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Derivatization of 1-phenyl substituted 4-amino-2-benzazepin-3-ones: evaluation of Pd-catalyzed coupling reactions

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Abstract—Several Pd-catalyzed reactions were explored to further functionalize the bromo-substituted 4-amino-1,2,4,5-tetrahydro-2-benzazepin-3-one scaffold (Aba). We report in this paper suitable reaction conditions for Suzuki, Buchwald–Hartwig, and Heck reactions. The substitution pattern of the starting aminobenzazepinone turned out to be crucial for the success of these transition metal-catalyzed reactions, which often required modifications of standard literature procedures. The Pd-catalyzed methods provide access to novel substitution patterns of the Aba scaffold.

1. Introduction

The 4-amino-1,2,4,5-tetrahydro-2-benzazepin-3-one (Aba) skeleton **1** is present in several bioactive compounds (Fig. 1).[1–5] This template is the basic unit in ACE-,[1] NEP-,[2] and farnesyl transferase inhibitors,[3] fibrinogen receptor antagonists,[4] and analgesics.[5] Synthetic methods, that allow the efficient introduction of a variety of substituents at different positions, are therefore of high value from a medicinal chemistry point of view.

Our research group has reported several methods to prepare disubstituted,[6–8] trisubstituted,[9,10] and tetrasubstituted[11] 4-amino-2-benzazepin-3-ones with a wide range of substituents, but until now we never explored the possibilities to further derivatize the scaffold. Since drug development is often based on further 'functionalization' of an already existing lead compound, a convergent method for modifying a common intermediate would increase the efficiency of the synthesis. An interesting strategy to introduce new vinyl-, aryl-, arylamino- or alkylamino-type substituents, that would serve as eventual pharmacophoric groups, is to use Pd chemistry. In this way new C–C and C–N bonds should be easily formed in the late stage of the synthesis route of the target compounds.

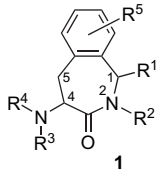

Figure 1. The 4-amino-1,2,4,5-tetrahydro-2-benzazepin-3-one scaffold **1**.

The substrates for the evaluation of the Pd-catalyzed methods were the phthaloyl-protected bromo-substituted Aba analogs **2** and **3** obtained through two different, earlier reported, *N*-acyliminium ion based cyclizations **A** and **B**, depicted in Scheme 1.[11] Method **A** allows the simultaneous introduction of a substituent at positions 1 (R^1 in **1**) and 2 (R^2 in **1**), although there were limitations for the choice of the 2-substituent, caused by steric hindrance. No cyclohexyl group could, for example, be introduced as an R^2 substituent. The method yields a 1:1 mixture of stereoisomers. Method **B**, a procedure based on Katritzky's benzotriazole chemistry,[12] allowed the introduction of different 1-substituents and yields selectively the cis-stereoisomer. Only R^2=H was however allowed.[11] Despite the lower reactivity of the aromatic ring in **6** (due to the bromine atom) for ring closure of type **B** (Scheme 1), we were able to prepare compound **3**. This 8-bromo-substituted analog is unavailable through method **A** as reported earlier.[11] The aryl bromide moiety in scaffolds **2** and **3** allows to further elaborate

Keywords: 4-Amino-1,2,4,5-tetrahydro-2-benzazepin-3-ones; Pd[0] catalysis; Suzuki reaction; Buchwald–Hartwig reaction; Heck reaction; N-Arylation.
Abbreviations: Aba, 4-amino-1,2,4,5-tetrahydro-2-benzazepin-3-one; ACE, angiotensin converting enzyme; BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; Cy_2MeN, *N*,*N*-dicyclohexylmethylamine; dba, dibenzylideneacetone; DMA, dimethylacetamide; DME, ethylene glycol dimethyl ether; NEP, neutral endopeptidase; XANTPHOS, 9,9-dimethyl-4,5-bis(diphenylphosphine)-9*H*-xanthene.
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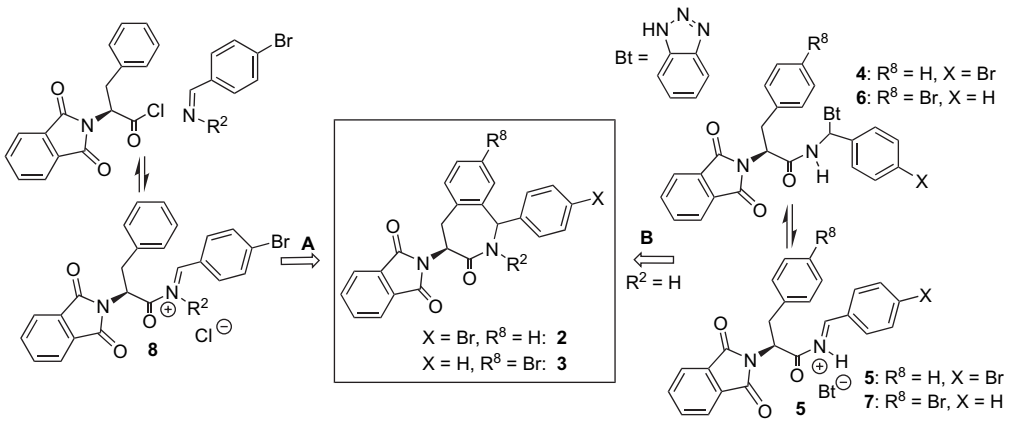


Scheme 1. Synthesis of 1-(4-bromophenyl)- and 1-phenyl-8-bromo-Aba scaffolds **2** and **3**.

functionalization at these positions via Pd-catalyzed reactions. For this purpose, we explored Buchwald–Hartwig aminations, Heck alkenylations, and Suzuki arylation reactions on **2** and **3**.

2. Results and discussion

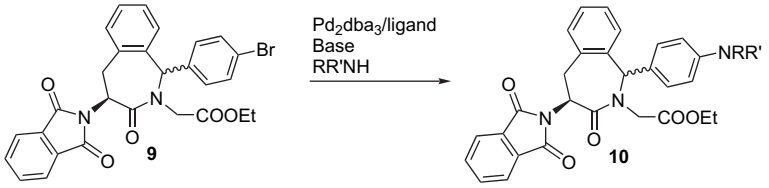
2.1. Buchwald–Hartwig reactions

Based on our earlier work on dihalopyridines,[13] XANTPHOS was chosen as a ligand and Pd_2dba_3 as Pd(0) source for the catalyst to couple anilines and heteroarylamines with **9** (see Scheme 2 and Table 1). Compound **9** was synthesized through method **A** in Scheme 1 as a 1:1.2 mixture of epimers at C1.[11] With this Pd/L (ratio 1:1.1) system, we were able to smoothly couple *p*-toluidine (entry 1) and 2-aminopyridine (entry 2). When we tried to introduce a cyclic aliphatic amine (entry 3), however, the target compound was only formed in a small amount. Therefore, the ligand of the catalytic system was changed. With racemic BINAP, only 10% conversion to the desired reaction product could be obtained (entry 4).[14] The use of biphenyl based 'Buchwald ligands', 2-dicyclohexylphosphinobiphenyl (entry 5) and 2-di-*tert*-butylphosphinobiphenyl (entry 6), in combination with K_3PO_4 induced the best conversions and isolated yields.[15] Increasing the catalyst loading from 5 to 7.5 mol % did not further improve conversion using 2-di-*tert*-butylphosphinobiphenyl as ligand. Interestingly, the recently introduced ligand 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl led to a reduced conversion of only 50% after 24 h reaction time (entry 7).[16] To verify if this incomplete conversion (90%) of entry 6 was not just due to the very specific amine selected as model, we repeated the same procedure with morpholine as another example of a cyclic aliphatic amine (entry 8). Gratifyingly, full conversion of the starting material was observed in this case and an isolated yield of 60% was achieved.

We then examined whether the presence of an unprotected secondary amide in benzazepinone **11** (Scheme 3) would influence the C–N bond formation. Compound **11** was obtained through method **B** in Scheme 1. Taking into account the success of the amination reaction with 2-aminopyridine (entry 2, Table 1), we first chose to investigate its coupling with **11**. The reaction did, however, not occur. No conversion to the desired compound was observed. Due to the fact that the reactivity of an amide might be comparable to that of the amidine 2-aminopyridine, we subsequently tried *p*-toluidine and morpholine as, respectively, examples of aniline type amines and cyclic aliphatic amines. This assumption of similar reactivity is based on a recent paper of Buchwald and coworkers in which they suggested that the chemoselectivity of palladium catalysts follows the rough amine reactivity order: aryl amines≫primary and secondary aliphatic amines>2-aminoheteroaromatics>primary amides~HN heterocycles.[17] Of course this order is based on the use of substituted dialkylphosphinobiphenyl ligands that act as monodentate P-ligands, while we used the bidentate XANTPHOS for the coupling of 2-aminopyridine. Unfortunately, also *p*-toluidine (reaction conditions of entry 1, Table 1) and morpholine (reaction conditions of entry 8, Table 1) did not result in any conversion to the desired compound **12**. From these results, we can conclude that position 2 in scaffold **1** has to be substituted/protected before Pd-catalyzed amination reactions are performed.

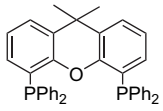
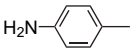
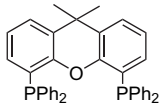
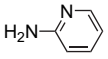
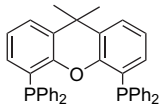
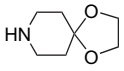
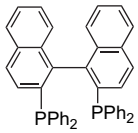
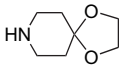
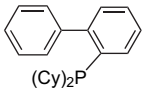
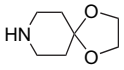
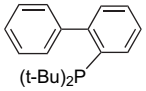
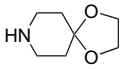
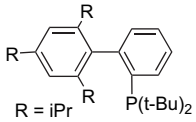
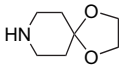
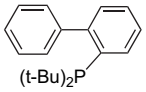
2.2. Heck reaction

Three different literature systems were examined (see Table 2) for the reaction of **9** with ethyl acrylate (Scheme 4). The combination Pd_2dba_3/(*t*-Bu)$_3$P (Pd/L ratio 1:1) with

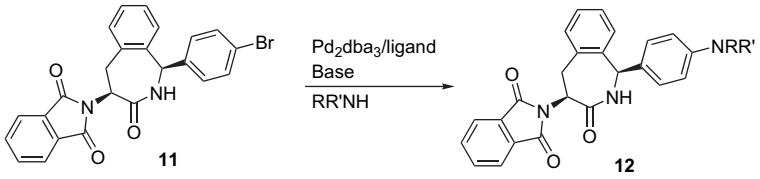


Scheme 2. Buchwald–Hartwig reaction of Pht-1-(*R*,*S*)-(4-bromophenyl)-(*S*)-Aba-Gly-OEt **9**.

Table 1. Overview of the Buchwald–Hartwig reaction conditions

Entry	Ligand (1.1 equiv)	Base (equiv)	Amine (1.2 equiv)	Solvent	Time (h)/Temp. (°C)	Conversion (%), Yield (%)
1		Cs_2CO_3 (4)		DME	20/95	**10a**, C: 100, Y: 60
2		Cs_2CO_3 (4)		DME	20/95	**10b**, C: 100, Y: 65
3		Cs_2CO_3 (4)		DME	20/95	**10c**, C: 100, Y: 7[a]
4		Cs_2CO_3 (2)		DME	20/95	**10c**, C: 10
5		K_3PO_4 (2)		Toluene	20/100	**10c**, C: 88
6		K_3PO_4 (2)		Toluene	20/100	**10c**, C: 90, Y: 54
7		K_3PO_4 (2)		Toluene	20/100	**10c**, C: 50
8		K_3PO_4 (2)		Toluene	20/100	**10d**, C: 100, Y: 60

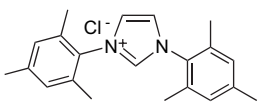
[a] Mostly side products were obtained.

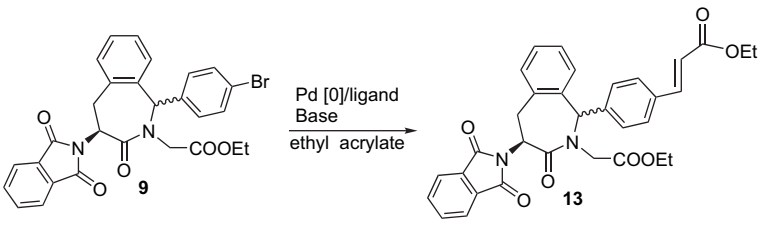


Scheme 3. Attempted Buchwald–Hartwig reaction of Pht-1-(*R*)-(4-bromophenyl)-(*S*)-Aba **11**.

Cy_2MeN as a base, introduced by Fu et al., gave a conversion of only 5% (entry 1).[18] The shift from a phosphine to a carbene ligand (Table 2, entry 2), as reported by Nolan et al., did not improve the yields.[19] Although both catalytic systems have been successfully used on a substantial set of substituted bromobenzene derivatives it is clear that the

Table 2. Overview of the Heck reaction conditions

Entry	Pd catalyst (mol %)	Base (equiv)	Added ligand (mol %)	Solvent	Time (h)/Temp. (°C)	Conversion (%), Yield (%)
1	Pd_2dba_3 (2.5)	Cy_2MeN (1.1)	(*t*-Bu)$_3$P (5)	Dioxane	24/105	**13**, C: 5
2	$Pd(OAc)_2$ (5)	Cs_2CO_3 (2)	 (10)	DMA	24/120	**13**, C: 5
3	$Pd(PPh_3)_4$ (30)	$NaHCO_3$ (2)	None	DMF	24/120	**13**, C: 100, Y: 66



Scheme 4. Heck reaction of Pht-1-(*R*,*S*)-(4-bromophenyl)-(*S*)-Aba-Gly-OEt **9**.

complexity of the starting material, as exemplified by substrate **9**, imposes serious limits on the use of standard, carefully optimized, literature protocols in medicinal chemistry programs.

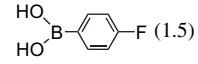
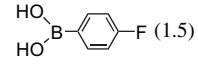
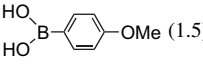
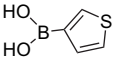
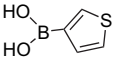
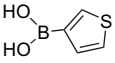
Remarkably, the best catalyst for the Heck reaction on **9** was standard tetrakis(triphenylphosphine)palladium (entry 3).[20,21] However, a very high catalyst loading was required (30%) to get full conversion in 24 h. This is probably due to the interference with other functionalities present on substrate **9**. However, this result demonstrated that benzazepine **9** can be further functionalized with a α,β-unsaturated ester function, thus meeting our primary medicinal chemistry goal.

2.3. Suzuki reaction

The functionalizations via Suzuki reaction were based on a methodology developed by Buchwald et al.[22] who reported that a mixture of $Pd(OAc)_2$ and 2-(di-*tert*-butylphosphino)-biphenyl **14** is a good precatalytic system for Suzuki arylation of aryl bromides with KF as base (Scheme 5). We were able to confirm these findings on our scaffold. Table 3 gives an overview of the experiments with 4-fluorophenylboronic acid as an organometallic partner. A loading of 5% Pd and 10% ligand **14** (Pd/L ratio 1:2) was chosen. Heating at 50 °C in THF (entry 1) resulted in an incomplete conversion of **9**. Switching to DME as a solvent (entry 2) permitted to increase the reaction temperature and resulted in complete conversion of starting material **9**. The electron rich *p*-methoxyphenyl group was also smoothly introduced by means of *p*-methoxyphenyl boronic acid (entry 3). Also heteroaromatic moieties can be introduced as exemplified by the 3-thienyl moiety (entries 4–6). In this case, an excess of 3.5 equiv arylboronic acid was required for a full conversion in 24 h.

We also investigated how cross-coupling with arylboronic acids would proceed in the presence of the unprotected/unsubstituted secondary amide in benzazepinone **11**. Interestingly, in contrast to the amination reactions, Suzuki cross-coupling on this substrate with 4-fluorophenylboronic acid gave, initially, partial conversion to the desired compound **16**.

Table 3. Reaction conditions for Suzuki couplings

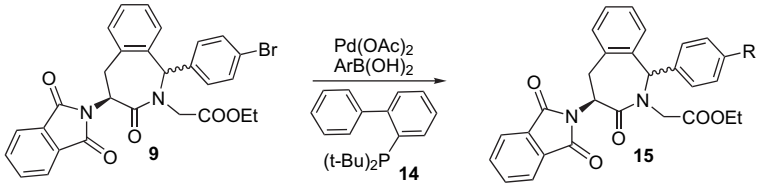
Entry	Base (3 equiv)	Boronic acid (equiv)	Solvent	Time (h)/ Temp. (°C)	Conversion (%), Yield (%)
1	KF	 (1.5)	THF	24/50	**15a**, C: 80
2	KF	 (1.5)	DME	24/95	**15a**, C: 100, Y: 71
3	KF	 (1.5)	DME	24/95	**15b**, C: 100, Y: 66
4	KF	 (1.5)	DME	24/95	**15c**, C: 50
5	KF	 (2.5)	DME	24/95	**15c**, C: 85
6	KF	 (3.5)	DME	24/95	**15c**, C: 100, Y: 64

As we observed the formation of a precipitate during the reaction, we considered solubility issues to be responsible for the incomplete conversion. Therefore DMA was added as a co-solvent. Gratifyingly, employing a 1:1 solvent mixture of DME/DMA yielded 70% of **16**. We assume that deprotonation of the lactam moiety by KF is responsible for the precipitation of **11** and consequently for the failure to fully convert **11** by Suzuki reaction in DME.

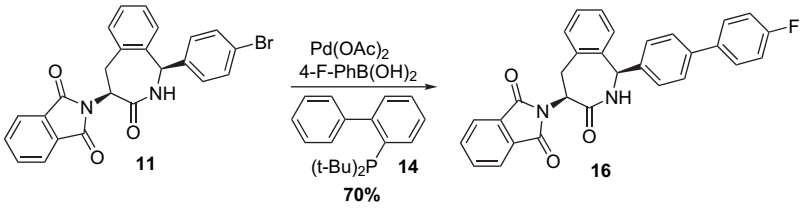
Identical conditions as found optimal for substrate **11** (Scheme 6) were also applied to the regioisomeric 8-bromo analog **3**. We were able to obtain **17** in a good yield (Scheme 7). This represents an additional functionalization opportunity of position 8 in the Aba scaffold. Analogs of type **17** would otherwise only be available from expensive unnatural amino acid precursors.

2.4. N-Arylation of the lactam nitrogen

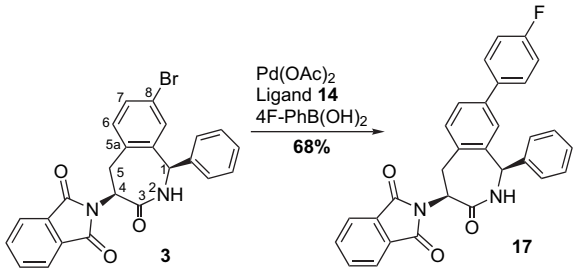
A further diversification of the N^2-unsubstituted Aba scaffold **11** can be obtained by N-arylation (Scheme 8). Le Diguarher



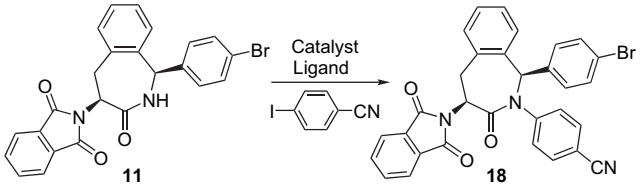
Scheme 5. Suzuki reaction of Pht-1-(*R*,*S*)-(4-bromophenyl)-(*S*)-Aba-Gly-OEt **9**.



Scheme 6. Suzuki couplings of Pht-1-(*R*)-(4-bromophenyl)-(*S*)-Aba **11**.



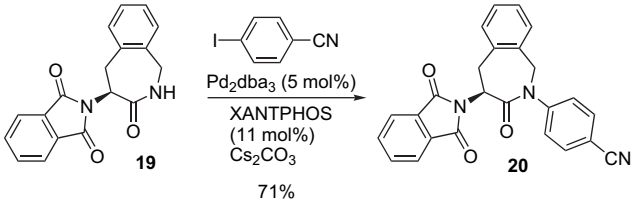
Scheme 7. Suzuki reaction of Pht-1-(*R*)-phenyl-8-bromo-(4*S*)-Aba **3** with 4-fluorophenylboronic acid.



Scheme 8. Attempted N-arylation of Pht-1-(*R*)-(4-bromophenyl)-(*S*)-Aba **11**.

already reported N-arylation of a 4-amino-2-benzazepin-3-one for the preparation of a farnesyl transferase inhibitor.[3] This procedure was however not catalytic and based on the use of an equimolar amount of $Cu(OAc)_2$. Moreover, triarylbismuth reagents were used as aryl source, limiting the functional group compatibility of the process. In addition, these organometallic partners are not easily accessible.

As N-arylation of amides has recently been described under Cu-catalysis,[23] we first investigated the reaction of **11** with 4-iodobenzonitrile, using a combination of CuI and *trans*-1,2-cyclohexanediamine in dioxane (Table 4, entry 1) as well as in toluene. This attempt was unsuccessful since no desired compound could be observed by LC–MS analysis. Switching back to an older literature procedure based on palladium catalysis, with XANTPHOS as ligand, also did not provide the desired compound **18** (Table 4, entry 2).[24] These failures were attributed to the bulky substituents on both sides of the lactam function. This leads to a problematic conversion due to a steric factor in the binding of the deprotonated amide to the Pd(II) intermediate, as also reported earlier by Buchwald for intermolecular coupling of aryl halides and amides.[24] To confirm this theoretical consideration, we repeated the arylation reaction using the same Pd_2dba_3/XANTPHOS precatalytic system on a compound where sterical hindrance was substantially reduced by removing the 1-substituent of **11** (Scheme 9). Interestingly, compound **19** smoothly coupled with the electron deficient aryl halide 4-iodobenzonitrile. Unfortunately, trying to extend the reaction to inactivated (electronically neutral) aryl halides, such as 2-iodotoluene and 4-iodotoluene, did not lead to the desired reaction products. As an amide group is not very nucleophilic, good results can only be achieved with sufficiently electron deficient aryl halides. This is based on the knowledge that reductive elimination of Pd(II)–amide complexes will go easier with electron deficient aryl groups and more nucleophilic amides.[25] Although the scope of this Pd-catalyzed N-arylation reaction is obviously hampered by steric as well as electronic factors, we were pleased to see that electron deficient aryl halides, exemplified by 4-iodobenzonitrile, are suitable substrates. To the best of our knowledge, the arylation of **19** is the first example in which a 4-amino-tetrahydro-2-benzazepin-3-one has been successfully used in a Pd-catalyzed N-arylation reaction.

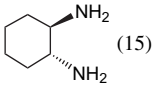


Scheme 9. N-Arylation of Pht-(*S*)-Aba **19**.

3. Conclusions

A variety of new substituents were introduced via Pd-catalyzed reactions. Buchwald–Hartwig as well as Suzuki reactions were successfully optimized by analyzing different Pd/L systems in a variety of solvents, using the N^2-substituted benzazepinone **9**. The presence of an unsubstituted secondary amide in the scaffold, i.e. using compound **11**, prevented the formation of C–N bonds through Pd-catalyzed amination

Table 4. N-Arylation of Pht-1-(*R*)-(4-bromophenyl)-(S)-Aba **11**

Entry	Catalyst (5 mol %)	Base (equiv)	Added ligand (mol %)	Solvent	Time (h)/Temp. (°C)	Conversion (%), Yield (%)
1	CuI	K_3PO_4 (1.6)	(+/-)  (15)	Dioxane	24/110	No conversion
2	Pd_2dba_3	Cs_2CO_3 (4)	XANTPHOS (11)	Dioxane	24/100	No conversion

reactions. Suzuki cross-coupling reactions were, however, still successfully performed on this type of substrate if a dipolar aprotic solvent was used as a co-solvent. 'Classical' Heck reaction conditions, based on tetrakis(triphenylphosphine)palladium as precatalytic system, lead to full conversion and consequently to a good isolated yield. Additionally, we examined steric as well as electronic factors for the N-arylation of N^2-unsubstituted benzazepin-3-ones, and concluded that the scope of this reaction is limited to electron deficient aryl halides and a benzazepinone scaffold without the 1-phenyl substitution. The investigated Pd-catalyzed conversions led to the preparation of several benzazepinones bearing new types of functionalities. This allows a considerable expansion of the range of substituent diversity available for the priviledged template. Moreover, since the phthaloyl protection of N^4 is easily removed, further functionalization at N^4 can easily be performed.[7]

4. Experimental

4.1. General

Thin layer chromatography (TLC) was performed on a plastic sheet precoated with silica gel $60F_{254}$ (Merck). Melting points (mp) were determined on a Büchi B540 Melting Point Apparatus with a temperature gradient of 1 °C/min. Mass spectra (MS) were recorded on a VG Quattro II spectrometer using electrospray (ESP) ionization (positive or negative ion mode). Data collection was done with MassLynx software. ^{1}H NMR and ^{13}C NMR spectra were recorded at 250 and 63 MHz, respectively, on an AC 250 Bruker spectrometer. Solvents and chemical shifts (δ), using TMS as an internal standard, are reported for each compound. When mixtures of diastereoisomers were analyzed, chemical shifts of identical protons or carbons in both isomers were grouped. The notations of $^nJ_1(H_x,H_y)$ and $^nJ_2(H_x,H_y)$ were used for the geminal (n=2) and vicinal (n=3) couplings constants of isomer 1 and isomer 2, respectively. Reverse phase (RP)-HPLC was performed using an Agilent 1100 Series system (Waldbronn, Germany) with a RP C-18 column (Supelco Discovery BIO Wide Pore®, 25 cm×4.6 mm, 5 μm). The mobile phase (water/acetonitrile) contained 0.1% TFA. The standard gradient consisted of a 20 min run from 3% to 97% acetonitrile at a flow of 1 mL min^{-1} with UV detection at 215 nm. Preparative RP-HPLC was performed on a Gilson apparatus and controlled by the software package Unipoint. The reverse phase C-18 column (Discovery Wide Pore, 25 cm×21.2 mm, 10 μm) was used under the same conditions as the analytical RP-HPLC, but at a flow rate of 20 mL min^{-1}. The following compounds were bought from commercial sources: XANTPHOS (Aldrich), 2-di-*tert*-butylphosphino-2′,4′,6′-triisopropylbiphenyl (Aldrich), rac. BINAP (Rhodia), 2-dicyclohexylphosphinobiphenyl (Acros), 2-di-*tert*-butylphosphinobiphenyl (Aldrich), (t-Bu)$_3$P (Aldrich), 1,3-bis(2,4,6-trimethylphenyl)-imidazolium chloride (Aldrich), $Pd(OAc)_2$, and Pd_2dba_3 (Acros).

4.2. Buchwald–Hartwig amination of compound 9

4.2.1. Synthesis of ethyl ((4*S*)-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1(*R*,*S*)-{4-[(4-methylphenyl)amino]-phenyl}-3-oxo-1,3,4,5-tetrahydro-2*H*-2-benzazepin-2-yl)acetate (10a, entry 1, Table 1). An oven dried 25 mL round-bottomed flask was charged with Pd_2dba_3 (9.2 mg, 0.010 mmol, 5 mol %) and XANTPHOS (12.8 mg, 0.022 mmol, 11 mol %). The flask was flushed with N_2 and subsequently DME (6 mL) was added. This solution was stirred for 10 min at rt. During these 10 min, **9** (109.5 mg, 0.20 mmol), *p*-toluidine (25.7 mg, 0.24 mmol, 1.2 equiv), and Cs_2CO_3 (261 mg, 0.8 mmol, 4 equiv) were weighed into another 25 mL flask. This flask was also flushed with N_2 and 3 mL of Pd(0)/XANTPHOS solution (0.005 mmol Pd_2dba_3 and 0.011 mmol XANTPHOS) was added. The reaction mixture was heated (oil bath temperature: 95 °C) and magnetically stirred for 20 h under N_2 atmosphere. After evaporation of the solvent, the crude product was dissolved in a minimum amount of acetonitrile/water (1.2:1), filtered, and purified by preparative HPLC. The desired compound **10a** (68.8 mg, 0.12 mmol, 60%) was obtained *as a mixture of diastereoisomers* in the form of a light brown solid. TLC: R_f 0.66 (EtOAc/hexanes 1:1), mp 125–127 °C. MS (ESP$^+$) found m/z=574 ([M+H]$^+$), $C_{35}H_{31}N_3O_5$ requires 573.64. HPLC: retention time=19.2 and 19.3 (min). ^{1}H NMR 250 MHz ($CDCl_3$): δ_H=1.08 and 1.22 (3H, 2t, H_{CH_3}, $^3J_1$=$^3J_2$=6.3 Hz), 2.30 (3H, s, H_{Ar-CH_3}), 2.54 and 3.20 (1H, 2dd, H_β, $^2J_1(H_\beta,H_{\beta'})$=14.5 Hz, $^2J_2(H_\beta,H_{\beta'})$=17.2 Hz, $^3J_1(H_\beta,H_\alpha)$=3.2 Hz, $^3J_2(H_\beta,H_\alpha)$=4.6 Hz), 3.66 (1H, d, H_α Gly, $^2J(H_\alpha,H_{\alpha'})$=16.7 Hz), 3.87 (0.6H, pseudo t, $H_{\beta'}$, $^2J(H_{\beta'},H_\beta)\approx$ $^3J(H_{\beta'},H_\alpha)$=14.1 Hz), 4.20 (2.4H, m, $H_{\beta'}+H_{CH_2}$), 4.86 and 5.43 (1H, 2dd, H_α Aba, $^3J_1(H_\alpha,H_\beta)$=3.2 Hz, $^3J_2(H_\alpha,H_\beta)$=4.5 Hz, $^3J_1(H_\alpha,H_{\beta'})$=13.4 Hz, $^3J_2(H_\alpha,H_{\beta'})$=12.2 Hz), 5.08 (1H, d, $H_{\alpha'}$ Gly, ^2J=17 Hz), 5.60 and 5.64 (1H, 2s, H_ε), 6.95–7.58 (13H, M, H arom), 7.63–7.78 (4H, M, H_{Pht}). ^{13}C NMR 63 MHz ($CDCl_3$): δ_C=14.1 and 14.2 (CH_3 Et), 20.6 (CH_3Ar), 34.1 and 35.1 (C_β), 52.5 and 53.3 (C_α Gly), 53.5 and 54.3 (C_α Aba), 61.5 (CH_2 Et), 69.3 and 70.1 (C_ε), 116.8 (CH arom), 117.3 (CH arom), 119.4 (CH arom), 124.0 (CH arom), 127.5 (CH arom), 130.0 (CH arom), 130.7 (CH arom), 131.1 (CH arom) 132.5 (CH arom), 133.3 (CH arom) 134.8 (C_{quat} arom), 134.9 (C_{quat} arom), 135.2 (C_{quat} arom), 137.0 (C_{quat} arom), 139.0 (C_{quat} arom), 139.9 (C_{quat} arom), 144.4 (C_{quat} arom), 168.3 (C=O), 168.8 (C=O), 170.2 (C=O).

4.2.2. Synthesis of ethyl {(4*S*)-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-oxo-1(*R*,*S*)-[4-(pyridine-2-ylamino)-phenyl]1,3,4,5-tetrahydro-2*H*-2-benzazepin-2-yl}acetate (10b, entry 2, Table 1). Identical reaction conditions as for the synthesis of **10a** were used.

The desired product **10b** (72.5 mg, 0.13 mmol, 65%) was obtained *as a mixture of diastereoisomers* in the form of a yellow solid. TLC: R_f 0.35 (EtOAc/hexanes 1:1), mp 132–134 °C. MS (ESP$^+$) found m/z=561 ([M+H]$^+$), $C_{35}H_{31}N_3O_5$ requires 560.60. HPLC: retention time=13.2 and 13.5 (min). ^{1}H NMR 250 MHz ($CDCl_3$): δ_H=1.12 and 1.23 (3H, 2t, H_{CH_3}, $^3J_1$=$^3J_2$=7.5 Hz), 2.55 and 3.18 (1H, 2dd, H_β, $^2J_1(H_\beta,H_{\beta'})$=13.5 Hz, $^2J_2(H_\beta,H_{\beta'})$=16.5 Hz, $^3J_1(H_\beta,H_\alpha)$=2.5 Hz, $^3J_2(H_\beta,H_\alpha)$=4.5 Hz), 3.61 (1H, d, H_α Gly, $^2J(H_\alpha,H_{\alpha'})$=17.5 Hz), 3.73 (0.6H, pseudo t, $H_{\beta'}$, $^2J(H_{\beta'},H_\beta)\approx$ $^3J(H_{\beta'},H_\alpha)$=14.0 Hz), 4.08–4.35 (2.8H, m, $H_{\beta'}+H_{CH_2}$), 4.77 and 5.10 (1H, 2d, $H_{\alpha'}$ Gly, $^2J(H_{\alpha'},H_\alpha)$=18.0 Hz), 4.86 and 5.26 (1H, 2dd, H_α Aba, $^3J_1(H_\alpha,H_\beta)$=3.0 Hz, $^3J_2(H_\alpha,H_\beta)$=4.0 Hz, $^3J_1(H_\alpha,H_{\beta'})$=$^3J_2(H_\alpha,H_{\beta'})$=14.0 Hz), 5.65

and 5.69 (1H, 2s, H_ε), 6.82 (1H, m, NH), 7.16–7.56 (10H, M, H arom), 7.63–7.75 (6H, M, H arom). ^{13}C NMR 63 MHz ($CDCl_3$): δ_C=14.2 and 14.3 (CH_3 Et), 32.1 and 33.5 (C_β), 51.6 and 53.0 (C_α Gly), 53.1 and 54.1 (C_α Aba), 62.0 (CH_2 Et), 68.5 and 69.3 (C_ε), 111.5 (CH arom), 112.1 (CH arom), 114.3 (CH arom), 125.1 (CH arom), 126.5 (CH arom), 128.5 (CH arom), 129.0 (CH arom), 130.0 (CH arom), 130.2 (CH arom), 131.2 (CH arom), 134.0 (CH arom), 135.1 (C_{quat} arom), 137.0 (C_{quat} arom), 137.3 (C_{quat} arom), 137.5 (C_{quat} arom), 138.0 (C_{quat} arom), 144.0 (C_6H pyridine), 154.5 ($C2_{quat}$ pyridine), 168.3 (C═O), 169.0 (C═O), 170.1 (C═O).

4.2.3. Synthesis of ethyl [(4*S*)-1(*R*,*S*)-[4-(1,4-dioxa-8-azaspiro[4.5]dec-8-yl)phenyl]-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-oxo-1,3,4,5-tetrahydro-2*H*-2-benzazepin-2-yl]acetate (10c, entry 6, Table 1). An oven dried 25 mL round-bottomed flask was charged with Pd_2dba_3 (9.2 mg, 0.010 mmol, 5 mol %) and 2-(di-*tert*-butylphosphino)biphenyl (12.0 mg, 0.040 mmol, 20 mol %). The flask was flushed with N_2 and subsequently toluene (6 mL) was added. This solution was stirred for 10 min at rt. During these 10 min, **9** (109.5 mg, 0.20 mmol), 1,4-dioxa-8-azaspiro[4,5]decane (0.030 mL, 0.24 mmol, 1.2 equiv), and K_3PO_4 (85 mg, 0.4 mmol, 2 equiv) were weighed into another 25 mL flask. This flask was also flushed with N_2 and 3 mL of the Pd(0)/ligand solution (0.005 mmol Pd_2dba_3 and 0.010 mmol 2-(di-*tert*-butylphosphino)biphenyl) was added. The reaction mixture was heated (oil bath temperature: 100 °C) and magnetically stirred for 20 h under N_2 atmosphere. After evaporation of the solvent, the crude product was dissolved in a minimum amount of acetonitrile/water (1.2:1), filtered, and purified by preparative HPLC. The desired product **10c** (65.7 mg, 0.11 mmol, 54%) was obtained *as a mixture of diastereoisomers* in the form of a white solid. TLC: R_f 0.33 (EtOAc/hexanes 1:1), mp 128.7–131.1 °C. MS (ESP^+) found m/z=610 ($[M+H]^+$), $C_{35}H_{35}N_3O_7$ requires 609.67. HPLC: retention time=13.8 and 14.0 (min). ^1H NMR 250 MHz ($CDCl_3$): δ_H=1.12 and 1.22 (3H, 2t, H_{CH_3}, $^3J_1$=$^3J_2$=7.6 Hz), 2.11 (4H, m, $2CH_2$), 2.53 and 3.16 (1H, 2dd, H_β, $^2J_1(H_\beta,H_{\beta'})$=15.2 Hz, $^2J_2(H_\beta,H_{\beta'})$=17.7 Hz, $^3J_1(H_\beta,H_\alpha)$=3.0 Hz, $^3J_2(H_\beta,H_\alpha)$=5.0 Hz), 3.60 (6H, m, $2NCH_2$+H_α Gly+$H_{\beta'}$), 4.01 and 4.03 (4H, 2s, $–OCH_2CH_2O–$), 4.17 (2H, m, H_{CH_2}), 4.68 and 5.06 (1H, 2d, $H_{\alpha'}$ Gly, $^2J(H_{\alpha'},H_\alpha)$=17.7 Hz), 4.85 and 5.16 (1H, 2dd, H_α Aba, $^3J_1(H_\alpha,H_\beta)$=3.0 Hz, $^3J_2(H_\alpha,H_\beta)$=4.5 Hz, $^3J_1(H_\alpha,H_{\beta'})$=13.0 Hz, $^3J_2(H_\alpha,H_{\beta'})$=12.5 Hz), 5.60 and 5.68 (1H, 2s, H_ε), 7.20–7.55 (8H, M, H arom), 7.65–7.75 (2H, M, H arom), 7.85–7.91 (2H, M, H arom). ^{13}C NMR 63 MHz ($CDCl_3$): δ_C=13.8 and 14.1 (CH_3 Et), 33.1 and 33.2 (C_β), 34.2 ($C_{NCH_2CH_2}$), 52.2 and 52.6 (C_α Gly), 52.4 (C_α Aba), 53.5 (NCH_2), 61.5 (CH_2 Et), 64.7 (OCH_2CH_2O), 68.5 and 69.6 (C_ε), 104.9 (C_{quat} azaspirodecane), 119.7 (CH arom), 124.0 (CH arom), 127.8 (CH arom), 128.3 (CH arom), 129.9 (CH arom), 130.0 (CH arom), 130.1 (CH arom), 131.15 (C_{quat} arom), 130.4 (CH arom), 134.9 (C_{quat} arom), 137.0 (C_{quat} arom), 138.2 (C_{quat} arom), 144.8 (C_{quat} arom), 168.9 (C═O), 169.8 (C═O), 170.0 (C═O).

4.2.4. Synthesis of ethyl [(4*S*)-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1(*R*,*S*)-(4-morpholin-4-ylphenyl)-3-oxo-1,3,4,5-tetrahydro-2*H*-2-benzazepin-2-yl]acetate (10d, entry 8, Table 1). Identical reaction conditions as for the synthesis of **10c** were used.

The desired product **10d** (66.4 mg, 0.12 mmol, 60%) was obtained *as a mixture of diastereoisomers* in the form of a white solid. TLC: R_f 0.32 (EtOAc/hexanes 1:1), mp 95.8–98.0 °C. MS (ESP^+) found m/z=554 ($[M+H]^+$), $C_{32}H_{31}N_3O_6$ requires 553.61. HPLC: retention time=15.1 and 15.3 (min). ^1H NMR 250 MHz ($CDCl_3$): δ_H=1.12 and 1.22 (3H, 2t, H_{CH_3}, $^3J_1$=$^3J_2$=7.5 Hz), 2.53 and 3.16 (1H, 2dd, H_β, $^2J_1(H_\beta,H_{\beta'})$=14.0 Hz, $^2J_2(H_\beta,H_{\beta'})$=17.0 Hz, $^3J_1(H_\beta,H_\alpha)$=3.0 Hz, $^3J_2(H_\beta,H_\alpha)$=4.2 Hz), 3.41 and 3.49 (4H, 2m, $2NCH_2$), 3.61 and 4.31 (1H, 2d, H_α Gly, $^2J(H_\alpha,H_{\alpha'})$=17.0 Hz), 3.67 (1H, pseudo t, $H_{\beta'}$, $^2J(H_{\beta'},H_\beta)\approx$ $^3J(H_{\beta'},H_\alpha)$=13.8 Hz), 4.07 and 4.10 (4H, 2m, $–CH_2OCH_2–$), 4.17 (2H, m, H_{CH_2}), 4.69 and 5.07 (1H, 2d, $H_{\alpha'}$ Gly, $^2J(H_{\alpha'},H_\alpha)$=17.0 Hz), 4.86 and 5.16 (1H, 2dd, H_α Aba, $^3J_1(H_\alpha,H_\beta)$=3.0 Hz, $^3J_2(H_\alpha,H_\beta)$=4.2 Hz, $^3J_1(H_\alpha,H_{\beta'})$=13.0 Hz, $^3J_2(H_\alpha,H_{\beta'})$=13.3 Hz), 5.62 and 5.68 (1H, 2s, H_ε), 7.18–7.55 (8H, M, H arom), 7.65–7.75 (2H, M, H arom), 7.85–7.91 (2H, M, H arom). ^{13}C NMR 63 MHz ($CDCl_3$): δ_C=13.8 and 14.1 (CH_3 Et), 33.1 and 34.2 (C_β), 52.4 and 52.7 (C_α Gly), 52.8 (C_α Aba), 53.5 (NCH_2), 61.5 (CH_2 Et), 65.3 (CH_2OCH_2), 68.4 and 69.6 (C_ε), 118.9 (CH arom), 123.4 (CH arom), 127.8 (CH arom), 128.4 (CH arom), 129.9 (CH arom), 130.1 (CH arom), 130.4 (CH arom), 131.7 (C_{quat} arom), 134.0 (CH arom), 134.2 (C_{quat} arom), 136.6 (C_{quat} arom), 137.2 (C_{quat} arom), 144.8 (C_{quat} arom), 168.9 (C═O), 169.8 (C═O), 170.0 (C═O).

4.3. Heck coupling between 9 and ethyl acrylate

4.3.1. Synthesis of ethyl (2*E*)-3-{4-[(4*S*)-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-2-(2-ethoxy-2-oxoethyl)-3-oxo-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-yl]phenyl}-prop-2-enoate (13, entry 3, Table 2). An oven dried 25 mL round-bottomed flask was charged with **9** (109.5 mg, 0.20 mmol), $NaHCO_3$ (33.6 mg, 0.40 mmol, 2 equiv), and ethyl acrylate (0.050 mL, 0.4 mmol, 2 equiv). The flask was flushed with Ar and DMF (3 mL) was added. Subsequently, addition of $Pd(PPh_3)_4$ (70 mg, 0.06 mmol, 30 mol %) to the flask was followed by stirring the reaction mixture for 24 h at 130 °C (oil bath temperature). After evaporation of the solvent, the crude product was dissolved in a minimum amount of acetonitrile/water (1.2:1), filtered, and purified by preparative HPLC. The desired product (74.7 mg, 0.13 mmol, 66%) was obtained *as a mixture of diastereoisomers* in the form of a white solid. TLC: R_f 0.64 (EtOAc/hexanes 1:1), mp 122.6–125.1 °C. MS (ESP^+) found m/z=567 ($[M+H]^+$), $C_{33}H_{30}N_2O_7$ requires 566.60. HPLC: retention time=18.1 and 18.5 (min). ^1H NMR 250 MHz ($CDCl_3$): δ_H=1.11 and 1.22 (3H, 2t, H_{CH_3}(Gly ester), $^3J_1$=$^3J_2$=7.5 Hz), 1.33 and 1.34 (3H, 2t, H_{CH_3}(acrylate ester), $^3J_1$=$^3J_2$=7.3 Hz), 2.53 and 3.18 (1H, 2dd, H_β, $^2J_1(H_\beta,H_{\beta'})$=13.6 Hz, $^2J_2(H_\beta,H_{\beta'})$=16.6 Hz, $^3J_1(H_\beta,H_\alpha)$=3.3 Hz, $^3J_2(H_\beta,H_\alpha)$=4.0 Hz), 3.61 (0.6H, 2d, H_α Gly $^2J(H_\alpha,H_{\alpha'})$=17.5 Hz), 3.72 (0.6H, pseudo t, $H_{\beta'}$, $^2J(H_{\beta'},H_\beta)\approx{}^3J(H_{\beta'},H_\alpha)$=13.8 Hz), 4.20 (5.0H, m, H_{CH_2} acrylate ester + H_{CH_2}Gly ester + $H_{\beta'}$ + H_αGly), 4.73 and 5.11 (1H, 2d, $H_{\alpha'}$ Gly, $^2J(H_{\alpha'},H_\alpha)$=17.1 Hz), 4.85 and 5.26 (1H, 2dd, H_α Aba $^3J_1(H_\alpha,H_\beta)$=3.0 Hz, $^3J_2(H_\alpha,H_\beta)$=4.5 Hz, $^3J_1(H_\alpha,H_{\beta'})$=13.3 Hz, $^3J_2(H_\alpha,H_{\beta'})$=12.6 Hz), 5.64 and 5.70 (1H, 2s, H_ε), 6.42 and 6.46 (1H, d, $H_{CHC=O}$ acrylate,

$^3J(H_{CHC=O},H_{PhCH=CH})$=16.1 Hz), 7.09–7.89 (13H, M, H arom). ^{13}C NMR 63 MHz ($CDCl_3$): δ_C=13.8 and 14.1 (CH_3 Et), 14.2 and 14.3 (CH_3 Et), 33.1 and 34.4 (C_β), 53.4 (C_α Gly), 54.6 (C_α Aba), 61.5 (CH_2 Et), 62.5 (CH_2 Et), 69.2 and 70.4 (C_ε), 118.2 (*CH*C=O acrylate), 123.2 (CH arom), 127.0 (CH arom), 127.8 (CH arom), 128.2 (CH arom), 128.8 (CH arom), 129.9 (CH arom), 130.1 (CH arom), 130.5 (CH arom), 133.8 (C_{quat} arom), 134.2 (CH arom), 136.9 (C_{quat} arom), 138.4 (C_{quat} arom), 141.6 (Ph*CH*=CH), 143.9 (C_{quat} arom), 163.1 (C=O acrylate), 168.8 (C=O), 169.8 (C=O), 170.0 (C=O).

4.4. Suzuki couplings on compound 9

4.4.1. Synthesis of ethyl [(4*S*)-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1(*R*,*S*)-(4′-fluoro-1,1′-biphenyl-4-yl)-3-oxo-1,3,4,5-tetrahydro-2*H*-2-benzazepin-2-yl]acetate (15a, entry 2, Table 3). An oven dried 25 mL round-bottomed flask was charged with $Pd(OAc)_2$ (7.3 mg, 0.033 mmol, 16.65 mol %) and 2-(di-*tert*-butylphosphino)-biphenyl (20.0 mg, 0.067 mmol, 33.5 mol %). The flask was flushed with N_2 and subsequently DME (10 mL) was added. This solution was stirred for 10 min at rt. During these 10 min **9** (109.5 mg, 0.20 mmol), 4-fluorophenylboronic acid (42.0 mg, 0.30 mmol, 1.5 equiv), and KF (34.9 mg, 0.6 mmol, 3 equiv) were weighed into another 25 mL flask. This flask was also flushed with N_2 and 3 mL of the Pd(0)/2-(di-*tert*-butylphosphino)biphenyl solution (0.010 mmol $Pd(OAc)_2$ and 0.020 mmol 2-(di-*tert*-butylphosphino)biphenyl) was added. The reaction mixture was heated (oil bath temperature: 95 °C) and magnetically stirred for 24 h under N_2 atmosphere. After evaporation of the solvent, the crude product was dissolved in a minimum amount of acetonitrile/water (1.2:1), filtered, and purified by preparative HPLC. The desired product **15a** (79.8 mg, 0.142 mmol, 71%) was obtained *as a mixture of diastereoisomers* in the form of a white solid. TLC: R_f 0.75 (EtOAc/hexanes 1:1), mp 152.2–154.3 °C. MS (ESP^+) found *m*/*z*=563 ($[M+H]^+$), $C_{34}H_{27}FN_2O_5$ requires 562.59. HPLC: retention time=19.6 and 19.7 (min), ^{1}H NMR 250 MHz ($CDCl_3$): δ_H=1.12 and 1.22 (3H, 2t, H_{CH_3}, $^3J_1$=$^3J_2$=7.3 Hz), 2.54 and 3.21 (1H, 2dd, H_β, $^2J_1(H_\beta,H_{\beta'})$=13.8 Hz, $^2J_2(H_\beta,H_{\beta'})$=18.0 Hz, $^3J_1(H_\beta,H_\alpha)$=3.0 Hz, $^3J_2(H_\beta,H_\alpha)$=4.4 Hz), 3.65 (1H, d, H_α Gly, $^2J(H_\alpha,H_{\alpha'})$=17.0 Hz), 3.83 (1H, pseudo t, $H_{\beta'}$, $^2J(H_{\beta'},H_\beta)\approx{}^3J(H_{\beta'},H_\alpha)$=13.5 Hz), 4.18 (2H, m, H_{CH_2}), 4.88 (1H, dd, H_α Aba, $^3J(H_\alpha,H_\beta)$=3.0 Hz, $^3J(H_\alpha,H_{\beta'})$=13.2 Hz), 5.13 (1H, d, $H_{\alpha'}$ Gly, $^2J(H_{\alpha'},H_\alpha)$=17.0 Hz), 5.32 (0.3H, m, $H_{\alpha'}$) 5.69 and 5.72 (1H, 2s, H_ε), 7.16–7.76 (16H, M, H arom). ^{13}C NMR 63 MHz ($CDCl_3$): δ_C=14.0 and 14.2 (CH_3 Et), 34.3 (C_β), 52.7 (C_α Gly), 53.6 (C_α Aba), 61.4 (CH_2 Et), 69.8 and 71.1 (C_ε), 116.1 (CH arom), 116.2 (CH arom), 123.2 (CH arom), 127.1 (CH arom), 128.5 (CH arom), 129.5 (CH arom), 129.6 (CH arom), 130.0 (CH arom), 130.3 (C_{quat} arom), 130.4 (C_{quat} arom), 131.0 (CH arom), 134.1 (C_{quat} arom), 137.4 (C_{quat} arom), 138.6 (C_{quat} arom), 139.0 (C_{quat} arom), 139.7 (C_{quat} arom), 169.7 (C=O), 169.8 (C=O), 170.1 (C=O).

4.4.2. Synthesis of ethyl [(4*S*)-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1(*R*,*S*)-(4′-methoxy-1,1′-biphenyl-4-yl)-3-oxo-1,3,4,5-tetrahydro-2*H*-2-benzazepin-2-yl]acetate (15b, entry 3, Table 3). Identical reaction conditions as for the synthesis of **15a** were used. The desired product **15b** (75.7 mg, 0.132 mmol, 66%) was obtained *as a mixture of diastereoisomers* in the form of a white solid. TLC: R_f 0.65 (EtOAc/hexanes 1:1), mp 137.5–141.6 °C. MS (ESP^+) found *m*/*z*=575 ($[M+H]^+$), $C_{35}H_{30}N_2O_6$ requires 574.62. HPLC: retention time=19.4 (min). ^{1}H NMR 250 MHz ($CDCl_3$): δ_H=1.11 and 1.22 (3H, 2t, H_{CH_3}, $^3J_1$=$^3J_2$=7.5 Hz), 2.55 and 3.21 (1H, 2dd, H_β, $^2J_1(H_\beta,H_{\beta'})$=14.0 Hz, $^2J_2(H_\beta,H_{\beta'})$=12.0 Hz, $^3J_1(H_\beta,H_\alpha)$=3.6 Hz, $^3J_2(H_\beta,H_\alpha)$=4.6 Hz), 3.65 (1H, d, H_α Gly, $^2J(H_\alpha,H_{\alpha'})$=17.5 Hz), 3.83–3.85 (4H, 2s+pseudo t, OMe+$H_{\beta'}$), 4.20 (2H, m, H_{CH_2}), 4.87 and 5.37 (1H, 2dd, H_α Aba, $^3J_1(H_\alpha,H_\beta)$=3.6 Hz, $^3J_2(H_\alpha,H_\beta)$=5.0 Hz, $^3J_1(H_\alpha,H_{\beta'})$=14.0 Hz, $^3J_2(H_\alpha,H_{\beta'})$=12.0 Hz), 4.88 and 5.13 (1H, 2d, $H_{\alpha'}$ Gly, $^2J(H_{\alpha'}–H_\alpha)$=17.0 Hz), 5.68 and 5.74 (1H, 2s, H_ε), 6.95 (2H, m, H arom), 7.20–7.75 (14H, M, H arom). ^{13}C NMR 63 MHz ($CDCl_3$): δ_C=13.8 and 14.1 (CH_3 Et), 34.3 and 33.3 (C_β), 52.1 and 52.7 (C_α Gly), 53.6 (C_α Aba), 55.4 (OCH_3), 61.4 (CH_2 Et), 68.8 and 69.9 (C_ε), 114.2 (CH arom), 123.3 (CH arom), 126.8 (CH arom), 127.6 (CH arom), 128.0 (CH arom), 128.2 (CH arom), 129.7 (CH arom), 129.9 (CH arom), 130.4 (CH arom), 132.8 (C_{quat} arom), 133.9 (C_{quat} arom), 134.2 (CH arom), 137.0 (C_{quat} arom), 137.4 (C_{quat} arom), 138.8 (C_{quat} arom), 139.9 (C_{quat} arom), 159.0 (C_{quat} arom), 169.1 (C=O), 169.9 (C=O), 170.1 (C=O).

4.4.3. Synthesis of ethyl [(4*S*)-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-oxo-1(*R*,*S*)-(4-thien-3-ylphenyl)-1,3,4,5-tetrahydro-2*H*-2-benzazepin-2-yl]acetate (15c, entry 6, Table 3). An oven dried 25 mL round-bottomed flask was charged with $Pd(OAc)_2$ (7.3 mg, 0.033 mmol, 16.65 mol %) and 2-(di-*tert*-butylphosphino)biphenyl (20.0 mg, 0.067 mmol, 33.5 mol %). The flask was flushed with N_2 and subsequently DME (10 mL) was added. This solution was stirred for 10 min at rt. During these 10 min **9** (109.5 mg, 0.20 mmol), 3-thiophene boronic acid (90.0 mg, 0.70 mmol, 3.5 equiv), and KF (34.9 mg, 0.6 mmol, 3 equiv) were weighed into another 25 mL flask. This flask was also flushed with N_2 and 3 mL of the Pd(0)/ligand solution (0.010 mmol $Pd(OAc)_2$ and 0.020 mmol 2-(di-*tert*-butylphosphino)biphenyl) was added. The reaction mixture was heated (oil bath temperature: 95 °C) and magnetically stirred for 24 h under N_2 atmosphere. After evaporation of the solvent, the crude product was dissolved in a minimum amount of acetonitrile/water (1.2:1), filtered, and purified by preparative HPLC. The desired product **15c** (70.5 mg, 0.128 mmol, 64%) was obtained *as a mixture of diastereoisomers* in the form of a white solid. TLC: R_f 0.47 (EtOAc/hexanes 1:1), mp 140.2–142.0 °C. MS (ESP^+) found *m*/*z*=551 ($[M+H]^+$), $C_{32}H_{26}N_2O_5S$ requires 550.63. HPLC: retention time=19.2 and 19.4 (min). ^{1}H NMR 250 MHz ($CDCl_3$): δ_H=1.10 and 1.22 (3H, 2t, H_{CH_3}, $^3J_1$=$^3J_2$=6.5 Hz), 2.54 and 3.20 (1H, 2dd, H_β, $^2J_1(H_\beta,H_{\beta'})$=14.0 Hz, $^2J_2(H_\beta,H_{\beta'})$=15.2 Hz, $^3J_1(H_\beta,H_\alpha)$=3.5 Hz, $^3J_2(H_\beta,H_\alpha)$=4.0 Hz), 3.65 (1H, d, H_α Gly, $^2J(H_\alpha,H_{\alpha'})$=17.3 Hz), 3.82 (1H, pseudo t, $H_{\beta'}$, $^2J(H_{\beta'},H_\beta)\approx{}^3J(H_{\beta'},H_\alpha)$=13.0 Hz), 4.18 (2H, m, H_{CH_2}), 4.87 and 5.36 (1H, 2dd, H_α Aba, $^3J_1(H_\alpha,H_\beta)$=3.5 Hz, $^3J_2(H_\alpha,H_\beta)$=4.5 Hz, $^3J_1(H_\alpha,H_{\beta'})$=14.0 Hz, $^3J_2(H_\alpha,H_{\beta'})$=12.0 Hz), 5.65 and 5.72 (1H, 2s, H_ε), 7.20 (2H, m, H arom), 7.26–7.70 (11H, M, H arom), 7.72 (2H, m, H arom). ^{13}C NMR 63 MHz ($CDCl_3$): δ_C=13.8 and 14.1 (CH_3 Et), 34.3 and 33.3 (C_β), 52.2 and 52.7 (C_α Gly), 53.6 (C_α Aba), 61.4 (CH_2 Et), 68.8 and 69.9 (C_ε),

120.5 (CH arom), 123.3 (CH arom), 126.2 (CH arom), 126.3 (CH arom), 126.6 (CH arom), 127.0 (CH arom), 127.6 (CH arom), 129.6 (C_{quat} arom), 129.7 (CH arom), 129.9 (CH arom), 130.4 (CH arom), 134.1 (CH arom), 134.9 (C_{quat} arom), 136.9 (C_{quat} arom), 137.9 (C_{quat} arom), 138.8 (C_{quat} arom), 142.0 (C_{quat} arom), 169.1 (C═O), 169.8 (C═O), 170.1 (C═O).

4.5. Suzuki coupling of compound 11

4.5.1. Synthesis of 2-[(1*R*,4*S*)-1-(4′-fluoro-1,1′-biphenyl-4-yl)-3-oxo-2,3,4,5-tetrahydro-1*H*-2-benzazepin-4-yl]-1*H*-isoindole-1,3(2*H*)-dione 16 (Scheme 6). An oven dried 25 mL round-bottomed flask was charged with $Pd(OAc)_2$ (7.3 mg, 0.033 mmol, 16.65 mol %) and 2-(di-*tert*-butylphosphino)biphenyl (20.0 mg, 0.067 mmol, 33.5 mol %). The flask was flushed with N_2 and subsequently DME (5 mL) and DMA (5 mL) were added. This solution was stirred for 10 min at rt. During these 10 min **11** (92.0 mg, 0.20 mmol), 4-fluorophenylboronic acid (42.0 mg, 0.30 mmol, 1.5 equiv), and KF (34.9 mg, 0.6 mmol, 3 equiv) were weighed into another 25 mL flask. This flask was also flushed with N_2 and 3 mL of the Pd(0)/ligand solution (0.010 mmol $Pd(OAc)_2$ and 0.020 mmol 2-(di-*tert*-butylphosphino)biphenyl) was added. The reaction mixture was heated (oil bath temperature: 95 °C) and magnetically stirred for 24 h under N_2 atmosphere. After evaporation of the solvent, the crude product was dissolved in a minimum amount of acetonitrile/water (1.2:1), filtered, and purified by preparative HPLC. The desired product **16** (66.7 mg, 0.14 mmol, 70%) was obtained as a white solid. TLC: R_f 0.45 (EtOAc/hexanes 1:1), mp 179.2–182.1 °C. MS (ESP^+) found m/z=477 ($[M+H]^+$), $C_{30}H_{21}FN_2O_3$ requires 476.50. HPLC: retention time=17.3 (min). ^1H NMR 250 MHz ($CDCl_3$): δ_H=2.66 (1H, 2dd, H_β, $^2J(H_\beta,H_{\beta'})$=14.6 Hz, $^3J(H_\beta,H_\alpha)$=3.0 Hz), 3.76 (1H, pseudo t, $H_{\beta'}$, $^2J(H_{\beta'},H_\beta)\approx{}^3J(H_{\beta'},H_\alpha)$=13.3 Hz), 4.89 (1H, dd, H_α Aba, $^3J(H_\alpha,H_\beta)$=3.0 Hz, $^3J(H_\alpha,H_{\beta'})$=13.3 Hz), 5.65 (1H, d, H_ε, $^3J(H_\varepsilon,NH)$=7.3 Hz), 7.10–7.75 (17H, M, H arom). ^{13}C NMR 63 MHz ($CDCl_3$): δ_C=34.3 (C_β), 52.4 (C_α Aba), 61.6 (C_ε), 115.5 (CH arom), 115.8 (CH arom), 123.5 (CH arom), 127.0 (CH arom), 127.8 (CH arom), 128.6 (CH arom), 128.7 (CH arom), 129.3 (CH arom), 129.6 (C_{quat} arom), 130.7 (CH arom), 132.0 (CH arom), 134.1 (C_{quat} arom), 136.5 (C_{quat} arom), 138.9 (C_{quat} arom), 139.3 (C_{quat} arom), 140.0 (C_{quat} arom), 160.7 (C_{quat} arom), 171.2 (C═O), 183.8 (C═O).

4.6. Synthesis of/and Suzuki coupling of compound 3

4.6.1. Synthesis of 2-(8-bromo-3-oxo-1-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-4-yl)-isoindole-1,3-dione 17 (Scheme 7). *N*-Phthaloyl-pBr-(*S*)-phenylalanine amide (1 g, 2.75 mmol), benzotriazole (1 equiv, 0.306 g, 2.75 mmol), and *p*-TsOH (0.1 equiv, 0.056 g, 0.275 mmol) were added to an oven dried 100 mL flask and dissolved in dry benzene (35 mL). After addition of benzaldehyde (1 equiv, 0.261 mg, 2.75 mmol), the flask, mounted by a Dean–Stark apparatus, was heated by means of an oil bath (115 °C) and the solution was refluxed over night. After evaporation of the solvent, trituration with Et_2O gave compound **6** quantitatively. The benzotriazole adduct **6** (0.300 g, 0.52 mmol) was dissolved in dry CH_2Cl_2 (40 mL). Then, $AlCl_3$ (0.420 g, 3.1 mmol, 6 equiv) was added and the solution was refluxed over night. The reaction mixture was cooled down to room temperature after which H_2O (20 mL) was added to quench the reaction. Washing the organic layer with brine (20 mL), drying over $MgSO_4$, and evaporation of the solvent gave the crude product, which was crystallized in EtOH. The desired compound **3** (0.067 g, 0.15 mmol, 28%) was obtained. TLC: R_f 0.30 (EtOAc/hexanes 1:1), mp 300–302 °C. MS (ESP^+) found m/z=461 and 463 ($[M+H]^+$), $C_{24}H_{17}BrN_2O_3$ requires 461.31. HPLC: retention time=16.2 (min). ^1H NMR 250 MHz (DMSO-d_6): δ_H=2.74 (1H, dd, H_β, $^2J(H_\beta,H_{\beta'})$=14.0 Hz, $^3J(H_\beta,H_\alpha)$=3.0 Hz), 3.61 (1H, pseudo t, $H_{\beta'}$, $^2J(H_{\beta'},H_\beta)\approx{}^3J(H_{\beta'},H_\alpha)$ J=13.0 Hz), 4.84 (1H, dd, H_α Aba, $^3J(H_\alpha,H_\beta)$=3.0 Hz, $^3J(H_\alpha,H_{\beta'})$=12.8 Hz), 5.65 (1H, d, H_ε, $^3J(H_\varepsilon,NH)$=7.0 Hz), 7.15–7.55 (8H, M H arom), 7.70–7.75 (4H, M, H Pht), 8.93 (1H, d, NH, $^3J(NH,H_\varepsilon)$=7.0 Hz). ^{13}C NMR 63 MHz (DMSO-d_6): δ_C=34.5 (C_β), 52.8 (C_α Aba), 61.7 (C_ε), 115.6 (CH arom), 120.5 (C_q arom), 123.9 (CH arom), 126.3 (CH arom), 128.1 (CH arom), 128.6 (CH arom), 129.9 (CH arom), 130.1 (CH arom), 131.9 (CH arom), 134.6 (C_{quat} arom), 136.7 (C_{quat} arom), 140.5 (C_{quat} arom), 142.5 (C_{quat} arom), 171.8 (C═O), 183.8 (C═O).

4.6.2. Synthesis of 2-[(1*R*)-8-(4-fluorophenyl)-3-oxo-1-phenyl-2,3,4,5-tetrahydro-1*H*-2-benzazepin-4-yl]-1*H*-isoindole-1,3(2*H*)-dione 17 (Scheme 7). Identical reaction conditions as for the synthesis of **16** were used.

The desired product **17** (64.8 mg, 0.136 mmol, 68%) was obtained as a white solid. TLC: R_f 0.58 (EtOAc/hexanes 1:1), mp 244.0–246.6 °C. MS (ESP^+) found m/z=477 ($[M+H]^+$), $C_{30}H_{21}FN_2O_3$ requires 476.50. HPLC: retention time=17.4 (min). ^1H NMR 250 MHz ($CDCl_3$): δ_H=2.67 (1H, dd, H_β, $^2J(H_\beta–H_{\beta'})$=14.4 Hz, $^3J(H_\beta–H_\alpha)$=3.3 Hz), 3.74 (1H, pseudo t, $H_{\beta'}$, $^2J(H_{\beta'},H_\beta)\approx{}^3J(H_{\beta'},H_\alpha)$, J=13.3 Hz), 4.90 (1H, dd, H_α Aba, $^3J(H_\alpha,H_\beta)$=3.2 Hz, $^3J(H_\alpha,H_{\beta'})$=13.0 Hz), 5.68 (1H, d, H_ε, $^3J(H_\varepsilon,NH)$=7.0 Hz), 7.20–7.65 (12H, M, H arom), 7.75 (2H, M, H Pht), 7.85 (2H, M, H Pht). ^{13}C NMR 63 MHz ($CDCl_3$): δ_C=33.9 (C_β), 52.4 (C_α Aba), 61.9 (C_ε), 115.6 (CH arom), 115.7 (CH arom), 123.6 (CH arom), 126.5 (CH arom), 127.8 (CH arom), 128.6 (CH arom), 128.7 (CH arom), 128.8 (CH arom), 129.6 (C_{quat} arom), 131.2 (CH arom), 132.0 (CH arom), 134.1 (C_{quat} arom), 135.5 (C_{quat} arom), 139.5 (C_{quat} arom), 139.6 (C_{quat} arom), 140.8 (C_{quat} arom), 160.7 (C_{quat} arom), 168.2 (C═O), 171.2 (C═O).

4.7. N-Arylation of 19 with 4-iodobenzonitrile

4.7.1. Synthesis of 4-[(4*S*)-4-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-oxo-1,3,4,5-tetrahydro-2*H*-2-benzazepin-2-yl]benzonitrile 20 (Scheme 9). An oven dried 25 mL round-bottomed flask was charged with Pd_2dba_3 (9.2 mg, 0.010 mmol, 5 mol %) and XANTPHOS (12.8 mg, 0.022 mmol, 11 mol %). The flask was flushed with Ar and subsequently dioxane (6 mL) was added. This solution was stirred for 10 min at rt. During these 10 min **19** (61.0 mg, 0.20 mmol), 4-iodobenzonitrile (55.0 mg, 0.24 mmol, 1.2 equiv), and Cs_2CO_3 (261 mg, 0.8 mmol, 4 equiv) were weighed into another 25 mL flask. This flask was also flushed with N_2 and 3 mL of the Pd(0)/XANTPHOS solution (0.005 mmol Pd_2dba_3 and 0.011 mmol XANTPHOS) was added. The reaction mixture was heated (oil bath

temperature: 100 °C) and magnetically stirred for 24 h under Ar atmosphere. After evaporation of the solvent, the crude product was dissolved in a minimum amount of acetonitrile/water (1.2:1), filtered, and purified by preparative HPLC. The desired product (53.7 mg, 0.132 mmol, 66%) was obtained as a white solid. TLC: R_f 0.78 (EtOAc/hexanes 1:1), mp 113.5–115.4 °C. MS (ESP^+) found m/z=408 ($[M+H]^+$), $C_{25}H_{17}N_3O_3$ requires 407.42. HPLC: retention time=15.1 (min). ^1H NMR 250 MHz ($CDCl_3$): δ_H=3.27 (1H, dd, H_β, $^2J(H_\beta,H_{\beta'})$=15.9 Hz, $^3J(H_\beta,H_\alpha)$=4.6 Hz), 4.31 (1H, dd, $H_{\beta'}$, $^2J(H_{\beta'},H_\beta)$=16.4 Hz, $^3J(H_{\beta'},H_\alpha)$= 13.0 Hz), 4.98 (1H, d, H_α Gly, $^2J(H_\alpha–H_{\alpha'})$=16.0 Hz), 5.12 (1H, d, $H_{\alpha'}$ Gly $^2J(H_{\alpha'}–H_\alpha)$=16.1 Hz), 5.59 (1H, dd, H_α Aba, $^3J(H_\alpha,H_\beta)$=4.9 Hz, $^3J(H_\alpha,H_{\beta'})$=13.1 Hz), 7.22–7.41 (6H, M, H arom), 7.65 (2H, d, H arom (2CHCCN), ^3J=8.7 Hz), 7.76 (2H, M, H Pht), 7.91 (2H, M, H Pht). ^{13}C NMR 63 MHz ($CDCl_3$): δ_C=35.4 (C_β), 50.6 (C_ε), 52.8 (C_α Aba), 110.1 (C_{quat} arom), 116.5 (C_{quat} CN), 122.2 (CH arom), 128.0 (CH arom), 128.4 (CH arom), 129.0 (CH arom), 129.9 (CH arom), 130.1 (CH arom), 131.7 (C_{quat} arom), 132.0 (CH arom), 132.2 (CH arom), 134.1 (C_{quat} arom), 137.2 (C_{quat} arom), 144.8 (C_{quat} arom), 167.8 (C═O), 174.4 (C═O).

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References and notes

1. Flynn, G. A.; Giroux, E. L.; Dage, R. C. *J. Am. Chem. Soc.* **1987**, *109*, 7914–7915.
2. Warchawsky, A. M.; Flynn, G. A.; Koehl, J. R.; Mehdi, S.; Vaz, R. J. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 957–962.
3. Le Diguarher, T.; Ortono, J.-C.; Shanks, D.; Guilbaud, N.; Pierré, A.; Raimbaud, E.; Fauchère, J.-L.; Hickman, J. A.; Tucker, G. C.; Casara, P. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 767–771.
4. Keenan, R. M.; Callahan, J. F.; Samanen, J. M.; Bondinell, W. E.; Calvo, R. R.; Chen, L.; DeBrosse, C.; Eggleston, D. S.; Haltiwanger, R. C.; Hwang, S.-M.; Jakas, D. R.; Ku, T. W.; Miller, W. H.; Newlander, K. A.; Nichols, A.; Parker, M. F.; Southhal, L. S.; Uzinskas, I.; Vasko-Moser, J. A.; Venslavsky, J. W.; Wong, A. S.; Huffman, W. F. *J. Med. Chem.* **1999**, *42*, 545–559.
5. Sawa, Y.; Takeshi, K.; Toru, M.; Mikio, H.; Hajime, F. *Chem. Pharm. Bull.* **1975**, *23*, 1917–1927.
6. Van Rompaey, K.; Van den Eynde, I.; De Kimpe, N.; Tourwé, D. *Tetrahedron* **2003**, *59*, 4421–4432.
7. Van den Eynde, I.; Van Rompaey, K.; Lazzaro, F.; Tourwé, D. *J. Comb. Chem.* **2004**, *6*, 468–473.
8. Tourwé, D.; Verschueren, K.; Frycia, A.; Davis, P.; Porreca, F.; Hruby, V. J.; Toth, G.; Jaspers, H.; Verheyden, P.; Van Binst, G. *Biopolymers* **1995**, *38*, 1–12.
9. Casimir, J. R.; Tourwé, D.; Iterbeke, K.; Guichard, G.; Briand, J.-P. *J. Org. Chem.* **2000**, *65*, 6487–6492.
10. Ballet, S.; Frycia, A.; Piron, J.; Chung, N. N.; Schiller, P. W.; Kosson, P.; Lipkowski, A. W.; Tourwé, D. *J. Pept. Res.* **2005**, *66*, 222–230.
11. Ballet, S.; Urbanczyk-Lipkowska, Z.; Tourwé, D. *Synlett* **2005**, 2791–2795.
12. Katritzky, A. R.; Lan, X.; Zhang, Z. *J. Heterocycl. Chem.* **1993**, *30*, 381–387.
13. Loones, K. T. J.; Maes, B. U. W.; Meyers, C.; Deruytter, J. *J. Org. Chem.* **2006**, *71*, 260–264; For a recent paper providing new insights in Xantphos/Pd-catalyzed C–N bond formation, see: Klingensmith, L. M.; Strieter, E. R.; Barder, T. E.; Buchwald, S. L. *Organometallics* **2006**, *25*, 82–91.
14. Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144–1157.
15. Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158–1174.
16. Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696.
17. Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6523–6527.
18. Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989–7000.
19. Yang, C.; Nolan, S. P. *Synlett* **2001**, 1539–1542.
20. Wang, Z.; Elokdah, H.; McFarlene, G.; Pan, S.; Antane, M. *Tetrahedron Lett.* **2006**, *47*, 3365–3369.
21. Battace, A.; Zair, T.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2006**, *47*, 459–462.
22. Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561.
23. Clapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428.
24. Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101–1104.
25. Hartwig, J. F. *Synlett* **2006**, 1283–1294.