presence of the $Pd(OAc)_2/PPh_3/Ag_2CO_3$ system in acetone. In contrast with **(±)-11**, no migration of the olefinic bond was detected during the transformation. Instead, after the *syn* addition and β-elimination

steps, the obtained was identified by COSY and HSQC analyses as **(±)-14**, an α,β-unsaturated phenyl-substituted aminolactone (Scheme 6).



Scheme 6. Arylation of *N*-protected bicyclic aminolactones with PhI.

In conclusion, the reactions illustrate a substrate-directed Pd-catalyzed arylation protocol providing access to novel aryl-substituted alicyclic β-amino acid derivatives. Depending on the structure of the starting β-aminocycloalkenecarboxylate and the position of the ring C-C double bond, the palladium coupling under Heck reaction conditions somewhat surprisingly afforded a different type of aryl-substituted cyclic β-amino acid derivatives. For the elucidation of further aspects of such unexpected arylations, additional experiments are currently ongoing in our laboratories. These novel π-electron-rich conformationally restricted β-amino acid derivatives may well be of interest in the synthesis of oligopeptides.

Experimental

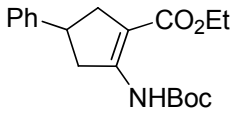
The chemicals were purchased from Sigma-Aldrich. The NMR spectra were recorded at 400 MHz with $CDCl_3$ or DMSO as solvent and tetramethylsilane as internal standard. The solvents were used as received from the suppliers. Melting points were determined with a Kofler apparatus. Elemental analyses were recorded on a Perkin-Elmer CHNS-2400 Ser II Elemental

Analyzer. Silica gel 60 F254 has been purchased from Merck. Mass spectra were recorded on a Finnigan MAT 95S spectrometer.

General procedure for the arylation of ethyl 2-aminocycloalkanecarboxylates

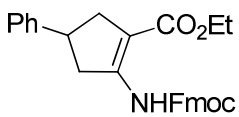
To a solution of *N*-protected 2-aminocycloalkenecarboxylate (1 mmole), base (3 equiv.) and aryl iodide (1 equiv.) in solvent (10 mL), phosphine (20 mol%) and $Pd(OAc)_2$ (10 mol%) were added. The solution was stirred at 25 °C or 40 °C for 14 h. The solid material was then filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: *n*-hexane-EtOAc 5:1) or crystallized from a mixture of *n*-hexane-EtOAc.

Ethyl 2-(*tert*-butoxycarbonylamino)-4-phenylcyclopent-1-enecarboxylate ((±)-5a)



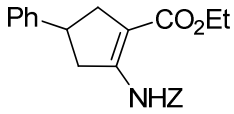
A white solid (*n*-hexane-EtOAc), mp 95-96 °C, yield: 65%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.31 (t, 3H, CH_3, J = 7.15 Hz), 1.51 (s, 9H, *t*-Bu), 2.61-2.69 (m, 1H, CH_2), 2.97-3.04 (m, 1H, CH_2), 3.15-3.24 (m, 1H, CH_2), 3.48-3.56 (m, 1H, CH_2), 3.62-3.67 (m, 1H, H-4), 4.18-4.28 (m, 2H, OCH_2), 7.22-7.36 (m, 5H, Ar-H). ^{13}C NMR (DMSO, 400 MHz): δ = 15.1, 28.6, 37.3, 40.6, 41.7, 60.5, 82.0, 104.5, 127.1, 127.5, 129.3, 145.9, 151.8, 154.3, 167.6. MS: (ES, pos) m/z = 332 (M + 1).

Ethyl 2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-phenylcyclopent-1-enecarboxylate ((±)-5b)



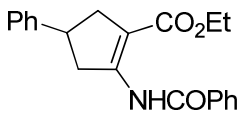
A colourless oil, yield: 53%. ^{1}H NMR (DMSO, 400 MHz): δ = 1.29 (t, 3H, CH_3, J = 7.15 Hz), 2.40-2.48 (m, 1H, CH_2), 2.77-2.94 (m, 2H, CH_2), 3.25-3.30 (m, 1H, CH_2), 3.39-3.50 (m, 1H, H-4), 4.12-4.23 (m, 2H, OCH_2), 4.25-4.30 (m, 1H, ArCH), 5.52-4.59 (m, 2H, OCH_2), 7.23-7.28 (m, 3H, Ar-H), 7.30-7.37 (m, 6H, Ar-H), 7.59-7.64 (m, 2H, Ar-H), 7.77-7.86 (m, 2H, Ar-H), 9.54 (brs, 1H, N-H). ^{13}C NMR (DMSO, 400 MHz): δ = 15.0, 39.8, 40.4, 41.7, 47.3, 60.6, 67.6, 105.5, 121.0, 125.6, 127.1, 127.6, 128.0, 128.6, 129.3, 141.7, 144.7, 145.9, 152.7, 153.3, 167.4. MS: (ES, pos) m/z = 454 (M + 1).

Ethyl 2-(benzyloxycarbonylamino)-4-phenylcyclopent-1-enecarboxylate ((±)-5c)



A white solid (*n*-hexane-EtOAc), mp 56-57 °C, yield: 50%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.33 (t, 3H, CH_3, J = 7.15 Hz), 2.64-2.72 (m, 1H, CH_2), 3.01-3.10 (m, 1H, CH_2), 3.19-3.28 (m, 1H, CH_2), 3.50-3.58 (m, 1H, CH_2), 3.66-3.75 (m, 1H, H-4), 4.20-4.28 (m, 2H, OCH_2), 5.19 (s, 2H, OCH_2), 7.27-7.43 (m, 5H, Ar-H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 14.8, 37.4, 41.1, 41.7, 60.3, 67.7, 105.8, 126.7, 127.3, 128.7, 127.8, 128.9, 129.0, 136.2, 145.7, 153.2, 153.5, 167.8. MS: (ES, pos) m/z = 454 (M + 1).

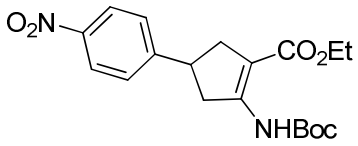
Ethyl 2-benzamido-4-phenylcyclopent-1-enecarboxylate ((±)-5d)



A white solid (*n*-hexane-EtOAc), mp 90-91 °C, yield: 36%. ^{1}H NMR (DMSO, 400 MHz): δ = 1.26 (t, 3H, CH_3, J = 7.20 Hz), 2.49-2.59 (m, 1H, CH_2), 2.92-3.00 (m, 1H, CH_2), 3.20-3.35 (m, 1H, CH_2), 3.52-3.60 (m, 1H, CH_2), 3.70-3.75 (m, 1H, H-4), 4.17-4.25 (m, 2H, OCH_2), 7.19-7.25

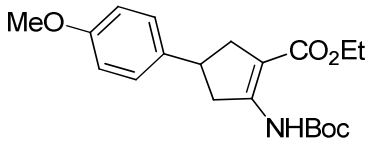
(m, 1H, Ar-H), 7.28-7.35 (m, 4H, Ar-H), 7.57-7.89 (m, 3H, Ar-H), 7.87-7.91 (m, 2H, Ar-H), 11.2 (brs, 1H, N-H).). ^{13}C NMR (DMSO, 400 MHz): δ = 15.0, 37.2, 41.0, 42.3, 60.9, 107.8, 127.1, 127.6, 128.0, 129.4, 130.0, 133.7, 133.9, 146.0, 153.9, 164.6, 167.9.

Ethyl 2-(*tert*-butoxycarbonylamino)-3-(4-nitrophenyl)cyclopent-1-enecarboxylate ((±)-6a)



A white solid (*n*-hexane-EtOAc), mp 142-145 °C, yield: 74%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.33 ((t, 3H, CH_3), 1.50 (s, 9H, *t*-Bu), 2.56-2.61 (m, 1H, CH_2), 3.02-3.12 (m, 1H, CH_2), 3.12-3.18 (m, 1H, CH_2), 3.62-3.67 (m, 1H, CH_2), 3.70-3.76 (m, 1H, H-4), 4.26-4.31 (m, 2H, OCH_2), 7.42-7.49 (d, 2H, Ar-H, J = 9 Hz), 8.20-8.28 (d, 2H, Ar-H, J = 9 Hz), 9.58 (brs, 1H, N-H). ^{13}C NMR (DMSO, 400 MHz): δ = 15.1, 28.6, 39.8, 40.9, 41.3, 60.6, 82.1, 104.3, 124.5, 129.0, 146.9, 151.8, 153.9, 154.0, 167.4.

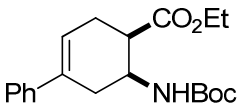
Ethyl 2-(*tert*-butoxycarbonylamino)-4-(4-methoxyphenyl)cyclopent-1-enecarboxylate ((±)-6b)



A white solid (*n*-hexane-EtOAc), mp 130-132 °C, yield: 46%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.32 (t, 3H, CH_3), 1.49 (s, 9H, *t*-Bu), 2.53.2.58 (m, 1H, CH_2), 2.93-3.02 (m, 1H, CH_2), 3.11-3.20 (m, 1H, CH_2), 3.48-3.3.52 (m, 1H, CH_2), 3.60-3.67 (m, 1H, H-4), 3.79 (s, 3H, OMe), 4.18-4.24 (m, 2H, OCH_2), 6.82-6.90 (d, 2H, Ar-H, J = 9 Hz), 7.18-7.22 (d, 2H, Ar-H, J = 9 Hz), 9.60 (brs,

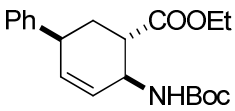
1H, N-H). ^{13}C NMR (DMSO, 400 MHz): δ = 15.1, 28.6, 37.5, 40.2, 41.9, 55.9, 60.4, 81.9, 104.5, 114.7, 128.5, 137.8, 151.8, 154.3, 158.6, 167.6.

Ethyl (1*R,2*S**)-2-(*tert*-butoxycarbonylamino)-4-phenylcyclohex-3-enecarboxylate ((±)-8)**



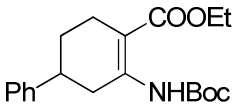
A white solid (*n*-hexane-EtOAc), mp 115-118 °C, yield: 34%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (t, 3H, CH_3, J = 7.20 Hz), 1.49 (s, 9H, *t*-Bu), 1.83-1.95 (m, 1H, CH_2), 2.25-2.36 (m, 2H, CH_2), 2.55-2.69 (m, 1H, CH_2), 2.90-3.00 (m, 1H, H-1), 4.22-4.37 (m, 2H, OCH_2), 4.66 (brs, 1H, N-H), 4.79-4.82 (m, 1H, H-2), 7.22-7.38 (m, 6H, Ar-H and H-5). ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 14.9, 29.1, 34.2, 34.6, 36.8, 43.6, 60.7, 80.5, 127.1, 127.7, 129.3, 140.8, 143.3, 148.9, 150.5, 157.5. MS: (ES, pos) m/z = 367 (M + Na).

Ethyl (1*S,2S*,5*R**)-2-(*tert*-butoxycarbonylamino)-4-phenylcyclohex-2-enecarboxylate ((±)-10)**



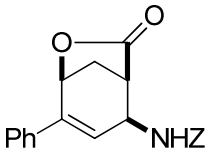
A white solid (*n*-hexane-EtOAc), mp 139-140 °C, yield 81%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (t, 3H, CH_3, J = 7.20 Hz), 1.50 (s, 9H, *t*-Bu), 1.85-1.93 (m, 1H, CH_2), 2.35-2.41 (m, 1H, CH_2), 2.64-2.70 (m, 1H, H-1), 3.52-3.58 (m, 1H, H-2), 4.15-4.23 (m, 2H, OCH_2), 4.56-4.60 (m, 1H, H-5), 4.65 (brs, 1H, N-H), 5.91-5.93 (m, 2H, H-2 and H-3), 7.21-7.39 (m, 5H, Ar-H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 14.6, 28.8, 31.8, 39.4, 43.3, 48.0, 61.1, 81.5, 120.0, 127.0, 128.3, 129.0, 129.3, 132.5, 158.5, 166.8. MS: (ESI, pos) m/z = 367 (M + Na).

Ethyl 2-(*tert*-butoxycarbonylamino)-4-phenylcyclohex-1-enecarboxylate ((±)-12)



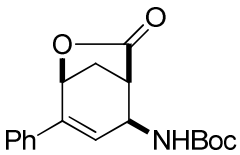
A white solid (*n*-hexane-EtOAc), mp 70-75 °C, yield 62%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.34 (t, 3H, CH_3, J = 7.20 Hz), 1.48 (s, 9H, *t*-Bu), 1.70-1.76 (m, 1H, CH_2), 1.97-2.03 (m, 1H, CH_2), 2.38-2.46 (m, 1H, CH_2), 2.58-2.67 (m, 1H, CH_2), 2.79-2.95 (m, 1H, CH_2), 3.37-3.44 (m, 1H, H-4), 4.20-4.28 (m, 2H, OCH_2), 7.19-7.37 (m, 5H, Ar-H), 10.9 (brs, 1H, N-H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 14.7, 25.1, 28.6, 29.4, 35.8, 40.0, 60.5, 80.8, 102.5, 126.8, 127.3, 128.9, 145.8, 151.9, 152.7, 170.2.

Benzyl (1*R,2*S**,5*S**)-7-oxo-4-phenyl-6-oxabicylo[3.2.1]oct-3-ene-2-ylcarbamate ((±)-14a)**



A white solid (*n*-hexane-EtOAc), mp 160-162 °C, yield 43%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.19-2.21 (m, 2H, CH_2), 3.27-3.29 (m, 1H, H-1), 3.89-3.91 (m, 1H, H-2), 4.72-4.74 (m, 1H, H-5), 5.15-5.24 (m, 2H, OCH_2), 5.87 (brs, 1H, N-H), 6.37-6.38 (m, 1H, H-3), 7.27-7.43 (m, 5H, Ar-H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 28.9, 42.0, 46.4, 67.7, 81.5, 127.9, 128.8, 128.9, 129.1, 129.3, 129.4, 132.5, 133.0, 152.0, 155.4.

***tert*-Butyl (1*R**,2*S**,5*S**)-7-oxo-4-phenyl-6-oxabicyclo[3.2.1]oct-3-ene-2-ylcarbamate ((±)-14b)**



A white solid (*n*-hexane-EtOAc), mp 177-179 °C, yield 62%. ^{1}H NMR (DMSO, 400 MHz): δ = 1. 51 (s, 9H, *t*-Bu), 1.92-1.99 (m, 1H, CH_2), 2.14-2.22 (m, 1H, CH_2), 3.30-3.38 (m, 1H, H-1), 3.70-3.77 (m, 1H, H-2), 4.59-4.66 (m, 1H, H-5), 7.30-7.41 (m, 5H, Ar-H), 8.92-8.99 (brs, 1H, N-H). ^{13}C NMR (DMSO, 400 MHz): δ = 28.5, 28.9, 41.1, 46.0, 80.2, 81.1, 105.8, 127.9, 129.5, 134.6, 140.8, 153.5, 175.9.

Crystal structure determination for (±)-5

Data collection was performed at 123K by ∏ and ω rotation scans using a Nonius Kappa CCD diffractometer with graphite monochromatized Mo Kα radiation (λ = 0.71073 A). Collected data was processed with the Denzo-SMN software.[13] The structure was solved by direct methods with SHELXS and full-matrix, least-squares refinement on F^2 was performed with SHELXL from SHELX-2013 package using Olex2 software suite.[14, 15] The CH hydrogen atoms (except the disordered CH_2 hydrogens on C8 which were treated similarly to NH hydrogen, see below) were included at fixed distances from their host atoms with the fixed displacement parameters. The NH hydrogen atom was located from the Fourier difference maps and refined isotropically with the fixed displacement parameter and restrained (0.87 Å) N–H bond length. The figure was drawn using Diamond 3 program.[16]

Methine carbon (C4) and the phenyl group attached to it are disordered over two positions by symmetry operation (mirror plane) hence the occupation ratio of the two distinct parts is 1:1. In addition, ethyl group attached to carboxylate functionality is similarly disordered. The general planar structure (reinforced with strong intramolecular NH···O hydrogen bond) containing only few bendable groups generates voids in the crystal lattice which (with the lack of solvent of crystallization) most likely causes the observed disorders.

The deposition number CCDC 1038709 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystal Data for $C_{19}H_{25}NO_4$ (M =331.40 g/mol): orthorhombic, space group P*nma* (no. 62), a = 14.778(3) Å, b = 6.9181(14) Å, c = 17.853(4) Å, V = 1825.2(6) Å3, Z = 4, T = 123 K, μ(MoKα) = 0.084 mm-1, D_{calc} = 1.206 g/cm^3, 3465 reflections measured (5.332° ≤ 2Θ ≤ 51.994°), 1951 unique (R_{int} = 0.0224, R_{sigma} = 0.0232) which were used in all calculations. The final R_1 was 0.0549 (I > 2σ(I)) and *w*R_2 was 0.1478 (all data).

Acknowledgements

We are grateful to the Hungarian Research Foundation (OTKA Nos. K100530 and NK81371) and TÁMOP-4.2.2.A-11/1/KONV-2012-0035 for financial support. This work was supported by the János Bolyai Research Scholarship to L.K. of the Hungarian Academy of Sciences. One of the authors (M.N.) is grateful for the support of the European Union and the State of Hungary, co-financed by the European Social Fund in the framework of TÁMOP 4.2.4. A/2/11-1-2012-0001 "National Excellence Program".

References

1 (a) J.Tsuji, in *Palladium in Organic Synthesis, Topics in Organometallic Chemistry*, ed. Springer, 2005, vol. 14. (b) L. F. Tietze, H. Ila, H. P. Bell, *Chem. Rev*. 2004, **104**, 3453. (c) K. C. Majumdar, B. Sinha, *Synthesis* 2013, **45**, 1271. (d) T. W. Lyons, M. S. Sanford, *Chem. Rev.* 2010, **110**, 1147. (e) K. C. Majumdar, S. Samanta, B. Sinha, *Synthesis* 2012, **44**, 817. (f) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed*. 2005, **44**, 4442. (g) I.

Nakamura, Y. Yamamoto, *Chem. Rev*. 2004, **104**, 2127. (h) B. Magano, J. R. Dunetz, *Chem. Rev*. 2011, **111**, 2177. (i) G. P. McGlacken, I. J. S. Fairlamb, *Eur. J. Org. Chem*. 2009, 4011. (j) X. Chen, K. M. Engle, D-H. Wang, J-Q. Yu, *Angew. Chem. Int. Ed*. 2009, **48**, 5094. (k) A. de Meijere, F. Diederich, in *Metal-Catalyzed Cross Coupling Reactions*, ed. Wiley-VCH: Weinheim, 2nd edn., 2004. (l) N. Miyaura, in *Cross-Coupling Reaction, Topics in Current Chemistry*, ed. Springer, 2002, vol. 219. (m) Á. Molnár, *Chem. Rev*. 2011, **111**, 2251. (n) V. P. Mehta, E. V. Van der Eycken, *Chem. Soc. Rev*. 2011, **40**, 4925. (o) N. Kambe, T. Iwasaki, J. Terao, *Chem. Soc. Rev*. 2011, **40**, 4937. (p) C. M. So, F. Y. Kwong, *Chem. Soc. Rev.* 2011, **40**, 4963.

2 (a) L. Kiss, F. Fülöp, *Chem. Rev*. 2014, **114**, 1116. (b) N. Griebenov, in *Medicinal chemistry of alicyclic beta-amino acids. Amino Acids, Peptides and Proteins in Organic Chemistry*, ed. Hughes, A. B. Wiley: Weinheim, 2011, vol. 4. (c) F. Kudo, A. Miyanaga, T. Eguchic, *Nat. Prod. Rep*. 2014, **31**, 1056. (d) E. Juaristi, V. A. Soloshonok in *Enantioselective Synthesis of β-Amino Acids*, ed. Wiley-VCH, New York, 2nd edn., 2005. (e) S. H. Choi, M. Ivancic, I. A. Guzei, S. H. Gellman, *Eur. J. Org. Chem*. 2013, 3464. (f) E. Mayans, A. Gargallo, A. Álvarez-Larena, O. Illa, R. M. Ortuño, *Eur. J. Org. Chem*. 2013, 1425. (g) L. Berlicki, M. Kaske, R. Gutiérrez-Abad, G. Bernhardt, O. Illa, R. M. Ortuño, C. Cabrele, A. Buschauer, O. Reiser, *J. Med. Chem*. 2013, **56**, 8422. (h) L. Berlicki, L. Pilsl, E. Wéber, I. M. Mándity, C. Cabrele, T. Martinek, F. Fülöp, O. Reiser, *Angew. Chem. Int. Ed*. 2012, **51**, 2208. (i) D. Fernandez, E. Torres, F. X. Aviles, R. M. Ortuno, J. Vendrell, *Bioorg. Med. Chem*. 2009, **17**, 3824. (j) C. Fernandes, S. Faure, E. Pereira, V. V. Declerck, R. Guillot, D. J. Aitken, *Org. Lett*. 2010, **12**, 3606.

3 (a) T. A. Martinek, F. Fülöp, *Chem. Soc. Rev*. 2012, **41**, 687. (b) I. M. Mándity, A. Monsignori, L. Fülöp, E. Forró, F. Fülöp. *Chem. Eur. J.* 2014, **20**, 4591. (c) D.-W. Zhang, X. Zhao, J.-

L.Hou, Z.-T. Li, *Chem. Rev*. 2012, **112**, 5271. (d) J. M. Rodriguez, A. D. Hamilton, *Angew. Chem. Int. Ed.* 2007, **46**, 8614. (e) H. Jiang, J. M. Léger, I. Huc, *J. Am. Chem. Soc.* 2003, **125**, 3448. (f) T. Steiner, *Angew. Chem. Int. Ed.* 2002, **41**, 48. (g) A. Ruffoni, N. Ferri, S. K. Bernini, C. Ricci, A. Corsini, I. Maffucci, F. Clerici, A. Contini, *J. Med. Chem.* 2014, **57**, 2953. (h) A. Brik, *Adv. Synth. Catal*. 2008, **350**, 1661. (i) A. S. Kamlet, C. Préville, K. A. Farley, D. W. Piotrowski, *Angew. Chem. Int. Ed.* 2013, **52**, 10607. (j) T. J. Ritchie, S. J. F. Macdonald, *Drug Discov. Today* 2009, **14**, 1011. (k) T. J. Ritchie, S. J. F. Macdonald, R. J. Young, S. D. Pickett, *Drug Discov. Today* 2011, **16**, 164. (l) F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* 2009, **52**, 6752.

4 (a) M. Risseeuw, M. Overhand, G. W. J. Fleet, M. I. Simone, *Amino Acids* 2013, **45**, 613. (b) L. Kiss, F. Fülöp, *Synlett* 2010, 1302. (c) J. Mittendorf, F. Kunisch, M. Matzke, H-C. Militzer, A. Schmidt, W. Schönfeld, *Bioorg. Med. Chem. Lett*. 2003, **13**, 433. (d) M. Palkó, L. Kiss, F. Fülöp, *Curr. Med. Chem.* 2005, **12**, 3063.

5 M. C. Whisler, P. Beak, *J. Org. Chem*. 2003, **68**, 1207.

6 T. Miura, T. Harumashi, M. Murakami, *Org. Lett*. 2007, **9**, 741.

7 V. Sridharan, J. C. Menendez, *Org. Lett.* 2008, **10**, 4303.

8 (a) S. G. Davies, M. J. Durbin, S. J. Hartman, A. Matsuno, P. M. Roberts, A. J. Russell, A. D. Smith, J. E. Thomson, S. M. Toms, *Tetrahedron: Asymmetry* 2008, **19**, 2870. (b) E. Abraham, S. G. Davies, A. J. Docherty, K. B. Ling, P. M. Roberts, A. J. Russell, J. E. Thomson, S.M. Toms, *Tetrahedron: Asymmetry* 2008, **19**, 1356.

9 (a) D. Pan, N. Joao, *Synlett* 2010, 1577. (b) J. Muzart, *Tetrahedron* 2013, **69**, 6735. (c) B. Karimi, H. Behzadnia, D. Elhamifar, P. F. Akhavan, F. K. Esfahani, A. Zamani, *Synthesis* 2010, 1399. (d) D. McCartney, P. J. Guiry, *Chem. Soc. Rev*. 2011, **40**, 5122. (e) D. W. Piotrowski, J. Polivkova, *Tetrahedron Lett.* 2010, **51**, 17. (f) C. C. Oliveira, E. A. D. Santos, J.

H. B. Nunes, C. R. D. Correira, *J. Org. Chem*. 2012, **77**, 8182. (g) C. G. Hartung, K. Köhler, M. Beller, *Organic Lett*. 1999, **1**, 709. (h) Z. Yang, J. Zhou, *J. Am. Chem. Soc.* 2012, **134**, 11833. (i) X. Wu, J. Zhou, *Chem. Commun*. 2013, **49**, 4794. (j) A. B. Dounay L. E. Overman, The Mizoroki–Heck Reaction, ed. M. Oestreich, Wiley, 2009. (k) L. E. Overman, D. J. Poon, *Angew. Chem., Int. Ed.* 1997, *36*, 518. (l) A. Ashimori, B. Bachand, M. A. Calter, S. P. Govek, L. E. Overman, D. J. Poon, *J. Am. Chem. Soc*. 1998, **120**, 6488. (m) A. B. Dounay, P. G. Humphreys, L. E. Overman, A. D. Wrobleski, *J. Am. Chem. Soc*. 2008, **130**, 5368. (n) M. Shibasaki, E. M. Vogl, T. Ohshima, *Adv. Synth. Catal.* 2004, **346**, 1533. (o) M. Shibasaki, C. D. J. Boden, A. Kojima, *Tetrahedron* 1997*,* **53**, 7371.

10 (a) L. Kiss, E. Forró, R. Sillanpää, F. Fülöp, *J. Org. Chem*. 2007, **72**, 8786. (b) L. Kiss, M. Nonn, E. Forró, R. Sillanpää, F. Fülöp, *Tetrahedron Lett.* 2009, **50**, 2605.

11 L. Kiss, E. Forró, F. Fülöp, *Tetrahedron* 2012, **68**, 4438.

12 (a) M. Nonn, L. Kiss, R. Sillanpää, F. Fülöp, *Tetrahedron* 2012, **68**, 9942. (b) L. Kiss, E. Forró, S. Fustero, F. Fülöp, *Eur. J. Org. Chem.* 2011, 4993. (c) E. Forró, L. Schönstein, L. Kiss, A. Vega-Peñaloza, E. Juaristi, F. Fülöp, *Molecules* 2010, **15**, 3998.

13 Z. Otwinowski, W. Minor in *Methods in Enzymology*, *Macromolecular Crystallograph*y, Part A, ed. C. W. Carter Jr., R. M. Sweet, Academic Press: New York, 1997, vol. 276, pp 307–326.

14 G. M. Sheldrick, *Acta Crystallogr.* 2008, **A64**, 112.

15 O. V. Dolomanov, J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Cryst.*, 2009, **42**, 339.

16 *Diamond - Crystal and Molecular Structure Visualization*, Crystal Impact - Dr. H. Putz & Dr. K. Brandenburg GbR, Kreuzherrenstr. 102, 53227 Bonn, Germany http://www.crystalimpact.com/diamond