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Functionalization of (2*S*)-Isopropyl-5-iodo-2,3-dihydro-4(*H*)-pyrimidin-4-ones by a Suzuki–Miyaura Cross-Coupling Reaction Using Aryltrifluoroborate Salts: Convenient Enantioselective Preparation of α-Substituted β-Amino Acids

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Keywords: Palladium / Borates / Cross-coupling / Nitrogen heterocycles / Amino acids / Enantioselective synthesis

A simple protocol for the $Pd(OAc)_2$-catalyzed cross-coupling reaction of 1-benzoyl-(2*S*)-isopropyl-5-iodo-2,3-dihydro-4(*H*)-pyrimidin-4-ones with potassium aryltrifluoroborates was developed. The reaction is performed at 110 °C with a ligand-free catalyst. In all cases, complete conversion of the 1-benzoyl-(2*S*)-isopropyl-5-iodo-2,3-dihydro-4(*H*)-pyrimidin-4-ones and aryltrifluoroborates into the C–C coupling products was observed within 30–360 min. It is noteworthy that a large variety of groups present in the potassium aryltrifluoroborates (–CF_3, –OMe, –SEt, –CN, –CHO, –Cl, –Cbz, –NCbz, –OH, –CO_2H) could be tolerated. Hydrogenation of the endocyclic double bonds in the Suzuki–Miyaura products followed by acid hydrolysis afforded highly enantioenriched α-aryl-substituted β-amino acids.

Introduction

Many types of cross-coupling reactions have been known for several decades, and recent advances have greatly increased their scope and practicality. This progress has had a significant impact on academic research, and cross-coupling reactions are now widely employed in a variety of synthetic protocols, from the total synthesis of natural products to the preparation of relevant targets in bioorganic chemistry, pharmaceuticals, agrochemicals, and polymers. Indeed, transition-metal-catalyzed cross-coupling processes are no longer considered out of the ordinary but have become part of the everyday repertoire of the synthetic chemist.[1]

In recent years, organoboron compounds have become some of the most popular organometallic reagents for carbon–carbon bond formation.[2] The great applicability of organoboron compounds is due to several factors, such as (1) compatibility with many functional groups in the substrate, (2) availability of the desired reagents through hydroboration and transmetallation, (3) low toxicity of organoboranes, (4) their ultimate degradation into environmentally friendly boric acids, and (5) the handling and removal of boron-containing byproducts is relatively simple compared to the disposal of other organometallic reagents. The most commonly used organoboron compounds are boronic acids and boronate esters, but these compounds present some drawbacks, such as their low stability, very high cost, and high sensitivity to air and moisture. To solve these problems, boronic acids and boronate esters have been replaced by organotrifluoroborate salts in several cross-coupling reactions.[3]

In particular, organotrifluoroborates are very useful reagents in the Suzuki–Miyaura cross-coupling reaction, which is among the most powerful and mild protocols currently available for the formation of carbon–carbon bonds.[3,4] Unlike their tricoordinate organoboron counterparts, these tetracoordinate species are less prone to undergo protodeboronation. Consequently, near-stoichiometric amounts of the nucleophilic partner are employed for cross-coupling reactions. Furthermore, organotrifluoroborates provide several additional advantages over the corresponding boronic acids and boronate esters. For example, they are easily prepared by the addition of inexpensive KHF_2 to commercially available organoboron compounds, and they can then be stored indefinitely without special precaution due to the air- and moisture-stable nature of these crystalline reagents. Moreover, organotrifluoroborates are inert to many nucleophilic reagents such as cyanide, azide, amines, enolates, alkoxides, and organometallic reagents because the boron atom in organotrifluoroborates does not have an empty p orbital to interact with the incoming nucleophile.

In the last two decades, the synthesis of β-amino acids has been of increasing interest, owing to their presence in biologically active compounds, either in free form or as constituents in various peptides. Indeed, β-amino acids are the main components of several medicinally useful molecules. For these reasons, numerous methodologies for the synthesis of racemic and enantiomerically pure compounds have emerged.[5]

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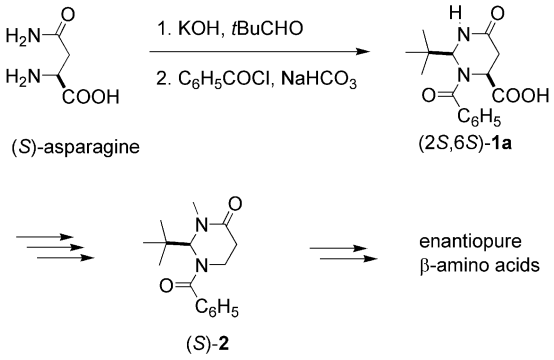
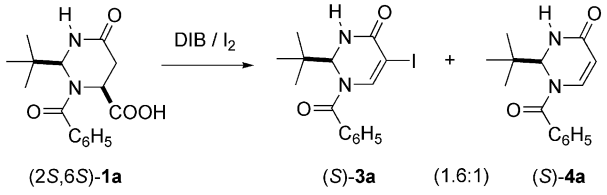
In this regard, perhydropyrimidin-4-one carboxylic acid [(2*S*,6*S*)-**1a**] has been used as an efficient starting material for the enantioselective synthesis of (*R*)- and (*S*)-α-substituted[6] and α,α-disubstituted β-amino acids.[7] Furthermore, several analogs of pyrimidinone (*S*)-**2** have proven useful for the asymmetric synthesis of β-substituted, α,β-disubstituted, and β,β-disubstituted β-amino acids (Scheme 1).[8]



Scheme 1. Enantioselective synthesis of β-amino acids via chiral pyrimidinones.

Recently, we reported that treatment of carboxylic acid (2*S*,6*S*)-**1a** with diacetoxyiodobenzene/iodine (DIB/I_2)[9] afforded a 1.6:1.0 mixture of iodoenone (*S*)-**3a** and enone (*S*)-**4a**.[10] In view of the structural similarity between 5-iodopyrimidinone (*S*)-**3a** and various 5-halouracils that show antiviral activity,[11] reaction conditions were developed for the decarboxylation/β-iodination of (2*S*,6*S*)-**1a** to provide (*S*)-**3a** as the single product (Scheme 2).[12]



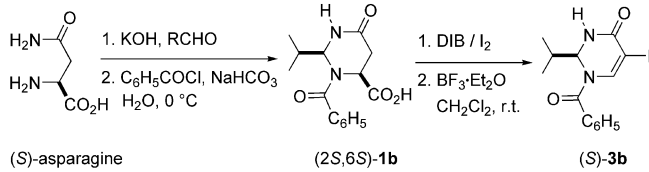
Scheme 2. Preparation of 5-iodopyrimidinone (*S*)-**3a**.

The structural similarity of haloenones **3** and 5-halouracils has suggested that they should present the same chemical reactivity. For example, there are successful reports of the application of Suzuki–Miyaura couplings to substitute the halogen in 6-chloropurine derivatives.[13] Thus, iodopyrimidin-4-ones (*S*)-**3** presented themselves as interesting substrates for this kind of coupling. This paper reports the use of pyrimidinone **3b** as a substrate in Suzuki–Miyaura cross-coupling reactions. The resulting products proved to be suitable precursors to enantiomerically pure β-amino acids.

Herein, we describe the preparation of a variety of pyrimidinones **5a**–**q**, which were obtained by the efficient cross-coupling reaction of (*S*)-**3b** with a broad range of aryltrifluoroborates by using a simple reaction protocol that employs near stoichiometric amounts of the nucleophilic reagent.

Results and Discussion

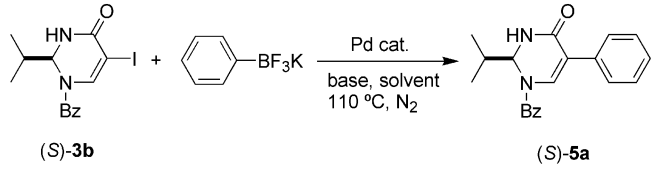
In connection with our research interest in the preparation and evaluation of potassium organotrifluoroborate salts as intermediates in organic synthesis,[14] we wish to report here a general procedure to convert (*S*)-5-substituted iodopyrimidinone precursors to enantiomerically pure β-amino acids. Diastereomerically pure (2*S*,6*S*)-**1b** acid was prepared by condensation of (*S*)-asparagine with isobutyraldehyde, followed by in situ *N*-benzoylation (Scheme 3).[7a,15]



Scheme 3. Preparation of enantiopure (*S*)-2-isopropyl-5-iodopyrimidinone **3**.

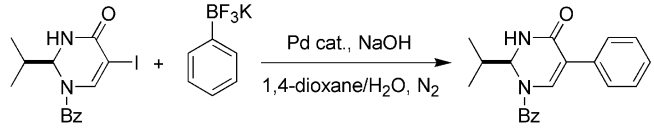
Treatment of perhydropyrimidin-4-one-6-carboxylic acid (2*S*,6*S*)-**1b** with 2 equiv. of diacetoxyiodobenzene and 1 equiv. of iodine (DIB/I_2), followed by addition of BF_3·Et_2O (2 equiv.) to the resulting reaction mixture resulted in the fast conversion of the (*S*)-pyrimidinone into the corresponding 1-benzoyl-(2*S*)-isopropyl-5-iodo-2,3-dihydro-4(*H*)-pyrimidin-4-one (*S*)-**3b**, as the sole reaction product in 78% yield (Scheme 3).

With the starting material in hand, optimization of the reaction conditions for the cross-coupling of (*S*)-**3b** with potassium aryltrifluoroborate salts[16] was undertaken. Ini-



Scheme 4. Cross-coupling of (*S*)-**3b** with potassium phenyltrifluoroborate.

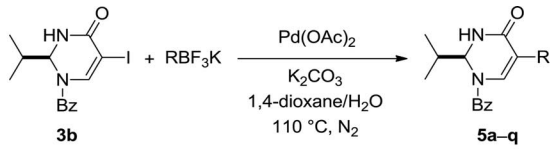
Table 1. Effect of palladium catalyst on the Suzuki–Miyaura reaction.[a]



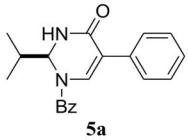
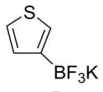
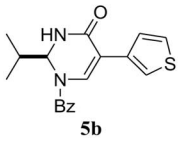
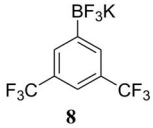
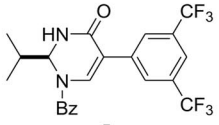
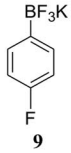
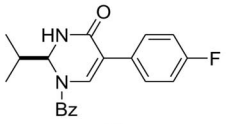
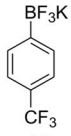
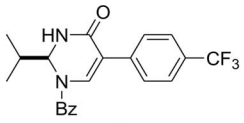
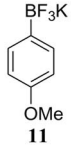
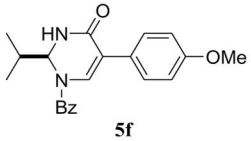
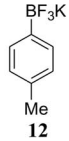
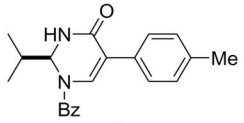
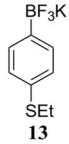
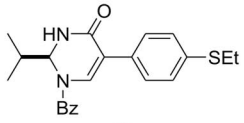
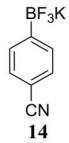
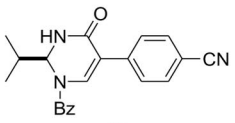
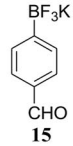
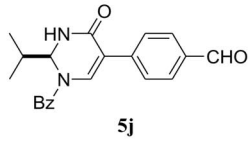
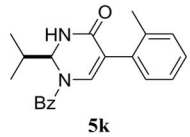
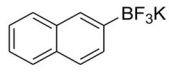
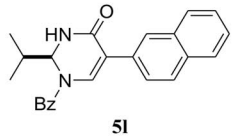
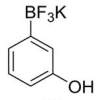
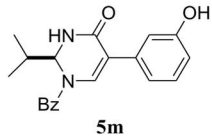
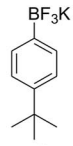
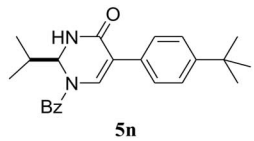
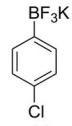
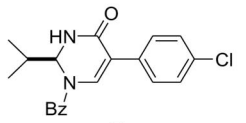
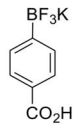
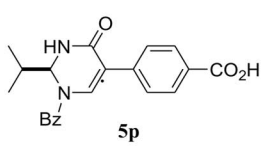
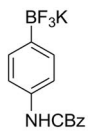
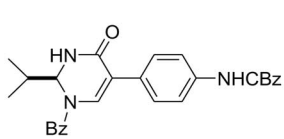
Entry	Catalyst	GC yield [%]
1	$PdCl_2$	66
2	$Pd(acac)_2$	74
3	$Pd(PPh_3)_4$	52
4	$PdCl_2(dppf)$·CH_2Cl_2	84
5	$Pd(OAc)_2$	84
6	–	n.r.
7	$NiCl_2(dppe)$	n.r.

[a] The reaction was carried out with (*S*)-**3b** (0.50 mmol), BF_3K (0.60 mmol), Pd cat. (9 mol-%), and NaOH (1.0 mmol) in dioxane/H_2O (3:1, 5 mL) under a nitrogen atmosphere at reflux.

Table 2. $Pd(OAc)_2$-catalyzed Suzuki–Miyaura reaction of (*S*)-**3b** (1 equiv.) with various potassium aryltrifluoroborates (1.2 equiv.).[a]



3b **5a–q**

Entry	$RBF_3^-K^+$	Product	Time [min]	Yield [%][b]
1	 **6**	 **5a**	30	86
2	 **7**	 **5b**	30	78
3	 **8**	 **5c**	360	n.r.
4	 **9**	 **5d**	30	73
5	 **10**	 **5e**	30	72
6	 **11**	 **5f**	30	95
7	 **12**	 **5g**	30	72
8	 **13**	 **5h**	30	65
9	 **14**	 **5i**	90	60
10	 **15**	 **5j**	30	62
11	 **16**	 **5k**	30	66
12	 **17**	 **5l**	30	70
13	 **18**	 **5m**	30	72
14	 **19**	 **5n**	30	75
15	 **20**	 **5o**	30	59
16	 **21**	 **5p**	360	n.r.
17	 **22**	 **5q**	30	62

[a] The reaction was carried out with (*S*)-**3b** (0.50 mmol), BF_3K (0.60 mmol), $Pd(OAc)_2$ (9 mol-%), and K_2CO_3 (1.0 mmol) in dioxane/H_2O (3:1, 5 mL) under a nitrogen atmosphere at reflux. [b] Isolated yield.

tially, we conducted a palladium catalyst screening with phenyltrifluoroborate salt (Scheme 4).

A comparison of different palladium catalysts [$PdCl_2$, $Pd(OAc)_2$, $Pd(acac)_2$, $Pd(PPh_3)_4$, $PdCl_2(dppf)$, and $NiCl_2$-(dppe)] showed that $Pd(OAc)_2$ (9 mol-%) was the best catalyst for the reaction (Table 1, Entry 5). It should be mentioned that the reaction does not proceed in the absence of a Pd catalyst (Table 1, Entry 6).

Once $Pd(OAc)_2$ had been established as the best catalyst, several organic and inorganic bases were tested as additives. In the present system, inexpensive K_2CO_3 was the most effective (99%), although Cs_2CO_3 also afforded an excellent yield (90%). Bases like Et_3N, DIPEA, $(iPr)_2NH$, and NaOH all gave somewhat lower yields, in the 85–89% range. When NaOH was used, dehalogenation of the starting material leading to corresponding enone (*S*)-**4b** was observed.

Another reaction parameter investigated was the solvent. When MeOH, CH_3CN, and dry α,α,α-trifluorotoluene were employed, the reaction did not proceed. The use of water as solvent in ether mixtures like THF/H_2O (5:1) and 1,4-dioxane/H_2O (3:1) afforded the desired product in 71 and 99% yield, respectively. The use of water as a solvent promoted the formation of the coupled product in 50% yield; however, we also observed the presence of enone (*S*)-**4b** as a direct consequence of dehalogenation of the starting material.

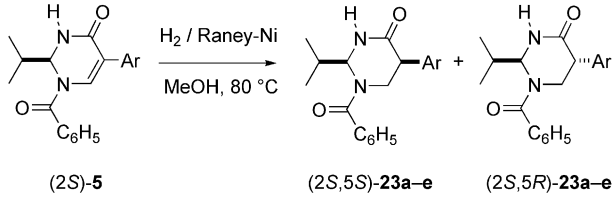
Finally, we tested catalyst loadings from 2.0 to 10 mol-% and found that 9 mol-% of $Pd(OAc)_2$ gave the best results. When the amount of $Pd(OAc)_2$ was less than 9 mol-%, the yields were much lower.

Thus, it was concluded that the use of $Pd(OAc)_2$ (9 mol-%) as catalyst, in the presence of K_2CO_3 as base, in a 3:1 mixture of 1,4-dioxane/H_2O and at 110 °C provided the most suitable conditions for the cross-coupling of (*S*)-**3b** (1 equiv.) with potassium aryltrifluoroborate (1.2 equiv.).

To demonstrate the efficiency of this cross-coupling reaction, we explored its generality with a variety of aryltrifluoroborates **6**–**22**. The results are summarized in Table 2. The Pd^0-catalyzed Suzuki reaction proved to be exceptionally efficient. It is clear that this is a general method that tolerates both electron-withdrawing and electron-donating substituents on the aromatic ring of the aryltrifluoroborate. In addition, even an *ortho*-methyl substituent at the aryltrifluoroborate afforded the corresponding product in moderate yield (Table 2, Entry 11). This method was effective for the aryltrifluoroborate containing a *meta*-hydroxy group, giving a moderate yield and a mixture of products (Table 2, Entry 13); however, no reaction was observed with organotrifluoroborates **8** and **21**. The reaction of 3-thiophenetrifluoroborate afforded the cross-coupled product in 78% yield (Table 2, Entry 2), whereas 4-cyanophenyltrifluoroborate and 4-chlorophenyltrifluoroborate afforded the cross-coupled products in 60 and 59% yield, respectively (Table 2, Entries 9 and 15). Additionally, the 4-formyltrifluoroborate afforded the desired product in 62% yield (Table 2, Entry 10).

Hydrogenation and Subsequent Hydrolysis of the Suzuki–Miyaura Products To Afford Highly Enantiomerically Enriched α-Substituted β-Amino Acids

Hydrogenation of the endocyclic double bonds in arylated enones **5** with H_2/Raney-Ni/AcOH/CH_3OH at 80 °C provided epimers (2*S*,5*S*)-**23** and (2*S*,5*R*)-**23** (*cis*-**23** and *trans*-**23**),[12] with the former product always predominating, as anticipated in terms of a more facile approach of the reducing agent from the face of the double bond opposite the isopropyl group[6,7] (Scheme 5).



Scheme 5. Raney-Ni-catalyzed hydrogenation of the endocyclic bond in the Suzuki–Miyaura cross-coupling products.

For example, cross-coupled product **5a** (Ar = C_6H_5) was hydrogenated for 24 h at 1500 psi of hydrogen pressure to afford **23a** in 73% yield as a 95:5 mixture of the *cis* and *trans* diastereomers, which were separated by flash chromatography. Following recrystallization of **23a**, suitable crystals were obtained, and the corresponding X-ray crystallographic structure is shown in Figure 1. As shown in this figure, the six-membered heterocycle adopts a conformation that approaches a twisted chair.[17] The pseudo-axial orientation of the phenyl ring is a consequence of allylic strain.[18]

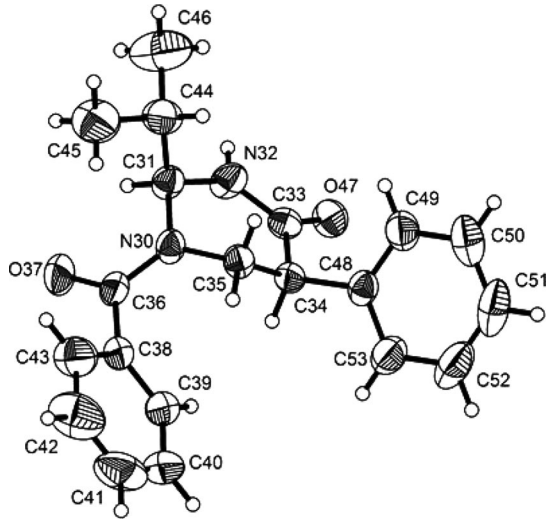


Figure 1. X-ray crystallographic structure and solid-state conformation of (2*S*,5*S*)-**23a**.

Cross-coupled product **5g** (Ar = 4-MeC_6H_4) was hydrogenated for 48 h at 1800 psi of hydrogen pressure to afford **23b** in 87% yield as essentially the pure *cis* diastereomer. Similarly, cross-coupled product **5n** (Ar = 4-$tBuC_6H_4$) was hydrogenated for 24 h at 1800 psi of hydrogen pressure to afford **23c** in 67% yield as a 89:11 mixture of the *cis* and

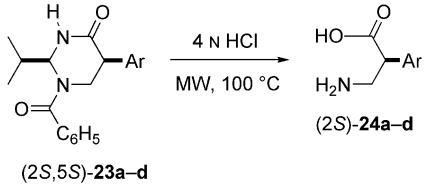
Table 3. Hydrogenation of the Suzuki–Miyaura products.

Entry	Suzuki–Miyaura products	Hydrogenation products (diastereomers)	Pressure H_2 [psi]	Time [h]	Yield [%] (*cis* and *trans*)
1[a]	**5a** (Ar = C_6H_5)	(2*S*,5*S*)-**23a**/(2*S*,5*R*)-**23a** (95:5)	1500	24	73
2[b]	**5g** (Ar = 4-MeC_6H_4)	(2*S*,5*S*)-**23b** (pure)	1800	48	87
3[c]	**5n** (Ar = 4-*t*BuC_6H_4)	(2*S*,5*S*)-**23c**/(2*S*,5*R*)-**23c** (89:11)	1800	24	67
4[d]	**5l** (Ar = 2-naph)	(2*S*,5*S*)-**23d**/(2*S*,5*R*)-**23d** (76:24)	1800	24	77
5[e]	**5f** (Ar = 4-MeOC_6H_4)	(2*S*,5*S*)-**23e**/(2*S*,5*R*)-**23e** (92:8)	1800	24	56

[a] The reaction was carried out with (2*S*)-**5a** (2.37 mmol) and Raney-Ni (7.6 g) under 1500 psi of H_2 at 80 °C for 24 h. [b] The reaction was carried out with (2*S*)-**5g** (2.39 mmol) and Raney-Ni (8.0 g) under 1800 psi of H_2 at 80 °C for 48 h. [c] The reaction was carried out with (2*S*)-**5n** (2.2 mmol) and Raney-Ni (8.3 g) under 1800 psi of H_2 at 80 °C for 24 h. [d] The reaction was carried out with (2*S*)-**5l** (2.47 mmol) and Raney-Ni (9.2 g) under 1800 psi of H_2 at 80 °C for 24 h. [e] The reaction was carried out with (2*S*)-**5f** (2.34 mmol) and Raney-Ni (8.2 g) under 1800 psi of H_2 at 80 °C for 24 h.

trans diastereomers, which were separated by flash chromatography. In another example, cross-coupled product **5l** (Ar = 2-naph) was hydrogenated for 24 h at 1800 psi of hydrogen pressure to afford tetrahydro derivative **23d** in 77% yield as a 76:24 mixture of the *cis* and *trans* diastereomers, which were separated by flash chromatography. It should be noted that in addition to reduction of the endocyclic double bond, substrate **5l** suffered partial hydrogenation of the aromatic naphthyl substituent. Finally, cross-coupled product **5f** (Ar = 4-MeOC_6H_4) was hydrogenated for 24 h at 1800 psi of hydrogen pressure to afford **23e** in 56% yield as a 92:8 mixture of the *cis* and *trans* diastereomers, which were separated by flash chromatography (Table 3).

Major diastereomeric products *cis*-**23a**–**d** were then exposed to hydrolytic conditions (4 N HCl at ca. 100 °C, temperature controlled with air) under microwave irradiation (200–250 W) to afford (2*S*)-arylsubstituted β-amino acids **24a**–**d** (Scheme 6).



(2*S*,5*S*)-**23a**–**d** (2*S*)-**24a**–**d**

Scheme 6. Acid-catalyzed hydrolysis of (2*S*,5*S*)-**23a**–**d** in the preparation of (2*S*)-arylpropionic acids **24a**–**d**.

For example, *cis*-disubstituted (2*S*,5*S*)-**23a** (Ar = C_6H_5, 105 °C, 250 W, 90 min) was hydrolyzed to afford (*S*)-3-amino-2-phenylpropionic acid (**24a**) in 78% yield and 90% *ee*. On the other hand, (2*S*,5*S*)-**23b** [(Ar = 4-MeC_6H_4), 98 °C, 200 W, 6 h] was hydrolyzed to afford (*S*)-3-amino-2-(4-methylphenyl)propionic acid (**24b**) in 48% yield and 95% *ee*. Similarly, (2*S*,5*S*)-**23c** [(Ar = 4-*t*BuC_6H_4), 98 °C, 200 W, 13 h] was hydrolyzed to afford (*S*)-3-amino-2-(4-*tert*-butylphenyl)propionic acid (**24c**) in 65% yield and 78% *ee*. Finally, (2*S*,5*S*)-**23d** [Ar = 2-(5,6,7,8-tetrahydronaphthalen-2-yl), 98 °C, 200 Ws, 10 h] was hydrolyzed to afford (*S*)-3-amino-2-(5,6,7,8-tetrahydronaphthalen-2-yl)propionic acid (**24d**) in 17% yield and 76% *ee*.

Conclusions

In summary, a simple protocol for the $Pd(OAc)_2$-catalyzed Suzuki–Miyaura cross-coupling of (*S*)-2-isopropyl-5-iodopyrimidinone with potassium aryltrifluoroborates has been developed. The reaction is performed at 110 °C with the use of a ligand-free catalyst. In all cases, complete conversion of the (*S*)-5-iodoenones and aryltrifluoroborates into the C–C coupling product was observed within 30–360 min. It is noteworthy that all functional groups present in the potassium aryltrifluoroborates (–CF_3, –OMe, –SEt, –CN, –CHO, –Cl, –CBz, –NCBz, –OH, –CO_2H) could be tolerated. Raney-Ni-catalyzed hydrogenation of Suzuki–Miyaura products **5a**, **5f**, **5g**, **5l**, and **5n** followed by acid-catalyzed hydrolysis of main products (2*S*,5*S*)-**23** afforded highly enantioenriched (*S*)-2-aryl-β-amino acids (*S*)-**24a**–**d** in moderate yields. These results indicate that the cross-coupling Suzuki–Miyaura cross-coupling reaction between potassium aryltrifluoroborates and (*S*)-5-iodopyrimidinone generate products that are suitable precursors to enantiomerically pure β-amino acids.

While the asymmetric synthesis of β^3 β-amino acids is well developed,[5] the preparation of β^2 β-amino acids is much less common.[5–7] Particularly difficult is the incorporation of aryl substituents α to the carboxylic group; thus, the present strategy employing the Suzuki–Miyaura coupling methodology for the enantioselective preparation of suitable precursos of β^2 β-amino acids is most relevant.

Experimental Section

Material and Methods: All air-sensitive and/or water-sensitive reactions were carried out with dry solvents under anhydrous conditions under a nitrogen atmosphere. Standard syringe techniques were applied for the transfer of dry solvents and air-sensitive reagents. The reactions were monitored by TLC on Merck silica gel (60 F_{254}) by using UV light as a visualizing agent and 5% vanillin in 10% H_2SO_4 with heating as a developing agent. Sigma–Aldrich silica gel (particle size 0.040–0.063 mm) was used for flash chromatography. NMR spectra of cross-coupling products **5a**–**q** were recorded with a Bruker DPX 300 (300 MHz) instrument by using $CDCl_3$ solvent. NMR spectra of hydrogenated products **23a**–**e** and β-amino acids **24a**–**d** were recorded with Jeol Eclipse-400 or Bruker Avance 300 DPX spectrometers in [D_6]DMSO or D_2O sol-

vent. Chemical shifts are reported in δ relative to $(CH_3)_4Si$ for ^1H and $CDCl_3$ for ^{13}C NMR spectroscopy. Ratios of mixtures of diastereomers were determined by peak integration in the ^1H NMR spectra of the crude products. Infrared (IR) spectra were obtained from $CHCl_3$ solutions using a Varian 3100 FTIR spectrophotometer or Perkin–Elmer Spectrum GX instrument. Mass spectra (MS) were measured with Shimadzu GC–MS-QP5050A or Hewlett–Packard Model 5989 mass spectrometer. HRMS spectra were measured with a Bruker Daltonics Micro TOF (direct inlet probe) or HPLC coupled to a MSD TOF Agilent Technologies Mod. 1969A instrument. Microwave heating was carried out with a single mode cavity Discover Microwave synthesizer (CEM Corporation, NC). The crystallographic structure and corresponding data were obtained with an Enraf–Nonius Kappa CCD diffractometer. CCDC-784491 [(2*S*,5*S*)-**23a**] 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. Elemental analyses were obtained by using a Thermo Finnigan CHNS-1112 instrument.

General Procedure for the Synthesis of the Potassium Aryltrifluoroborates:[19] The procedure for the synthesis of the potassium phenyltrifluoroborate is representative. A solution of phenylmagnesium bromide 0.5 M (10 mmol, 1.0 equiv.) in dry THF (20 mL) was cooled to –30 °C under a nitrogen atmosphere and trimethylborate (1.24 g, 12 mmol, 1.2 equiv.) was added dropwise. The solution was stirred at –30 °C for 1 h, after which it was warmed to room temperature for 1 h. A saturated aqueous solution of potassium hydrogen difluoride (3.12 g, 40 mmol, 4.0 equiv.) was added at –10 °C to the vigorously stirred solution. The resulting mixture was allowed to stir for 1 h at –10 °C, after which it was warmed to room temperature for 1 h. The solvent was removed under reduced pressure, and the resulting white solid was dried under high vacuum for 2 h to remove all water. The solid was then washed with acetone and hot acetone. The resulting organic solution was filtered, and the solvent was removed to afford a fluffy white solid. This solid was then dissolved in hot acetone and precipitated with diethyl ether, after which the solution was cooled to –20 °C to induce complete precipitation of the solid. The potassium phenyltrifluoroborate was collected as a white crystalline solid.

1-Benzoyl-5-iodo-(2*S*)-isopropyl-2,3-dihydro-4(*H*)-pyrimidin-4-one (3b):[12] A suspension of the carboxylic acid (2*S*,6*S*)-**1a**[15b] (1.0 mmol), DIB (644 mg, 2.0 mmol), and iodine (253 mg, 1.0 mmol) in CH_2Cl_2 (20 mL) was stirred at ambient temperature until TLC showed disappearance of the starting material (4–4.5 h). $BF_3{\cdot}OEt_2$ (0.25 mL, 2 equiv.) was added, and the resulting mixture was stirred for 1 h. Following the addition of CH_2Cl_2 (20 mL), the reaction mixture was washed with 5% aqueous $Na_2S_2O_3$ (4 × 15 mL), 3% aqueous $NaHCO_3$ (2 × 10 mL), and brine (2 × 10 mL), dried with anhydrous Na_2SO_4, and evaporated to afford the desired iodoenone as a yellow syrup that was purified by flash chromatography. Yield: 78%, m.p. 218–220 °C. $[\alpha]_D^{25}$ = +389.2 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.59 (m, 6 H), 6.95 (d, *J* = 4.5 Hz, 1 H), 5.6 (t, *J* = 6 Hz, 1 H), 2,26–2.36 (m, 1 H), 1.04 (d, *J* = 6.7 Hz, 3 H), 0.96 (d, *J* = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.0, 161.2, 142.0, 132.7, 131.4, 128.7 (2 C), 128.1 (2 C), 68.7, 32.4, 18.3, 17.6 ppm.

General Procedure for the Suzuki–Miyaura Cross-Coupling Reactions: To a 50-mL round-bottom flask under a nitrogen atmosphere was added potassium aryltrifluoroborate (1.2 mmol), (*S*)-5-iodopyrimidinone (1.0 mmol, 370 mg), $Pd(OAc)_2$ (9 mmol-%, 20.02 mg), K_2CO_3 (2 mmol, 276 mg), and degassed dioxane/H_2O (3:1, 16 mL). The reaction mixture was heated to reflux at 110 °C, and the reaction progress was monitored by TLC and GC. When the reaction was complete, the reaction mixture was cooled and then extracted with ethyl acetate (3 × 50 mL). The organic layers were combined and dried with $MgSO_4$, and the solvent was removed on a rotary evaporator to furnish a viscous oil. The product was purified by column chromatography (ethyl acetate/hexane, 1:1) to afford the cross-coupled product as a solid (see Table 2).

1-Benzoyl-(2*S*)-isopropyl-5-phenyl-2,3-dihydro-4(1*H*)-pyrimidin-4-one (5a): Yield: 86%, pale-yellow crystals, m.p. 173.2–174.8 °C, $[\alpha]_D^{20}$ = +325.2 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ = 7.48–7.59 (m, 6 H), 7.42 (dd, *J* = 8.1, 1.5 Hz, 2 H), 7.27–7.34 (m, 3 H), 6.66 (d, *J* = 4.38 Hz, 1 H), 5.68 (t, *J* = 6 Hz, 1 H), 2.36–2.43 (m, 1 H), 1.09 (d, *J* = 6.7 Hz, 3 H), 1.01 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.6, 163.7, 134.5; 133.6, 133.1, 131.6, 128.8 (2 C), 128.4 (2 C), 128.3 (2 C), 128.2, 127.7 (2 C), 116.9, 69.1, 33.0, 18.4, 17.6 ppm. MS (EI): *m*/*z* (%) = 320 (1) $[M]^+$, 277 (14), 105 (100), 89 (2), 77 (28), 51 (4), 43 (2). IR: $\tilde{\nu}$ = 3396, 3053, 2992, 2859, 1652, 1607 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{20}H_{20}N_2O_2 + H^+$ 321.1603; found 321.1611.

1-Benzoyl-(2*S*)-isopropyl-5-(thiophen-3-yl)-2,3-dihydro-4(1*H*)-pyrimidin-4-one (5b): Yield: 78%, pale-yellow crystals, m.p. 163.5–165.0 °C, $[\alpha]_D^{20}$ = +476.6 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ = 7.75 (d, *J* = 2.9 Hz, 1 H), 7.46–7.59 (m, 5 H), 7.36 (s, 1 H), 7.24–7.26 (m, 1 H), 7.13 (d, *J* = 5.0 Hz, 1 H), 6.9 (s, 1 H), 5.65 (s, 1 H), 2.31–2.43 (m, 1 H), 1.07 (d, *J* = 6.7 Hz, 3 H), 0.99 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.3, 163.4, 133.3, 132.9, 132.8, 131.4, 128.6 (2 C), 128.3 (2 C), 125.7, 125.0, 123.0, 112.0, 68.7, 32.6, 18.2, 17.5 ppm. IR: $\tilde{\nu}$ = 3398, 3045, 2989, 2862, 1670, 1608 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{18}H_{18}N_2O_2S + H^+$ 327.1167; found 327.1193.

1-Benzoyl-5-(4-fluorophenyl)-(2*S*)-isopropyl-2,3-dihydro-4(1*H*)-pyrimidin-4-one (5d): Yield: 73%, pale-yellow crystals, m.p. 152.0–153.0 °C, $[\alpha]_D^{20}$ = +461.2 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ = 7.59–7.49 (m, 5 H), 7.39 (dd, *J* = 8.4, 5.76 Hz, 2 H), 7.21 (s, 1 H), 7.01 (t, *J* = 8.5 Hz, 2 H), 6.8 (s, 1 H), 5.67 (s, 1 H), 2.32–2.43 (m, 1 H), 1.08 (d, *J* = 6.6 Hz, 3 H), 1.00 (d, *J* = 6.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.6, 163.6, 162.1 (d, *J* = 247 Hz, C-F), 134.5, 133.0, 131.7, 130.05 (d, ^3J = 8.4 Hz, C-F), 129.6 (d, ^4J = 2.77 Hz, C-F), 128.8 (2 C), 128.4 (2 C), 115.8, 115.2 (d, *J* = 21.82 Hz, C-F), 69.2, 33.0, 18.4, 17.6 ppm. MS (EI): *m*/*z* (%) = 338 (2) $[M]^+$, 295 (16), 105 (100), 77 (37), 51 (5), 43 (2). IR: $\tilde{\nu}$ = 3398, 3042, 2990, 2857, 1663, 1624 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{20}H_{19}FN_2O_2 + H^+$ 339.1509; found 339.1529.

1-Benzoyl-(2*S*)-isopropyl-5-[4-(trifluoromethyl)phenyl]-2,3-dihydro-4(1*H*)-pyrimidin-4-one (5e): Yield: 72%, pale-yellow crystals, m.p. 212.5–214.0 °C, $[\alpha]_D^{20}$ = +227.5 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ = 7.47–7.64 (m, 9 H), 7.32 (s, 1 H), 6.72 (d, *J* = 4.5 Hz, 1 H), 5.69 (t, *J* = 6.0 Hz, 1 H), 2.33–2.44 (m, 1 H), 1.08 (d, *J* = 6.9 Hz, 3 H), 1.01 (d, *J* = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.5, 163.1, 137.0, 135.6, 132.5, 131.7, 129.4 (q, *J* = 32.4 Hz), 128.7 (2 C), 128.3 (2 C), 128.2 (2 C), 125.0 (q, *J* = 3.75 Hz), 123.8 (q, *J* = 271 Hz), 115.0, 69.1, 32.9, 18.1, 17.3 ppm. MS (EI): *m*/*z* (%) = 388 (1) $[M]^+$, 345 (9), 105 (100), 77 (26), 51 (4), 43 (10). IR: $\tilde{\nu}$ = 3403, 3023, 2995, 2863, 1684, 1646, 1311 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{21}H_{19}F_3N_2O_2 + H^+$ 389.1477; found 389.1495.

1-Benzoyl-(2*S*)-isopropyl-5-(4-methoxyphenyl)-2,3-dihydro-4(1*H*)-pyrimidinone (5f): Yield: 95%, greenish crystals, m.p. 188.1–189.7 °C, $[\alpha]_D^{20}$ = +315.2 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ = 7.45–7.59 (m, 5 H), 7.35 (d, *J* = 8.7 Hz, 2 H), 7.16 (s, 1 H), 6.85 (d, *J* = 8.7 Hz, 2 H), 6.47 (d, *J* = 4.2 Hz, 1 H), 5.66 (t, *J* = 5.9 Hz, 1 H), 3.83 (s, 3 H), 2.33–2.42 (m, 1 H), 1.08 (d, *J* =

6.6 Hz, 3 H), 1.00 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.6, 164.0, 159.3, 137.5, 133.5, 133.2, 131.6, 129.5 (2 C), 128.8 (2 C), 128.4 (2 C), 116.6, 113.8 (2 C), 69.0, 55.3, 32.9, 18.4, 17.7 ppm. MS (EI): m/z (%) = 350 (4) $[M]^+$, 307 (4), 105 (100), 77 (25), 51 (3), 43 (2). IR: $\tilde{\nu}$ = 3422, 3027, 3995, 2875, 1670, 1617, 1245 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{21}H_{22}N_2O_3 + H^+$ 351.1709; found 351.1740.

1-Benzoyl-(2*S*)-isopropyl-5-*p*-tolyl-2,3-dihydro-4(1*H*)-pyrimidin-4-one (5g): Yield: 72%, pale-yellow crystals, m.p. 161.0–162.8 °C, $[\alpha]_D^{20}$ = +355.9 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.45–7.54 (m, 5 H), 7.31 (d, J = 8.1 Hz, 1 H), 7.19 (s, 1 H), 7.13 (d, J = 8.1 Hz, 2 H), 6.61 (d, J = 3.3 Hz, 1 H), 5.66 (s, 1 H), 2.35–2.42 (m, 1 H), 2.32 (s, 3 H), 1.08 (d, J = 6.9 Hz, 3 H), 1.00 (d, J = 6.9 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.3, 163.3, 137.4, 133.8, 132.9, 131.3, 130.4, 128.7 (2 C), 128.6 (2 C), 128.2 (2 C), 128.0 (2 C), 116.6, 68.9, 32.7, 20.9, 18.2, 17.4 ppm. MS (EI): m/z (%) = 334 (3) $[M]^+$, 291 (14), 105 (100), 77 (27), 51 (3), 43 (2). IR: $\tilde{\nu}$ = 3404, 3025, 2994, 2940, 2886, 1670, 1624 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{21}H_{22}N_2O_2 + H^+$ 335.1760; found 335.1789.

1-Benzoyl-5-[4-(ethylthio)phenyl]-(2*S*)-isopropyl-2,3-dihydro-4(1*H*)-pyrimidin-4-one (5h): Yield: 65%, pale-yellow crystals, m.p. 182.8–184.5 °C, $[\alpha]_D^{20}$ = +356.7 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.46–7.59 (m, 5 H), 7.35 (d, J = 8.4 Hz, 2 H), 7.24–7.27 (m, 3 H), 6.76 (d, J = 4.5 Hz, 1 H), 5.66 (s, 1 H), 2.92 (q, J = 7.5 Hz, 2 H), 2.31–2.43 (m, 1 H), 1.23–1.36 (m, 3 H), 1.08 (d, J = 6.7 Hz, 3 H), 1.00 (d, J = 6.8 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.3, 163.2, 136.2, 134.0, 132.8, 131.4, 130.7, 128.6 (2 C), 128.4 (2 C), 128.3 (2 C), 128.2 (2 C), 115.9, 68.9, 32.7, 27.2, 18.1, 17.4, 14.1 ppm. MS (EI): m/z (%) = 380 (5) $[M]^+$, 337 (7), 105 (100), 77 (26), 51 (3), 43 (3). IR: $\tilde{\nu}$ = 3393, 3058, 2991, 2945, 2898, 1668, 1630 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{22}H_{24}N_2O_2S + H^+$ 381.1637; found 381.1605.

1-Benzoyl-5-(4-benzonitrile)-(2*S*)-isopropyl-2,3-dihydro-4(1*H*)-pyrimidin-4-one (5i): Yield: 30%, white crystals, m.p. 194.9–196.2 °C, $[\alpha]_D^{20}$ = +160.8 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.51–7.58 (m, 9 H), 7.36 (s, 1 H), 6.94 (s, 1 H), 5.68 (s, 1 H), 2.33–2.40 (m, 1 H), 1.07 (d, J = 6.6 Hz, 3 H), 1.00 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.7, 163.1, 153.8, 138.4, 136.3, 132.6, 132.0 (2 C), 129.0 (2 C), 128.7 (2 C), 128.4 (2 C), 118.7, 114.6, 111.0, 69.3, 33.2, 18.3, 17.5 ppm. MS (EI): m/z (%) = 345 (4) $[M]^+$, 302 (7), 105 (100), 77 (28), 51 (5), 43 (3). IR: $\tilde{\nu}$ = 3410, 3055, 2951, 2898, 2227, 1688, 1625 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{21}H_{19}N_3O_2 + H^+$ 346.1556; found 346.1593.

1-Benzoyl-5-(4-formylphenyl)-(2*S*)-isopropyl-2,3-dihydro-4(1*H*)-pyrimidin-4-one (5j): Yield: 62%, yellowish crystals, m.p. 170.1–172.0 °C, $[\alpha]_D^{20}$ = +266.4 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.98 (s, 1 H), 7.84 (d, J = 8.01 Hz, 2 H), 7.49–7.64 (m, 7 H), 7.39 (s, 1 H), 6.71 (d, J = 4.56 Hz, 1 H), 5.69 (t, J = 5.64 Hz, 1 H), 2.34–2.45 (m, 1 H), 1.09 (d, J = 6.69 Hz, 3 H), 1.02 (d, J = 6.84 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 191.7, 168.6, 162.9, 139.8, 136.1, 135.3, 132.7, 131.9, 129.6 (2 C), 128.9 (2 C), 128.6 (2 C), 128.5 (2 C), 115.2, 69.4, 33.1, 18.4, 17.5 ppm. MS (EI): m/z (%) = 348 (2) $[M]^+$, 305 (9), 278 (3), 105 (100), 77 (32), 71 (32), 56 (4), 51 (4). IR: $\tilde{\nu}$ = 3420, 3055, 2952, 2883, 1699, 1647, 1593 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{21}H_{20}N_2O_3 + H^+$ 349.1552; found 349.1537.

1-Benzoyl-(2*S*)-isopropyl-5-*o*-tolyl-2,3-dihydro-4(1*H*)-pyrimidin-4-one (5k): Yield: 66%, pale-yellow crystals, m.p. 198.7–200.5 °C, $[\alpha]_D^{20}$ = +338.9 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.46–7.57 (m, 5 H), 7.12–7.22 (m, 3 H), 7.06 (d, J = 6.9 Hz, 2 H), 6.27 (d, J = 4.74 Hz, 1 H), 5.69 (s, 1 H), 2.48–2.57 (m, 1 H), 2.26 (s, 3 H), 1.16 (d, J = 6.69 Hz, 3 H), 1.03 (d, J = 6.84 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 17.7, 18.4, 20.4, 32.8, 69.3, 117.6, 125.8, 128.2 (2 C), 128.2, 128.7 (2 C), 129.9, 130.2, 131.5, 133.23, 133.29, 135.8, 137.6, 163.1, 168.6 ppm. MS (EI): m/z (%) = 334 (1) $[M]^+$, 291 (12), 105 (100), 77 (28), 71 (7), 43 (38), 40 (8). IR: $\tilde{\nu}$ = 3403, 3041, 2985, 2943, 2886, 1670, 1616 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{21}H_{22}N_2O_2 + H^+$ 335.1760; found 335.1748.

1-Benzoyl-(2*S*)-isopropyl-5-(naphthalen-2-yl)-2,3-dihydro-4(1*H*)-pyrimidin-4-one (5l): Yield: 70%, yellow-greenish crystals, m.p. 189.2–191.0 °C, $[\alpha]_D^{20}$ = +405.1 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.9 (s, 1 H), 7.79 (d, J = 8.4 Hz, 3 H), 7.43–7.63 (m, 8 H), 7.36 (s, 1 H), 6.87 (d, J = 4.2 Hz, 1 H), 5.7 (s, 1 H), 2.39–2.50 (m, 1 H), 1.12 (d, J = 6.69 Hz, 3 H), 1.04 (d, J = 6.84 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.6, 163.6, 134.8, 133.19, 133.11, 132.7, 131.7, 131.1, 128.8 (2 C), 128.5 (2 C), 128.0, 127.7, 127.5, 127.4, 126.1 (3 C), 116.8, 69.3, 33.0, 18.4, 17.7 ppm. MS (EI): m/z (%) = 370 (4) $[M]^+$, 327 (6), 105 (92), 77 (28), 71 (6), 44 (100), 43 (30). IR: $\tilde{\nu}$ = 3413, 3028, 2940, 2895, 1680, 1635 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{24}H_{22}N_2O_2 + H^+$ 371.1760; found 371.1790.

1-Benzoyl-5-(3-hydroxyphenyl)-(2*S*)-isopropyl-2,3-dihydro-4(1*H*)-pyrimidin-4-one (5m): Yield: 72%, yellow crystals, m.p. 123.2–125.0 °C, $[\alpha]_D^{20}$ = +405.1 (c = 1, MeOH). ^{1}H NMR (300 MHz, [D$_6$]DMSO) δ = 9.31 (d, J = 1.2 Hz, 1 H), 8.54 (d, J = 4.44 Hz, 1 H), 7.54–7.58 (m, 5 H), 7.17 (s, 1 H), 7.07 (t, J = 7.98 Hz, 1 H), 6.9 (s, 1 H), 6.78 (d, J = 7.17 Hz, 2 H), 6.65 (d, J = 8.01 Hz, 1 H), 5.39 (s, 1 H), 2.14–2.26 (m, 1 H), 0.97 (d, J = 6.27 Hz, 3 H), 0.90 (d, J = 6.45 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 168.4, 162.5, 157.3, 135.8, 134.2, 133.7, 131.8, 129.3, 129.2 (2 C), 128.7 (2 C), 119.1, 116.6, 115.6, 114.7, 68.5, 33.2, 18.8, 18.1 ppm. MS (EI): m/z (%) = 336 (1) $[M]^+$, 293 (10), 105 (100), 77 (27), 44 (16), 41 (4). HRMS (ESI-TOF): calcd. for $C_{20}H_{20}N_2O_3 + H^+$ 337.1552; found 337.1599.

1-Benzoyl-5-(4-*tert*-butylphenyl)-(2*S*)-isopropyl-2,3-dihydro-4(1*H*)-pyrimidin-4-one (5n): Yield: 75%, white crystals, m.p. 220.5–222.4 °C, $[\alpha]_D^{20}$ = +382.6 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.35–7.59 (m, 1 H), 7.22 (m, 5 H), 6.23 (s, 1 H), 5.67 (s, 1 H), 2.35–2.42 (m, 1 H), 1.27 (s, 9 H), 1.08 (d, J = 6.6 Hz, 3 H), 1.00 (d, J = 6.78 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.6, 163.4, 150.8, 134.1, 133.2, 131.6, 130.6, 128.8 (2 C), 128.4 (2 C), 127.9 (2 C), 125.3 (2 C), 115.4, 69.2, 34.5, 33.0, 31.3 (3 C), 18.4, 17.6 ppm. MS (EI): m/z (%) = 376 (1) $[M]^+$, 233 (10), 105 (100), 77 (19), 57 (3), 43 (4). IR: $\tilde{\nu}$ = 3409, 3028, 2992, 2895, 2835, 1675, 1632 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{24}H_{28}N_2O_2 + H^+$ 377.2229; found 377.2211.

1-Benzoyl-5-(4-chlorophenyl)-(2*S*)-isopropyl-2,3-dihydro-4-(1*H*)-pyrimidin-4-one (5o): Yield: 59%, pale-yellow crystals, m.p. 161.9–162.6 °C, $[\alpha]_D^{20}$ = +362.1 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01 (d, J = 6.84 Hz, 3 H), 1.08 (d, J = 6.69 Hz, 3 H), 2.32–2.42 (m, 1 H), 5.66 (s, 1 H), 6.47 (d, J = 4.47 Hz, 1 H), 7.26–7.30 (m, 3 H), 7.37 (d, J = 8.58 Hz, 2 H), 7.47–7.59 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6, 18.4, 33.0, 69.3, 115.5, 128.4, 128.46, 128.49, 128.9, 129.5, 131.8, 132.0, 132.9, 133.7, 134.7, 163.1, 168.6 ppm. MS (EI): m/z (%) = 354 (1) $[M]^+$, 311 (6), 277 (1), 105 (100), 77 (26), 51 (4). IR: $\tilde{\nu}$ = 3495, 3026, 2964, 2915, 2869, 1685, 1664 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{20}H_{19}ClN_2O_2 + H^+$ 355.1213; found 355.1215.

1-Benzoyl-(2*S*)-isopropyl-5-[4-(N-CBz)-phenyl]-2,3-dihydro-4(1*H*)-pyrimidin-4-one (5q): Yield: 62%, yellow-greenish crystals, m.p. 114.5–116.3 °C, $[\alpha]_D^{20}$ = +316.5 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.44–7.54 (m, 5 H), 7.30–7.35 (m, 9 H), 7.18 (s, 1 H), 6.68 (s, 1 H), 6.20 (d, J = 4.8 Hz, 1 H), 5.59 (s, 1 H), 5.17 (s, 2 H), 2.28–2.39 (m, 1 H), 1.03 (d, J = 6.7 Hz, 3 H), 0.96

(d, J = 6.81 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.6, 163.8, 153.4, 137.6, 136.0, 134.0, 133.1, 131.7, 128.9, 128.8, 128.6 (3 C), 128.48 (2 C), 128.40 (2 C), 128.3 (2 C), 118.5, 116.3, 69.0, 67.0, 32.9, 18.4, 17.6 ppm. MS (EI): *m*/*z* (%) = 469 (1) $[M]^+$, 318 (6), 105 (100), 77 (32), 71 (25), 56 (4), 44 (19), 43 (10). IR: $\tilde{\nu}$ = 3403, 3029, 2990, 2889, 1734, 1697, 1663 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{28}H_{27}N_3O_4 + H^+$ 470.2080; found 470.2099.

General Procedure for the Hydrogenation of the Suzuki–Miyaura Cross-Coupled Products: In a hydrogenation flask and under a nitrogen atmosphere, the required amount of aryl-substituted pyrimidinone, methanol (60 mL), Raney-Ni (1.0 g per 100 mg of heterocycle), and acetic acid (1.5 mL) were added. The resulting mixture was pressurized to 1500–1800 psi of hydrogen and stirred mechanically at 80 °C for 24–48 h. The reaction mixture was filtered, and the filtrate was concentrated on a rotary evaporator. The residue was dissolved in ethyl acetate and washed with a saturated solution of potassium and sodium tartrate. The organic phase was dried (anhydrous Na_2SO_4) and concentrated on a rotary evaporator to afford the crude product, which was purified by flash chromatography.

(2*S*,5*S*)-1-Benzoyl-2-isopropyl-5-phenylperhydropyrimidin-4-one-[(2*S*,5*S*)-23a]: Following the general procedure, (*S*)-**5a** (760 mg, 2.37 mmol) and Raney-Ni (7.6 g) under 1500 psi of hydrogen were heated with mechanical stirring at 80 °C for 24 h to afford a diastereomeric 95:5 mixture (561 mg, 73% yield). After purification, the *cis* and *trans* diastereomeric products were separated by flash chromatography (ethyl acetate/hexane, 70:30). Data for major diastereomer (2*S*,5*S*)-**23a**: Yield: 531 mg (69%), m.p. 217–218 °C (CH_2Cl_2/Hexane), $[\alpha]_D^{25}$ = –84.5 (c = 1, $CHCl_3$). HPLC (Chiralcel OD-H, hexane/EtOH = 90:10, 220 nm, 1 mL/min): t_R = 29.63 min. ^{1}H NMR (500 MHz, [D$_6$]DMSO, 120 °C): δ = 8.09 (s, 1 H, N*H*), 7.45 (s, 5 H, Ar*H*), 7.28–7.25 (m, 2 H, Ar*H*), 7.22–7.18 (m, 1 H, Ar*H*), 7.14–7.12 (m, 2 H, Ar*H*), 5.18 (s, 1 H, C*H*), 4.05 (s, 1 H, C*H*), 3.67 (dd, J = 7.1, 11.7 Hz, 1 H, CH_2), 3.45 (dd, J = 12.0, 13.5 Hz, 1 H, CH_2), 2.20–2.18 (m, 1 H, C*H*), 1.04 (d, J = 6.7 Hz, 3 H, CH_3), 0.92 (d, J = 6.7 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125.76 MHz, [D$_6$]DMSO, 120 °C): δ = 170.3, 169.5, 138.4, 136.1, 130.3, 130.2, 129.0, 128.8, 127.3, 127.1, 68.8, 48.3, 45.6, 34.6, 19.1, 18.7 ppm. IR: $\tilde{\nu}$ = 3266, 2927, 1727, 1663, 1636, 1433, 1388, 1319, 1273 cm^{-1}. MS (EI): *m*/*z* (%) = 322 (1) $[M]^+$, 279 (78), 216 (5), 175 (3), 118 (5), 105 (100), 77 (5). $C_{20}H_{22}N_2O_2$ (322.40): calcd. C 74.51, H 6.88, N 8.69; found C 74.73, H 6.92, N 8.91. Data for minor diastereomer (2*S*,5*R*)-**23a**: Yield: 30 mg (4%), m.p. 86–88 °C (CH_2Cl_2/Hexane), $[\alpha]_D^{25}$ = +53.2 (c = 0.63, $CHCl_3$). HPLC (Chiralcel OD-H, hexane/EtOH = 90:10, 220 nm, 1 mL/min): t_R = 35.30 min. ^{1}H NMR (500 MHz, [D$_6$]DMSO): δ = 8.65 (d, J = 3.3 Hz, 1 H, N*H*), 7.35–7.05 (m, 6 H, Ar*H*), 6.93 (s, 2 H, Ar*H*), 6.60 (d, J = 7.2 Hz, 2 H, Ar*H*), 5.54 (d, J = 6.8 Hz, 1 H, C*H*), 3.90 (dd, J = 3.0, 13.5 Hz, 1 H, C*H*), 3.50–3.40 (m, 2 H, CH_2), 2.2–2.1 (m, 1 H, C*H*), 1.03 (d, J = 6.2 Hz, 3 H, CH_3), 0.91 (d, J = 6.4 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125.76 MHz, [D$_6$]DMSO): δ = 170.8, 169.1, 140.1, 135.5, 129.8, 128.9, 128.6, 128.5, 127.4, 126.7, 66.3, 47.5 (2 C), 34.1, 19.2, 18.6 ppm. MS (EI): *m*/*z* (%) = 322 (3.2) $[M]^+$, 279 (73), 216 (11.6), 175 (1.9), 118 (3.5), 106 (7.5), 105 (100), 77 (4.3). IR: $\tilde{\nu}$ = 3200, 2965, 2360, 2162, 1979.1667, 1643, 1410, 1390, 698 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{20}H_{22}N_2O_2 + H^+$ 323.1754; found 323.1746.

(2*S*,5*S*)-1-Benzoyl-2-isopropyl-5-(4-methylphenyl)tetrahydropyrimidin-4-one [(2*S*,5*S*)-23b]: Following the general procedure, (*S*)-**5g** (800 mg, 2.39 mmol) and Raney-Ni (8.0 g) under 1800 psi of H_2 were heated with mechanical stirring at 80 °C for 48 h to give essentially one diastereomer (697 mg, 87% yield). Indeed, the *cis* diastereomer (2*S*,5*S*)-**23b** was determined by HPLC (Chiralcel OD-H, hexane/EtOH = 90:10, 220 nm, 1 mL/min) to predominate by a 99.7:0.3 ratio over the *trans* (2*S*,5*R*)-**23b** isomer. Data for major diastereomer (2*S*,5*S*)-**23b**: Yield: 697 mg (87%), m.p. 168–170 °C (MeOH/H_2O), $[\alpha]_D^{25}$ = –99 (c = 1, $CHCl_3$). ^{1}H NMR (500 MHz, [D$_6$]DMSO, 120 °C): δ = 8.06 (s, 1 H, N*H*), 7.44 (s, 5 H, Ar*H*), 7.06 (d, J = 7.9 Hz, 2 H, Ar*H*), 7.0 (d, J = 8.0 Hz, 2 H, Ar*H*), 5.17 (br., 1 H, *C*H*), 4.03 (br., 1 H, *C*H*), 3.60 (dd, J = 7.1, 11.6 Hz, 1 H, CH_2), 3.41 (dd, J = 12.0, 12.75 Hz, 1 H, CH_2), 2.24 (s, 3 H, CH_3), 2.20–2.12 (m, 1 H, C*H*), 1.03 (d, J = 6.6 Hz, 3 H, CH_3), 0.92 (d, J = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125.76 MHz, [D$_6$]DMSO, 120 °C): δ = 170.3, 169.6, 136.6, 136.1, 135.4, 130.3, 129.4, 129.0, 127.1, 68.8, 47.9, 34.6, 20.9, 19.1, 18.7 ppm. IR: $\tilde{\nu}$ = 3197, 3062, 2971, 2883, 1666, 1639, 1411, 1317, 1279, 1129, 1010 cm^{-1}. MS (EI): *m*/*z* (%) = 336 (1.1) $[M]^+$, 294.1 (9.5), 293 (49.6), 230 (3), 132 (14.3), 105 (100), 77 (41). HRMS (ESI-TOF): calcd. for $C_{21}H_{24}N_2O_2 + H^+$ 337.1910; found 337.1916. $C_{21}H_{24}N_2O_2$ (336.43): calcd. C 74.97, H 7.19, N 8.33; found C 74.97, H 7.53, N 8.22.

(2*S*,5*S*)-1-Benzoyl-5-(4-*tert*-butylphenyl)-2-isopropyltetrahydropyrimidin-4(1*H*)-one [(2*S*,5*S*)-23c]: Following the general procedure, (*S*)-**5n** (829 mg, 2.20 mmol) and Raney-Ni (8.3 g) under 1800 psi of H_2 were heated with mechanical stirring at 80 °C for 24 h to give a diastereomeric mixture of products (561 mg, 67% yield) in an 89:11 *cis*/*trans* ratio. After purification, these diastereomers were separated by flash chromatography (ethyl acetate/hexane, 70:30). Data for major diastereomer (2*S*,5*S*)-**23c**: Yield: 502 mg (60%), m.p. 140–141 °C (MeOH/H_2O), $[\alpha]_D^{25}$ = –91.5 (c = 1, $CHCl_3$). ^{1}H NMR (400 MHz, [D$_6$]DMSO, 120 °C): δ = 8.06 (s, 1 H, N*H*), 7.47 (s, 5 H, Ar*H*), 7.30 (d, J = 8.4 Hz, 2 H, Ar*H*), 7.07 (d, J = 8.4 Hz, 2 H, Ar*H*), 5.20 (d, J = 5.6 Hz, 1 H, *C*H*), 4.05 (br., 1 H, *C*H*), 3.63 (dd, J = 7.1, 11.6 Hz, 1 H, CH_2), 3.46 (dd, J = 11.9, 13.7 Hz, 1 H, CH_2), 2.27–2.15 (m, 1 H, C*H*), 1.27 (s, 9 H, CH_3), 1.06 (d, J = 6.6 Hz, 3 H, CH_3), 0.94 (d, J = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100.5 MHz, [D$_6$]DMSO, 120 °C): δ = 170.3, 169.7, 150.1, 136.2, 135.4, 130.3, 129.0, 128.8, 127.1, 125.6, 89.9, 68.8, 47.9, 45.7, 34.6, 31.6, 19.1, 18.7 ppm. IR: $\tilde{\nu}$ = 3199, 2961, 1668, 1650, 1403, 1277, 1209, 1012 cm^{-1}. MS (EI): *m*/*z* (%) = 379 (1) $[M + 1]^+$, 335 (66), 272 (6), 159 (6), 145 (4), 105 (100), 77 (2). $C_{24}H_{30}N_2O_2$ (378.51): calcd. C 76.16, H 7.99, N 7.40; found C 76.03, H 8.17, N 7.21.

(2*S*,5*S*)-1-Benzoyl-2-isopropyl-5-(5,6,7,8-tetrahydronaphthalen-2-yl)perhydropyrimidin-4-one [(2*S*,5*S*)-23d]: Following the general procedure, (*S*)-**5l** (916 mg, 2.47 mmol) and Raney-Ni (9.2 g) under 1800 psi of H_2 were heated with mechanical stirring at 80 °C for 24 h to give a diastereomeric 76:24 mixture (713 mg, 77% yield). The *cis* and *trans* diastereomeric products were separated by flash chromatography (ethyl acetate/hexane, 70:30). Data for major diastereomer (2*S*,5*S*)-**23d**: Yield: 538 mg (58%), m.p. 151–153 °C (CH_2Cl_2/Hexane), $[\alpha]_D^{25}$ = –86 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz, [D$_6$]DMSO, 120 °C): δ = 7.99 (s, 1 H, N*H*), 7.46 (s, 5 H, Ar*H*),7.01–6.8 (m, 3H Ar *H*), 5.20 (d, J = 7.2 Hz, 1 H, *C*H*), 4.03 (dd, J = 6.0, 12.6 Hz, 1 H, *C*H*), 3.56 (dd, J = 6.4, 11.5 Hz, 1 H, CH_2), 3.46 (dd, J = 11.7, 12.9 Hz, 1 H, CH_2), 2.66 (s, 4 H, CH_2), 2.27–2.13 (m, 1 H, C*H*), 1.72 (s, 4 H, CH_2), 1.05 (d, J = 6.6 Hz, 3 H, CH_3), 0.94 (d, J = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75.5 MHz, [D$_6$]DMSO, 120 °C): δ = 170.2, 169.86 137.2, 136.1, 136.0, 135.3, 130.2 129.4, 129.1, 128.9, 127.0, 126.1, 68.8, 48.0, 45.6, 34.5, 29.2,28.9 23.1, 19.0, 18.6 ppm. IR: $\tilde{\nu}$ = 3209, 2932, 2162, 1667, 1639, 1430, 1361, 1313, 1216, 1014 cm^{-1}. MS (EI): *m*/*z* (%) = 376 (5) $[M]^+$, 333 (100), 305 (9), 229 (42), 172 (12), 105 (98). HRMS (ESI-TOF): calcd. for $C_{24}H_{28}N_2O_2 + H^+$ 377.2223; found 377.2213. Data for minor diastereomer (2*S*,5*R*)-**23d**: Yield: 175 mg (19%),

foam, $[\alpha]_D^{25}$ = +64 (*c* = 1, $CHCl_3$). ^1H NMR (300 MHz, [D$_6$]DMSO, 120 °C): δ = 8.02 (s, 1 H, N*H*), 7.31–7.19 (m, 3 H, Ar*H*), 6.90 (d, *J* = 4.6 Hz, 1 H Ar*H*), 6.82–6.68 (m, 4 H, Ar*H*), 5.44 (br., 1 H, *C*H), 3.83 (dd, *J* = 4.8, 14 Hz, 1 H, CH_2), 3.7 (br., 1 H, C*H*), 3.48 (s, 1 H, CH_2), 2.68–2.54 (m, 4 H, CH_2), 2.20–2.13 (m, 1 H, C*H*), 1.78–1.68 (m, 4 H, CH_2), 1.03 (d, *J* = 6.75 Hz, 3 H, CH_3), 0.93 (d, *J* = 6.7 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125.76 MHz, [D$_6$]DMSO, 120 °C): δ = 170.7, 169.3, 137.2, 137.1, 136.04, 136.01, 129.0, 128.4,128.3, 127.0, 126.9, 125.7, 67.7, 47.4, 47.0, 34.4, 29.4, 29.3, 28.9, 23.3, 23.2, 18.9, 18.6 ppm. IR: $\tilde{\nu}$ = 3202, 2926, 2855, 1665, 1643, 1446, 1408, 1389, 1311, 1277, 1020 cm^{-1}. MS (EI): *m*/*z* (%) = 376 (12) $[M]^+$, 333 (100), 305 (9), 270 (15), 229 (13), 172 (7), 105 (82). HRMS (ESI-TOF): calcd. for $C_{24}H_{28}N_2O_2 + H^+$ 377.2223; found 377.2225.

1-Benzoyl-(2*S*)-isopropyl-(5S)-(4-methoxyphenyl)perhydropyrimidin-4-one, (2*S*,5*S*)-23e: Following the general procedure, (*S*)-**5f** (820 mg, 2.34 mmol) and Raney-Ni (8.2 g) under 1800 psi of H_2 were heated with mechanical stirring at 80 °C for 24 h to give a diastereomeric 92:8 *cis*/*trans* mixture (459 mg, 56% yield). The diastereomeric products were separated by flash chromatography (ethyl acetate/hexane, 70:30). Data for major diastereomer (2*S*,5*S*)-**2e**: Yield: 423 mg (51%), m.p. 188–189 °C (CH_2Cl_2/hexane), $[\alpha]_D^{25}$ = –107 (*c* = 1, $CHCl_3$). ^1H NMR (400 MHz, [D$_6$]DMSO, 120 °C): δ = 8.04 (s, 1 H, N*H*), 7.46 (s, 5 H, Ar*H*), 7.06 (d, *J* = 8.8 Hz, 2 H, Ar*H*), 6.85 (d, *J* = 8.6 Hz, 2 H, Ar*H*), 5.19 (d, *J* = 6.6 Hz, 1 H, *C*H), 4.05 (br., 1 H, *C*H), 3.74 (s, 3 H, CH_3), 3.62 (dd, *J* = 7.1, 11.6 Hz, 1 H, CH_2), 3.44 (dd, *J* = 12.0, 13.5 Hz, 1 H, CH_2), 2.26–2.14 (m, 1 H, C*H*), 1.05 (d, *J* = 6.5 Hz, 3 H, CH_3), 0.94 (d, *J* = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (100.5 MHz, [D$_6$]DMSO, 120 °C): δ = 170.3, 169.8, 159.2, 136.2, 130.5, 130.3, 130.2, 129.0, 127.1, 114.7, 68.9, 55.9, 47.5, 45.7, 34.6, 19.1, 18.7 ppm. IR: $\tilde{\nu}$ = 3199, 3062, 2966, 1666, 1639, 1514, 1421, 1318, 1279, 1242 cm^{-1}. MS (EI): *m*/*z* (%) = 352 (3) $[M]^+$, 309 (63), 281 (31), 205 (32), 148 (16), 105 (100), 83 (8). $C_{21}H_{24}N_2O_3$ (352.43): calcd. for $C_{21}H_{24}N_2O_3$ C 71.57, H 6.86, N 7.95; found C 71.19, H 7.24, N 7.98.

General Procedure for the Hydrolysis of (2*S*,5*S*)-23

Method A: In a 50-mL round-bottom flask was placed the required perhydropyrimidinone (2*S*,5*S*)-**23a**–**d** (100 mg), 4 N HCl (13 mL), and 1,4-dioxane (2 mL). The resulting mixture was placed inside a microwave apparatus adapted with a reflux condenser and irradiated with 200–250 W for 1.5–12 h at 98–105 °C by using an air-cooling system to control the temperature. The reaction mixture was allowed to reach room temperature and was then extracted with CH_2Cl_2 (3 × 20 mL). The aqueous phase was concentrated under reduced pressure, and the residue was purified by flash silica gel chromatography (230–400 mesh) using 2-propanol/methanol/NH_4OH (5:2:1) as eluent.[20]

Method B: A solution of compound (2*S*,5*S*)-**23a**–**d** (100 mg) in 1,4-dioxane (2 mL) and 12 N HCl (3 mL) was heated in a sealed ampoule at 100 °C for 8–12 d. The resulting mixture was cooled to room temperature and extracted with CH_2Cl_2 (3 × 10 mL), and the aqueous phase was concentrated under reduced pressure to afford a solid, which was purified by flash chromatography using 2-propanol/methanol/NH_4OH (5:2:1) as eluent.[20] Further evaporation afforded the corresponding amino acid.

(*S*)-3-Amino-2-phenylpropionic Acid [(*S*)-24a]: Following general procedure A (98 °C, 200 W, 6 h), (2*S*,5*S*)-**23a** (100 mg,0.31 mmol) afforded (*S*)-**24a** (40 mg, 78% yield) as a powder, which was recrystallized from methanol/ether. M.p. 236–238 °C, $[\alpha]_D^{25}$ = –81.7 (*c* = 0.2, H_2O) {ref.[21] $[\alpha]_D^{20}$ = –81 (*c* = 0.2, H_2O), 94% *ee* for the *S* enantiomer}. ^1H NMR (500 MHz, D_2O): δ = 7.23–7.15 (m, 3 H, Ar*H*), 7.14–7.10 (m, 2 H, Ar*H*), 3.86 (t, *J* = 7.5 Hz, 1 H, C*H*), 3.37 (dd, *J* = 13.1, 7.6 Hz, 1 H, CH_2), 3.13 (dd, *J* = 13.1, 7.4 Hz, 1 H, CH_2) ppm. ^{13}C NMR (125.76 MHz, D_2O): δ = 174.6 (*C*=O), 134.3 (C_{ipso}), 129.6 (*C*HAr), 128.9 (*C*HAr), 128.3 (*C*HAr), 48.5 (*C*H), 41.1 (*C*H_2) ppm. HPLC [Chirobiotic T column, EtOH/H_2O = 50:50, 210 nm, 1 mL/min; *er* = 5:95 (*R*/*S*)]: t_R = 6.93 (minor, *R*), 11.32 (major, *S*) min.

***rac*-3-Amino-2-phenylpropionic Acid (*rac*-24a):** This compound was prepared according to a literature procedure[22] to obtain *rac*-**24a** in an overall yield of 42%. Spectroscopic and physical data were consistent with the literature values.

(*S*)-3-Amino-2-(4-methylphenyl)propionic Acid [(*S*)-24b]: Following general procedure A (105 °C, 250 W, 90 min), (2*S*,5*S*)-**23b** (100 mg, 0.3 mmol) afforded (*S*)-**24b** (26 mg, 48% yield) as a powder, which was crystallized from methanol/ether. M.p. 229–230 °C, $[\alpha]_D^{25}$ = –54.2 (*c* = 0.48, 1 N HCl). ^1H NMR (500 MHz, D_2O): δ = 6.97 (d, *J* = 8.2 Hz, 2 H, Ar*H*), 6.9 (d, *J* = 8.1 Hz, 2 H, Ar*H*), 3.75 (t, *J* = 7.4 Hz, 1 H, C*H*), 3.28 (dd, *J* = 13.2, 7.7 Hz, 1 H, CH_2), 3.0 (dd, *J* = 13.0, 7.5 Hz, 1 H, CH_2), 2.0 (s, 3 H, CH_3) ppm. ^{13}C NMR (125.76 MHz, D_2O): δ = 174.7 (C=O), 139.1 (C_{ipso}), 131.0 (C_{ipso}), 130.0 (*C*HAr), 128.1 (*C*HAr), 48.0 (*C*H), 41.0 (*C*H_2), 20.1 (*C*H_3) ppm. IR: $\tilde{\nu}$ = 2922, 2858, 2756, 2624, 2162, 1624, 1570, 1512, 1380 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{10}H_{13}N_1O_2 + H^+$ 180.1019; found 180.1026. HPLC [Chirobiotic T column, EtOH/H_2O = 50:50, 210 nm, 1 mL/min; *er* = 2.5:97.5 (*R*/*S*)]: t_R = 6.46 (minor, *R*), 10.33 (major, *S*) min. MS (EI): *m*/*z* (%) = 179 (14) $[M^+]$, 162 (18), 150 (86), 132 (100), 117 (48), 105 (88), 91 (39), 77 (56).

***rac*-3-Amino-2-(4-methylphenyl)propionic Acid (*rac*-24b):** Following general procedure B (10 d), (2*S*,5*S*)-**23b** (100 mg, 0.3 mmol) afforded *rac*-**24b** (28 mg, 53% yield) as a powder, which was crystallized from methanol/diethyl ether. M.p. 226–228 °C. ^1H NMR (500 MHz, D_2O): δ = 6.71 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 6.68 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 3.5 (t, *J* = 7.4 Hz, 1 H, C*H*), 3.02 (dd, *J* = 13.02, 7.7 Hz, 1 H, CH_2), 2.78 (dd, *J* = 12.9, 7.6 Hz, 1 H, CH_2), 1.7 (s, 3 H, CH_3) ppm. ^{13}C NMR (125.76 MHz, D_2O): δ = 174.4 (C=O), 138.9 (C_{ipso}), 130.8 (C_{ipso}), 129.8 (*C*HAr), 127.9 (*C*HAr), 47.7 (*C*H), 40.8 (*C*H_2), 20.0 (*C*H_3) ppm. IR: $\tilde{\nu}$ = 3125, 3026, 2956, 2923, 2184, 1727, 1647, 1622, 1568, 1512, 1394 cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{10}H_{13}N_1O_2 + H^+$ 180.1019; found 180.1030. HPLC (Chirobiotic T column, EtOH/H_2O = 50:50, 210 nm, 1 mL/min): t_R = 6.4 (*R*), 11.02 (*S*) min. MS (EI): *m*/*z* (%) = 179 (16) $[M^+]$, 162 (46), 150 (100), 132 (96), 117 (76), 105 (98), 91 (50), 77 (46).

(*S*)-3-Amino-2-(4-*tert*-butylphenyl)propionic Acid [(*S*)-24c]: Following general procedure A (98 °C, 200 W, 13 h), (2*S*,5*S*)-**23c** (100 mg, 0.26 mmol) afforded (*S*)-**24c** (34 mg, 65% yield) as a powder, which was crystallized from methanol/diethyl ether. M.p. 249–251 °C, $[\alpha]_D^{25}$ = –78.22 (*c* = 0.45, 1 N HCl). ^1H NMR (500 MHz, D_2O): δ = 7.18 (d, *J* = 8.2 Hz, 2 H, Ar*H*), 6.96 (d, *J* = 8.3 Hz, 2 H, Ar*H*), 3.73 (t, *J* = 7.5 Hz, 1 H, C*H*), 3.25 (dd, *J* = 13.0, 7.9 Hz, 1 H, CH_2), 2.99 (dd, *J* = 12.88, 7.0 Hz, 1 H, CH_2), 0.92 (s, 9 *H*, CH_3) ppm. ^{13}C NMR (125.76 MHz, D_2O): δ = 174.6 (C=O), 152.4 (C_{ipso}), 131.3 (C_{ipso}), 128.0 (*C*HAr), 126.5 (*C*HAr), 47.9 (*C*H), 41.0 (*C*H_2), 33.9 (*C*), 30.3 (*C*H_3) ppm. IR: $\tilde{\nu}$ = 2954, 2901, 2768, 2655, 2162, 1625, 1575, 1525, 1384 cm^{-1}. MS (EI): *m*/*z* (%) = 221 (11) $[M]^+$, 192 (100), 177 (39), 174 (23), 159 (40), 136 (68), 131 (12), 57 (38). HRMS (ESI-TOF): calcd. for $C_{13}H_{20}N_1O_2$ 222.1488; found 222.1493. HPLC [Chirobiotic T column, EtOH/H_2O = 50:50, 210 nm, 1 mL/min; *er* = 11:89 (*R*/*S*)]: t_R = 7.13 (minor, *R*), 15.57 (major, *S*) min.

***rac*-3-Amino-2-(4-*tert*-butylphenyl)propionic Acid (*rac*-24c):** Following general procedure B (8 d), (2*S*,5*S*)-**23c** (100 mg, 0.26 mmol) afforded *rac*-**24c** (10 mg, 17% yield) as a powder, which was crys-

tallized from methanol/diethyl ether. M.p. 244–246 °C. ^{1}H NMR (500 MHz, D_2O): δ = 7.23 (d, J = 7.7 Hz, 2 H, Ar*H*), 7.0 (d, J = 7.83 Hz, 2 H, Ar*H*), 3.77 (t, J = 7.3 Hz, 1 H, C*H*), 3.29 (dd, J = 12.5, 8.0 Hz, 1 H, CH_2), 3.04 (dd, J = 12.8, 7.2 Hz, 1 H, CH_2), 0.97 (s, 9 *H*, CH_3) ppm. ^{13}C NMR (125.76 MHz, D_2O): δ = 174.6 (C=O), 152.5 (C_{ipso}), 131.4 (C_{ipso}), 128.0 (*C*HAr), 126.5 (*C*HAr), 47.9 (*C*H), 41.1 (*C*H_2), 34.0 (*C*), 30.4 (*C*H_3) ppm. IR: $\tilde{\nu}$ = 2955, 2926, 2863, 2649, 2162, 1731, 1623, 1566, 1524, 1387 cm^{-1}. MS (EI): *m*/*z* (%) = 222 (8) [M + 1]$^+$, 192 (100), 177 (50), 174 (25), 159 (39), 136 (64), 131 (12), 57 (34). HRMS (ESI-TOF): calcd. for $C_{13}H_{20}N_1O_2$ 222.1488; found 22.1491. HPLC (Chirobiotic T column, EtOH/H_2O = 50:50, 210 nm, 1 mL/min): t_R = 7.23 (*R*), 16.50 (*S*) min.

(*S*)-3-Amino-2-(5,6,7,8-tetrahydronaphthalen-2-yl)propionic Acid [(*S*)-24d]: Following general procedure A (98 °C, 200 W, 10 h), (2*S*,5*S*)-**23d** (100 mg, 0.265 mmol) afforded (*S*)-**24d** (10 mg, 17%) as a powder, which was recrystallized from methanol/diethyl ether. M.p. 224–225 °C, $[\alpha]_D^{25}$ = –28.8 (*c* = 0.52, 1 N HCl). ^{1}H NMR (500 MHz, D_2O): δ = 6.69 (d, J = 7.8 Hz, 1 H, Ar*H*), 6.61 (s, 2 H, Ar*H*), 3.56 (t, J = 7.5 Hz, 1 H, C*H*), 3.12 (dd, J = 13.1, 7.9 Hz, 1 H, CH_2), 2.86 (dd, J = 13.3, 6.85 Hz, 1 H, CH_2), 2.25 (s, 4 H, CH_2), 1.31–1.22 (m, 4 H, CH_2) ppm. ^{13}C NMR (125.76 MHz, D_2O): δ = 174.6 (*C*=O), 138.7 (C_{ipso}), 138.1 (C_{ipso}), 131.1 (C_{ipso}), 130.0 (*C*HAr), 128.5 (*C*HAr), 125.0 (*C*HAr), 47.9 (*C*H_2), 40.9 (*CH*), 28.5 (*C*H_2), 28.3 (*C*H_2), 22.33 (*C*H_2), 2.30 (CH_2) ppm. IR: $\tilde{\nu}$ = 2924, 2855, 2756, 2623, 1728, 1634, 1558, 1496, 1373 cm^{-1}. MS (EI): *m*/*z* (%) = 220 (11) [M$^+$ + 1], 190 (100), 172 (57), 145 (30), 131 (12), 89 (6). HRMS (ESI-TOF): calcd. for $C_{13}H_{17}N_1O_2$ + H$^+$ 220.1332; found 220.1343. HPLC [Chirobiotic T column, EtOH/H_2O = 50:50, 210 nm, 1 mL/min; *er* = 12:88 (*R*/*S*)]: t_R = 7.6 (minor, *R*), 10.4 (major, *S*) min.

***rac*-3-Amino-2-(5,6,7,8-tetrahydronaphthalen-2-yl)propionic Acid (*rac*-24d):** Following general procedure B (10 d), (2*S*,5*S*)-**23d** (100 mg, 0.265 mmol) afforded *rac*-**24d** (33 mg, 56% yield) as a powder, which was recrystallized from methanol/diethyl ether. M.p. 230–232 °C. ^{1}H NMR (500 MHz, D_2O): δ = 6.9 (d, J = 7.6 Hz, 1 H, Ar*H*), 6.83 (s, 2 H, Ar*H*), 3.77 (t, J = 7.5 Hz, 1 H, C*H*), 3.34 (dd, J = 8.0, 7.5 Hz, 1 H, CH_2), 3.08 (dd, J = 13.1, 7.0 Hz, 1 H, CH_2), 2.47 (s, 4 H, CH_2), 1.49 (s, 4 H, CH_2) ppm. ^{13}C NMR (125.76 MHz, D_2O): δ = 174.7 (*C*=O), 138.9 (C_{ipso}), 138.4 (C_{ipso}), 131.4 (C_{ipso}), 130.2 (*C*HAr), 128.7 (*C*HAr), 125.2 (*C*HAr), 48.1 (*CH*), 41.0 (*C*H_2), 28.7 (*C*H_2), 28.5 (*C*H_2), 22.5 (*C*H_2), 22.47 (*C*H_2) ppm. IR: $\tilde{\nu}$ = 3015, 2926, 2855, 2362, 2176, 1728, 1629, 1560, 1500, 1396, 1288 cm^{-1}. MS (EI): *m*/*z* (%) = 220 (15) [M + 1]$^+$, 190 (100), 172 (66), 145 (41), 131 (14), 89 (6). HRMS (ESI-TOF): calcd. for $C_{13}H_{17}N_1O_2$ + H$^+$ 220.1332; found 220.1339. HPLC (Chirobiotic T column, EtOH/H_2O = 50:50, 210 nm, 1 mL/min): t_R = 7.5 (*R*), 10.5 (*S*) min.

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[1] Special issue dedicated to cross-coupling reactions: S. L. Buchwald (Guest Ed.), *Acc. Chem. Res.* **2008**, *41*, 1439–1564.

[2] a) D. S. Matteson, *Stereodirected Synthesis with Organoboranes*, Springer, Berlin, **1995**; b) A. Pelter, K. Smith, H. C. Brown, *Borane Reagents*, Academic Press, London, **1988**; c) R. Ling, M. Yoshida, P. S. Mariano, *J. Org. Chem.* **1996**, *61*, 4439–4449.

[3] For reviews on organotrifluoroborate salts, see: a) S. Darses, J. P. Genet, *Eur. J. Org. Chem.* **2003**, 4313–4327; b) G. A. Molander, R. Figueroa, *Aldrichimica Acta* **2005**, *38*, 49–56; c) G. A. Molander, N. Ellis, *Acc. Chem. Res.* **2007**, *40*, 275–286; d) H. A. Stefani, R. Cella, A. S. Vieira, *Tetrahedron* **2007**, *63*, 3623–3658; e) S. Darses, J. P. Genet, *Chem. Rev.* **2008**, *108*, 288–325.

[4] For reviews on the Suzuki–Miyaura reaction, see: a) H. Doucet, *Eur. J. Org. Chem.* **2008**, 2013–2030; b) D. Benito-Garagorri, K. Kirchner, *Acc. Chem. Res.* **2008**, *41*, 201–213; c) M. Sasaki, H. Fuwa, *Synlett* **2004**, 1851–1874; d) S. Kotha, K. Lahiri, D. Kashinath, *Tetrahedron* **2002**, *58*, 9633–9695.

[5] For monographs, see: a) E. Juaristi (Ed.), *Enantioselective Synthesis of β-Amino Acids*, Wiley, New York, **1997**; b) E. Juaristi, V. Soloshonok, *Enantioselective Synthesis of β-Amino Acids*, 2nd ed., Wiley, New York, **2005**; for additional review articles, see: c) E. Juaristi, D. Quintana, J. Escalante, *Aldrichimica Acta* **1994**, *27*, 3–11; d) D. C. Cole, *Tetrahedron* **1994**, *50*, 9517–9582; e) G. Cardillo, C. Tomasini, *Chem. Soc. Rev.* **1996**, *25*, 117–128; f) E. Juaristi, H. López-Ruiz, *Curr. Med. Chem.* **1999**, *6*, 983–1004; g) S. Abele, D. Seebach, *Eur. J. Org. Chem.* **2000**, 1–15; h) F. Fülöp, *Chem. Rev.* **2001**, *101*, 2181–2204; i) M. Liu, M. P. Sibi, *Tetrahedron* **2002**, *58*, 7991–8035; j) F. Gnad, O. Reiser, *Chem. Rev.* **2003**, *103*, 1603–1623; k) J.-A. Ma, *Angew. Chem. Int. Ed.* **2003**, *42*, 4290–4299; l) N. Sewald, *Angew. Chem. Int. Ed.* **2003**, *42*, 5794–5795; m) G. Lelais, D. Seebach, *Biopolymers* **2004**, *76*, 206–243; n) M. Palko, K. Lorand, F. Fülöp, *Curr. Med. Chem.* **2005**, *12*, 3063–3083; o) N. M. Garrido, D. Diez, S. H. Domínguez, M. García, M. R. Sánchez, S. G. Davies, *Tetrahedron: Asymmetry* **2006**, *17*, 2183–2186; p) A. Dondoni, A. Massi, *Acc. Chem. Res.* **2006**, *39*, 451–463; q) D. J. Ager (Ed.), "Synthesis of Non-Natural Amino Acids" in *Handbook of Chiral Chemicals*, 2nd ed., DSM Pharma Chemicals, Raleigh, NC, **2006**; r) D. Seebach, A. K. Beck, S. Capone, G. Deniau, U. Groselj, E. Zass, *Synthesis* **2009**, 1–32; s) Y. Bandala, E. Juaristi in *Amino Acids, Peptides and Proteins in Organic Chemistry* (Ed.: A. B. Hughes), Wiley, Weinheim, **2009**, pp. 291–366; t) K. Lorand, E. Forro, F. Fülöp in *Amino Acids, Peptides and Proteins in Organic Chemistry* (Ed.: A. B. Hughes), Wiley, Weinheim, **2009**, pp. 367–409; u) B. E. Sleebs, T. T. van Nguyen, A. B. Hughes, *Org. Prep. Proced. Int.* **2010**, *41*, 429–478.

[6] a) E. Juaristi, D. Quintana, M. Balderas, E. García-Pérez, *Tetrahedron: Asymmetry* **1996**, *7*, 2233–2246; b) C. G. Avila-Ortiz, G. Reyes-Rangel, E. Juaristi, *Tetrahedron* **2005**, *61*, 8372–8381.

[7] a) E. Juaristi, M. Balderas, Y. Ramírez-Quirós, *Tetrahedron: Asymmetry* **1998**, *9*, 3881–3888; b) E. Juaristi, M. Balderas, H. López-Ruiz, V. M. Jiménez-Pérez, M. L. Kaiser-Carril, Y. Ramírez-Quiróz, *Tetrahedron: Asymmetry* **1999**, *10*, 3493–3505.

[8] a) J. P. Konopelski, K. S. Chu, G. R. Negrete, *J. Org. Chem.* **1991**, *56*, 1355–1357; b) E. Juaristi, J. Escalante, B. Lamatsch, D. Seebach, *J. Org. Chem.* **1992**, *57*, 2396–2398; c) K. S. Chu, G. R. Negrete, J. P. Konopelski, F. J. Lakner, W. Nam-Tae, M. M. Olmstead, *J. Am. Chem. Soc.* **1992**, *114*, 1800–1812; d) E. Juaristi, J. Escalante, *J. Org. Chem.* **1993**, *58*, 2282–2285; e) R. Amoroso, G. Cardillo, C. Tomasini, P. Tortoreto, *J. Org. Chem.* **1992**, *57*, 1082–1087; f) G. Cardillo, A. Tolomelli, C. Tomasini, *Tetrahedron* **1995**, *51*, 11831–11840; g) J. Escalante, E. Juaristi, *Tetrahedron Lett.* **1995**, *36*, 4397–4400; h) F. Beaulieu, J. Arora, V. Vieth, N. J. Taylor, B. J. Chapell, V. Snieckus, *J. Am. Chem. Soc.* **1996**, *118*, 8727–8728; i) E. Juaristi, H. López-Ruiz, D. Madrigal, Y. Ramírez-Quirós, J. Escalante, *J. Org. Chem.* **1998**, *63*, 4706–4710; j) D. Seebach, A. Boog, W. B. Schweizer, *Eur. J. Org. Chem.* **1999**, 335–360; k) E. Castellanos, G. Reyes-Rangel, E. Juaristi, *Helv. Chim. Acta* **2004**, *87*, 1016–1024; l) M. Nahrwold, A. Stoncius, A. Penner, B. Neumann, H.-G. Stammler, N. Sewald, *Beilstein J. Org. Chem.* **2009**, *5*, 43–49.

[9] A. Boto, R. Hernández, E. Suárez, *J. Org. Chem.* **2000**, *65*, 4930–4937.

[10] M. A. Iglesias-Arteaga, C. G. Avila-Ortiz, E. Juaristi, *Tetrahedron Lett.* **2002**, *43*, 5297–5300.

[11] a) Y. F. Shealy, C. A. O'Dell, W. M. Shannon, G. Arnett, *J. Med. Chem.* **1983**, *26*, 156–161; b) H. G. Howell, P. R. Brodfuehrer, S. P. Brundidge, D. A. Benigni, C. Sapino, *J. Org. Chem.* **1988**, *53*, 85–88; c) L. M. v. Beauchamp, B. L. Serling, J. E. Kelsey, K. K. Biron, P. Collins, J. Selway, J.-C. Lin, H. J. Schaeffer, *J. Med. Chem.* **1988**, *31*, 144–149.

[12] B. R. Díaz-Sánchez, M. A. Iglesias-Arteaga, R. Melgar-Fernández, E. Juaristi, *J. Org. Chem.* **2007**, *72*, 4822–4825.

[13] N. Alonso, O. Caamano, F. Fernández, X. García-Mera, M. Morales, J. E. Rodríguez-Borges, E. De Clercq, *Synthesis* **2008**, 1845–1852.

[14] a) R. Cella, R. C. Venturoso, H. A. Stefani, *Tetrahedron Lett.* **2008**, *49*, 16–19; b) H. A. Stefani, R. C. Guadagnin, A. F. Keppler, A. S. Vieira, J. V. Comasseto, C. A. Suganuma, G. V. Botteselle, A. L. Braga, *Beilstein J. Org. Chem.* **2008**, *4*, 1–4; c) A. Bellomo, D. Gonzalez, H. A. Stefani, *J. Organomet. Chem.* **2008**, *693*, 1136–1142; d) A. S. Vieira, R. C. Guadagnin, P. F. Fiorante, F. P. Ferreira, H. A. Stefani, *Tetrahedron* **2008**, *64*, 3306–3314; e) M. W. Paixão, M. Weber, H. A. Stefani, A. L. Braga, J. B. Azeredo, A. M. Deobald, *Tetrahedron Lett.* **2008**, *49*, 2366–2370; f) A. S. Vieira, P. F. Fiorante, J. Zukerman-Schpector, D. Alves, G. V. Botesselle, H. A. Stefani, *Tetrahedron* **2008**, *64*, 7234–7241; g) R. C. Guadagnin, C. Suganuma, A. S. Vieira, R. Cella, H. A. Stefani, *Tetrahedron Lett.* **2008**, *49*, 4713–4716; h) F. V. Singh, M. Weber, R. C. Guadagnin, H. A. Stefani, *Synlett* **2008**, *12*, 1889–1893; i) A. L. Braga, T. Barcellos, M. W. Paixão, A. M. Deobald, M. Godoy, H. A. Stefani, R. Cella, A. Sharma, *Organometallics* **2008**, *27*, 4009–4012; j) G. V. Botteselle, T. L. S. Hough, R. C. Venturoso, R. Cella, A. S. Vieira, H. A. Stefani, *Aust. J. Chem.* **2008**, *61*, 870–873; k) A. S. Vieira, P. F. Fiorante, T. L. S. Hough, F. P. Ferreira, D. S. Lüdtke, H. A. Stefani, *Org. Lett.* **2008**, *10*, 5215–5218; l) F. V. Singh, H. A. Stefani, *Synlett* **2008**, *20*, 3221–3225.

[15] a) E. Juaristi, D. Quintana, *Tetrahedron: Asymmetry* **1992**, *3*, 723–726; b) E. Juaristi, *Handbook of Reagents for Organic Synthesis. Chiral Reagents for Asymmetric Synthesis* (Ed.: L. A. Paquette), Wiley, Chichester, **2003**, pp. 53–56; c) S. A. Hopkins, T. A. Ritsema, J. P. Konopelski, *J. Org. Chem.* **1999**, *64*, 7885–7889.

[16] a) G. A. Molander, B. Biolatto, *J. Org. Chem.* **2003**, *68*, 4302–4314; b) G. A. Molander, B. Biolatto, *Org. Lett.* **2002**, *4*, 1867–1870.

[17] Y. Ramírez-Quirós, M. Balderas, J. Escalante, D. Quintana, I. Gallardo, D. Madrigal, E. Molins, E. Juaristi, *J. Org. Chem.* **1999**, *64*, 8668–8680.

[18] D. Seebach, B. Lamatsch, A. K. Beck, M. Dobler, M. Egli, R. Fitzi, M. Gautschi, B. Herradón, P. C. Hidber, J. J. Irwin, R. Locher, M. Maestro, T. Meetzke, A. Mouriño, E. Pfammatter, D. A. Plattner, C. Schickli, W. B. Schweiser, P. Seifer, G. Stucky, W. Petter, J. Escalante, E. Juaristi, D. Quintana, C. Miravitlles, E. Molins, *Helv. Chim. Acta* **1992**, *75*, 913–934.

[19] a) G. A. Molander, B. W. Katona, F. Machrouhi, *J. Org. Chem.* **2002**, *67*, 8416–8423; b) S. Darses, G. Michaud, J.-P. Genêt, *Eur. J. Org. Chem.* **1999**, 1875–1883.

[20] A. J. Mota, E. Castellanos, E. Juaristi, *Org. Prep. Proced. Int.* **2003**, *35*, 414–417.

[21] N. J. A. Martin, X. Cheng, B. List, *J. Am. Chem. Soc.* **2008**, *130*, 13862–13863.

[22] R. H. Prager, K. Schafer, *Aust. J. Chem.* **1997**, *50*, 813–823.

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