Check for updates

Chemistry–A European Journal   Full Paper
doi.org/10.1002/chem.202000870

Chemistry
Europe
European Chemical
Societies Publishing

❚ **Synthetic Methods** | *Hot Paper* |

Pyrrole-Protected β-Aminoalkylzinc Reagents for the Enantioselective Synthesis of Amino-Derivatives

Marcel Leroux, Wan-Yun Huang, Yannick Lemke, Thaddäus J. Koller, Konstantin Karaghiosoff, and Paul Knochel*[a]

Abstract: Chiral β-aminoalkylzinc halides were prepared starting from optically pure commercial β-amino-alcohols. These amino-alcohols were converted to the corresponding *N*-pyrrolyl-protected alkyl iodides which undergo a zinc insertion in the presence of LiCl (THF, 25 °C, 10–90 min). Subsequent Negishi cross-coupling or acylation reactions with acid chlorides produced amino-derivatives with retention of chir-

ality. Diastereoselective CBS-reductions of some prepared *N*-pyrrolyl-ketones provided 1,3-substituted *N*-pyrrolyl-alcohols with high diastereoselectivity. Additionally, a deprotection procedure involving an ozonolysis allowed the conversion of the pyrrole-ring into a formamide without loss of optical purity.

Introduction

The preparation of chiral amino-derivatives is of great synthetic importance for the development of new pharmaceuticals and agrochemicals.[1] In this context, the preparation of organometallic intermediates bearing an amino group in β-position may provide a powerful tool for the synthesis of functionalized amino-derivatives. Organozinc compounds are known to tolerate a broad range of functional groups[2] and are therefore well suited for synthesis of chiral amino-derivatives. Jackson has demonstrated the utility of serine derived chiral organozinc reagents for the preparation of novel amino acids using Negishi cross-coupling reactions.[3] Furthermore, chiral β-aminoalkylzinc reagents derived from the corresponding amino-alcohols have been already used for the synthesis of functionalized amines.[4,5]

In this work, we have envisioned to prepare stable zinc organometallics bearing an amino group in β-position as key organometallic intermediates. Thus, 2-amino-alcohols of type **1**, readily available by reduction of the corresponding natural amino-acid, will afford after protection of the amino group the corresponding amino-alcohol of type **2** and after functional

group interconversion the corresponding alkyl iodides of type **3**.

Treatment of these functionalized alkyl iodides (**3**) with zinc dust in the presence of LiCl should provide 2-aminoalkylzinc halides (**4**) which should readily react with various electrophiles in the presence of an appropriate transition-metal catalyst (Scheme 1a).
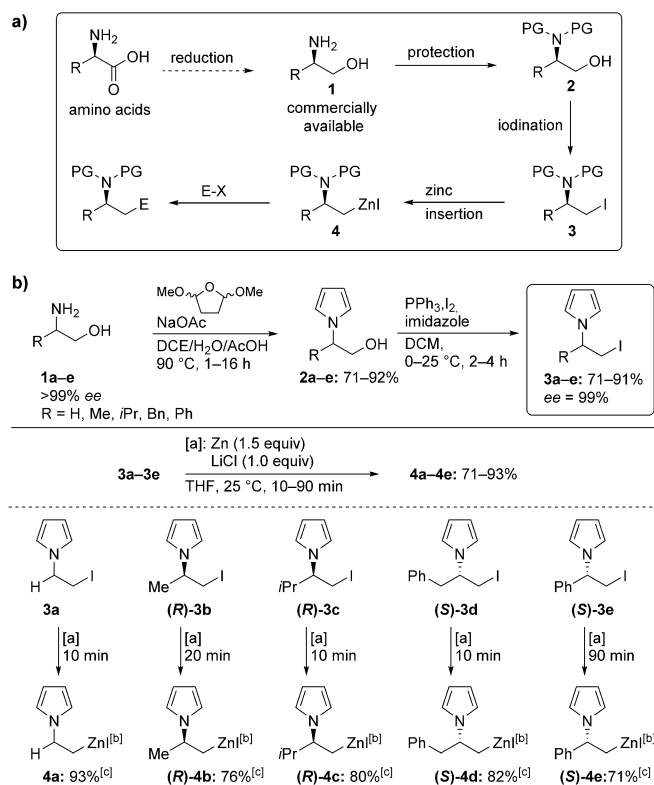
Results and Discussion

Preliminary results showed that the choice of the protecting group was essential for the success of the proposed reaction sequence (Scheme 1a). Whereas most electron-withdrawing amino-protecting groups[6] will enhance elimination side reactions for the resulting organozinc reagent of type **4**, most donating amino-protecting groups on the other hand will favor aziridination of the starting iodide **3**. After some experimentation, we have found that the use of a pyrrole ring as protecting group is an excellent compromise which allows to accomplish the proposed sequence with high efficiency (Scheme 1b).

Therefore, the treatment of commercially available 1,2-amino-alcohols (**1a–e**) derived from optically enriched amino-acids[8] with 2,5-dimethoxytetrahydrofuran in the presence of NaOAc/AcOH in 1,2-dichloroethane (DCE) and water (90 °C, 1–16 h) produced the pyrrol-1-yl-alcohol derivatives **2a–e** in 71–92 % yield.[9] An Appel reaction[10] (PPh₃, I₂, imidazole in dichloromethane (DCM)) allowed the conversion of the alcohols **2a–e** to the corresponding primary iodides **3a–e** in 71–91 % yield. Direct insertion of zinc powder (1.5 equiv, > 325 mesh) previously activated with 1,2-dibromoethane (DBE) and Me₃SiCl (TMSCl) to the alkyl iodides **3a–e** in presence of LiCl[11] proceeded smoothly in THF at 25 °C (10–90 min) furnishing the desired alkylzinc halides (**4a–e**) in 71–93 % yield. These alkylzinc reagents showed no tendency to undergo elimination re-

Chemistry–A European Journal

Full Paper
doi.org/10.1002/chem.202000870

Chemistry Europe
European Chemical
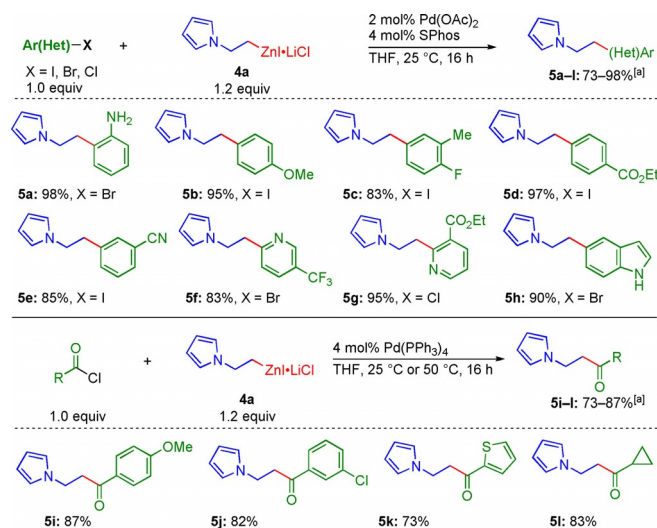Societies Publishing

Scheme 1. Preparation of chiral β-aminoalkylzinc halides of type **4** from optically pure amino-alcohols of type **1**. [a] Zinc insertion conditions: LiCl (1.0 equiv), Zn dust (1.5 equiv, activated with DBE/TMSCl) in THF at 25 °C. [b] Complexed with LiCl. [c] Determined by titration against iodine.[7]

Scheme 2. Palladium-catalyzed Negishi cross-coupling and acylation reactions of **4a** with various aryl halides and acid chlorides leading to functionalized pyrrole derivatives **5a–l**. [a] Yield of analytically pure isolated products.

Scheme 3. Negishi cross-coupling reactions of chiral β-N-pyrrolyl alkylzinc reagents **4b–e** with various functionalized aryl halides. [a] Yield of analytically pure isolated products.

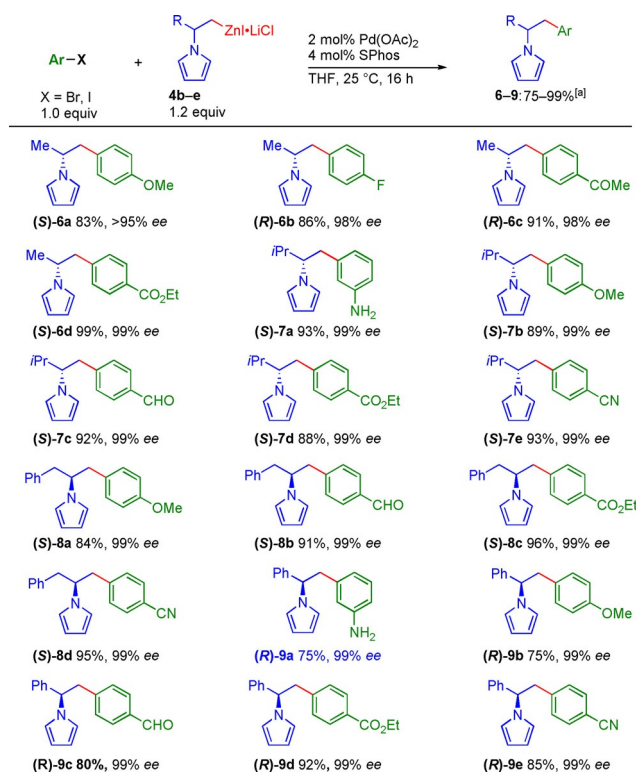actions and were stable at 25 °C for several days without decomposition.

In preliminary experiments, 2-(1H-pyrrol-1-yl)ethylzinc iodide (**4a**) was used to determine the optimum cross-coupling and acylation conditions. Negishi cross-coupling reactions[12] of **4a** were best performed using 2 mol% Pd(OAc)$_2$ and 4 mol% SPhos[13] as catalyst with both electron-rich or electron-poor aryl- and heteroaryl bromides or iodides in THF (25 °C, 16 h) affording the pyrrole derivatives **5a–h** in 83–98% yield. Negishi acylation reactions[14] of **4a** were also readily performed using aryl-, heteroaryl- and cyclopropyl-substituted acyl chlorides in the presence of 4 mol% Pd(PPh$_3$)$_4$ in THF (25–50 °C, 16 h) providing the β-pyrrolyl-ketones (**5i–l**) in 73–87% yield (Scheme 2). No significant amount of β-hydride elimination was observed in these cross-coupling reactions.

With these optimized conditions in hand, we have extended these reactions to the chiral organozinc reagents **4b–e**. Various chiral arylated pyrroles (**6a–d**, **7a–e**, **8a–d**, **9a–e**) were obtained after Negishi cross-couplings with aryl iodides and bromides in 75–99% isolated yield with full retention of configuration (ee = 99%, Scheme 3).

Similarly, the reagents **4b–e** were used in palladium-catalyzed acylation reactions with several aryl-, heteroaryl- and alkyl-substituted acyl chlorides providing the desired chiral ketones (**7f**, **7i,j** and **8e–h**) in 66–86% yield. Furthermore, as a cheap alternative to palladium-catalysis and to prevent cross-
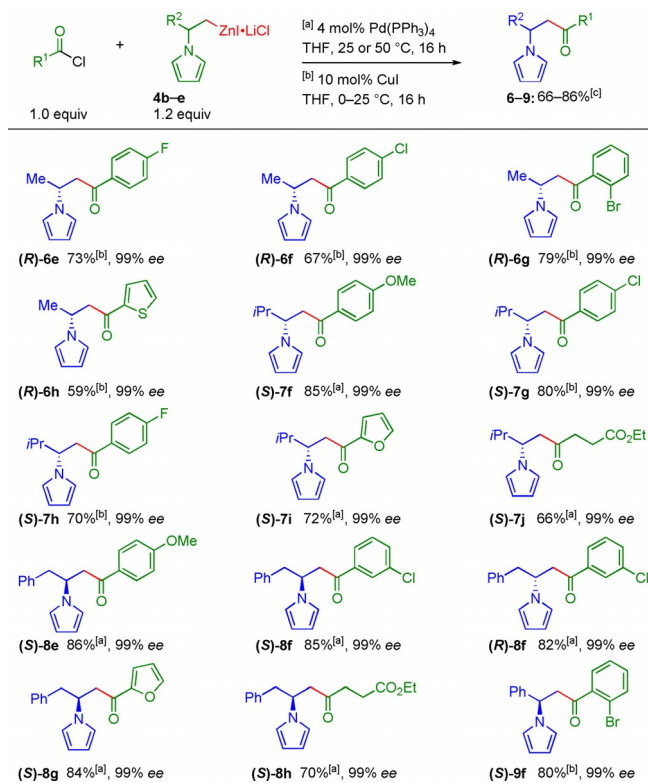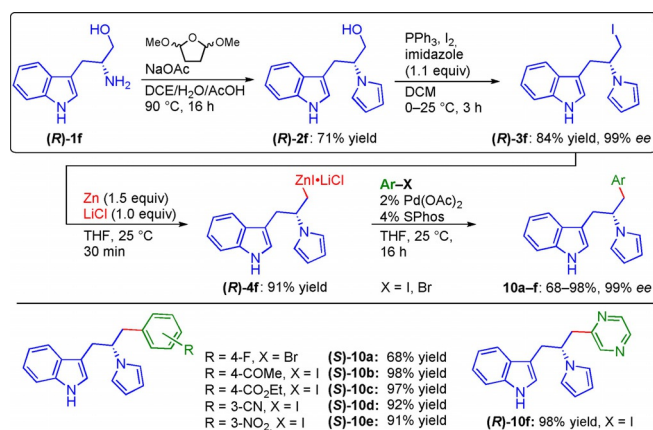
coupling side reactions, copper(I) iodide was used as a catalyst for acylations.[15] Chiral halogenated ketones (**6e–g**, **7g–h**, **9f**) and a 2-thienyl-ketone (**6h**) were obtained in 59–80% yield (Scheme 4). All ketones, whether prepared by using palladium- or copper-derivatives as catalyst, were obtained with full retention of configuration (ee = 99%).
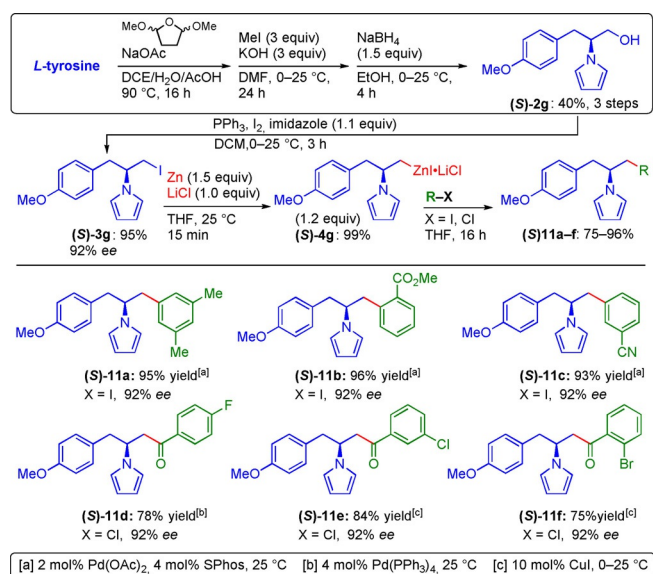
Scheme 4. Palladium- and copper-catalyzed acylation reactions using chiral organozinc reagents **4b–e** with various acyl chlorides. [a] Palladium-catalyzed acylation. [b] Copper-catalyzed acylation. [c] Yield of analytically pure isolated products.

Scheme 5. Preparation of a chiral pyrrole-protected alkylzinc reagent ((**R**)-**4f**) derived from tryptophanol (**R**)-**1f** bearing an unprotected indolyl-moiety and its use in Negishi cross-coupling reactions.
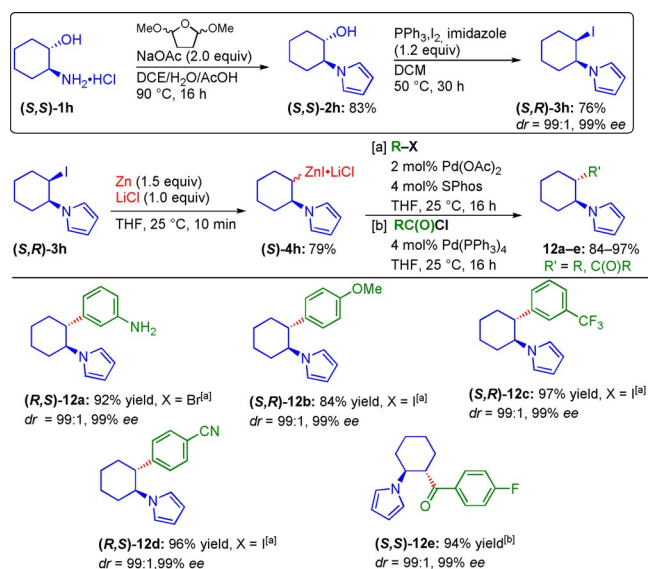

Scheme 6. Preparation of a chiral N-pyrrolyl-alkylzinc iodide ((**S**)-**4g**) derived from L-tyrosine and its use in Negishi cross-coupling and acylation reactions.

To further extend these reactions, we have prepared an indolyl-substituted zinc reagent.[16] Starting from tryptophanol (**R**)-**1f**, successive pyrrole-protection leading to (**R**)-**2f** and iodination using our standard procedures[17] provided the optically pure alkyl iodide (**R**)-**3f** which was converted to the corresponding organozinc reagent (**R**)-**4f**. Interestingly, the presence of a secondary amine of the indole side-chain did not interfere with the zinc insertion and the resulting organozinc reagent (**R**)-**4f** was prepared in 91% yield.[18] Palladium-catalyzed Negishi cross-coupling reactions with various aryl and heteroaryl iodides or bromides were performed and functionalized indole derivatives **10a–f** were obtained in 68–98% yield without racemization (Scheme 5).

Additionally, a tyrosine-based alkylzinc compound was prepared.[16] For this purpose, the acidic phenolic hydroxyl group of L-tyrosine was protected by methylation with MeI. Starting from L-tyrosine, a straightforward synthesis pathway including pyrrole formation, phenol protection, methyl esterification and subsequent reduction of the methyl ester was performed in 40% yield over three steps providing the pyrrol-1-yl-alcohol (**S**)-**2g** (Scheme 6). A subsequent conversion into the alkyl iodide (**S**)-**3g** using Appel-reaction conditions was proceeding in 95% yield and 92% ee. After oxidative addition of zinc dust into this alkyl iodide, the corresponding chiral N-pyrrolyl-alkyl-zinc halide (**S**)-**4g** was obtained after 15 min at 25 °C in 99% yield. Negishi cross-coupling reactions using electron-rich and electron-poor aryl iodides afforded the functionalized tyrosine

derivatives (**S**)-**11a–c** in 93–96% yield. Additional copper- and palladium-catalyzed acylation reactions were performed providing ketones (**S**)-**11d–f** bearing halogens in *ortho*-, *meta*- or *para*-position in 75–84% yield (Scheme 6). All products were obtained with retention of configuration with 92% ee as determined previously for the starting alkyl iodide (**S**)-**3g**.

In addition to the organozinc reagents derived from amino-acids, we have also prepared a chiral zinc reagent derived from *trans*-(1S,2S)-2-aminocyclohexanol ((**S,S**)-**1h**). After protection as a pyrrole ring, the corresponding N-pyrrolyl-alkyl alcohol (**S,S**)-**2h** was obtained in 83% yield and further Appel-iodination led to the desired cycloalkyl iodide (**S,R**)-**3h** at 50 °C in 76% yield after 30 h. Following zinc insertion of (**S,R**)-**3h** provided the alkylzinc reagent (**S**)-**4h** in 79% yield. The stereochemistry of the carbon bearing zinc is lost due to the radical insertion reaction.[19] However, cross-coupling reactions of the

Chemistry–A European Journal

Full Paper
doi.org/10.1002/chem.202000870

Chemistry Europe
European Chemical
Societies Publishing

organozinc reagent (**S**)-**4h** using Pd(OAc)$_2$ and SPhos as catalyst with different substituted electron-rich and electron-deficient electrophiles provided the cross-coupling products **12a–d** in 84–97% yield (Scheme 7). Remarkably, using this palladium system, the *trans*-cross-coupling products were formed selectively (*dr* = 99:1) and all products exhibit a high optical purity (99% *ee*).[19]


Scheme 7. Preparation of a chiral *N*-pyrrolyl-alkylzinc reagent starting from the 1,2-*cis* substituted iodocyclohexyl derivative (**S,R**)-**3h** providing exclusively *trans*-configured products using palladium-catalysis.

Reaction of (**S**)-**4h** with 4-fluorobenzoyl chloride using Pd(PPh$_3$)$_4$ as acylation catalyst led solely to the *trans*-ketone (**S,S**)-**12e** in 93% yield (*dr* = 99:1, 99% *ee*). The same reaction using copper(I) iodide as catalyst resulted in a diastereomeric mixture (*dr* = 83:17).

Furthermore, this method was extended to a *N*-pyrrolyl-alkylzinc reagent derived from *trans*-(1R,2R)-2-aminocyclopentanol ((**R,R**)-**1i**). After protection of the amino group as a pyrrole ring, the corresponding *N*-pyrrolyl-alcohol (**R,R**)-**2i** was obtained in 77% yield. Its iodination was rather difficult due to the increased formation of an elimination product and the *cis*-iodide[20] (**R,S**)-**3i** was obtained at 50°C in only 43% yield after 16 h reaction time. Subsequent insertion of zinc dust in the presence of LiCl led to the secondary organozinc reagent (**R**)-**4i** at 25°C after 10 min reaction time in 96% yield (Scheme 8).

A stereo-converging reaction occurred when using the diastereomeric mixture of organozinc reagent (**R**)-**4i** in palladium-catalyzed Negishi cross-coupling reactions with aryl iodides bearing various functional groups in *ortho*-, *meta*- or *para*-position providing selectively the *trans*-products **13a–f** in 75–93% yield with high enantiopurity (Scheme 8). Determination of the crystal structure of (**S,R**)-**13a** by X-ray analysis confirmed the *trans*-configuration.[20]

A post-functionalization of some chiral pyrrole-containing products was performed providing chiral amino-alcohol derivatives. Thus, the acylation products (**R**)-**8f** and (**S**)-**8f** were se-
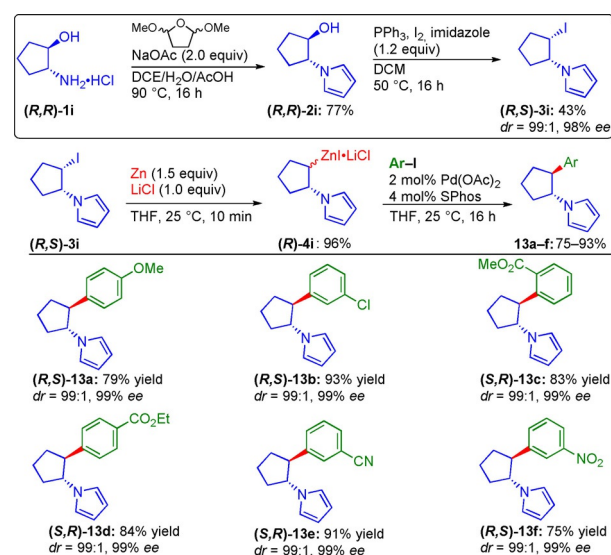
Scheme 8. Preparation of the 2-*N*-pyrrolyl-cyclopentlyzinc reagent (**R**)-**4i**. Exclusively *trans*-configured products of type **13** were obtained after palladium-catalyzed Negishi cross-coupling.

lectively reduced to optically pure 1,3-substituted *N*-pyrrolyl-alcohols using the Corey–Bakshi–Shibata asymmetric reduction.[21] Therefore, the CBS catalyst ((**R**)- or (**S**)-2-methyl-CBS-oxazaborolidine) was mixed with BH$_3$·SMe$_2$ at 0°C and the ketone **8f** was slowly added. The desired alcohols **14a–d** were obtained in 92–98% yield with a diastereomeric ratio of 99:1 and an enantiomeric excess of 99% (Scheme 9).

To confirm the absolute configuration, the alcohol (**R,S**)-**14d** was esterified with the (**R**)- as well as the (**S**)-Mosher acid (MTPA) and the resulting two diastereomeric esters were analyzed by NMR spectroscopy. The chemical shifts were compared and evaluated as reported in the literature (see Support-
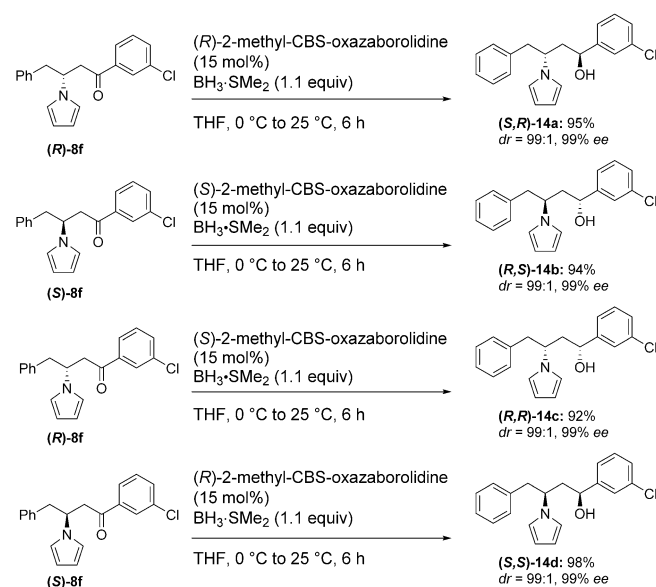
Scheme 9. Enantioselective CBS-reduction of the ketones (**R**)-**8f** and (**S**)-**8f** provides a pathway towards the 1,3-substituted *N*-pyrrolyl-alcohols **14a–d**.

Chemistry–A European Journal

Full Paper
doi.org/10.1002/chem.202000870

Chemistry Europe
European Chemical
Societies Publishing

ing Information).[22] The analysis confirmed the configuration previously predicted by the CBS-model. Thus, the (R)-CBS catalyst provided the (S)-alcohols (**14b**, **14c**) and vice versa the (S)-CBS catalyst led to the (R)-alcohols (**14a**, **14d**).

A deprotection procedure for the pyrrole group was developed based on literature procedures.[23] Ozonolysis converted pyrroles into solid formamides, which were easier to handle than the corresponding alkylamines. Thus, treatment of a pyrrole derivative with ozone at −78 °C in a DCM/MeOH mixture for 5 min, followed by a reductive work-up with methyl sulfide led to a mixture of the corresponding formamide and diformylamine. This mixture was then stirred in a diluted potassium hydroxide solution in ethanol (0.1 M) for 1 h leading selectively to formamides of type **15** (Table 1).[24]

This deprotection protocol was applied to selected cross-coupling products (**5g**, **8c**, **8d**, **11a**, **12c**, **13f**) as well as the CBS-reduced alcohol (S,R)-**14a** and the corresponding formamide derivatives **15a–g** were obtained 62–76% yield (Table 1). The stereocenters were not affected by this treatment and full retention of configuration was achieved for all compounds.

Additionally, the crystal structures of (S,R)-**15e** and (R,S)-**15g** were obtained by X-ray diffraction of single-crystals. The structure of (S,R)-**15e** (Figure 1) confirmed the *trans*-configuration of the formamide group to the aryl moiety which was determined for pyrrole derivative (S,R)-**12c** via NMR-spectroscopy.

Furthermore, the crystal structure of (R,S)-**15g** (Figure 2) showed an *anti*-configuration. This was in accordance with the results of the Mosher's ester analysis using NMR-spectroscopy described above.

Table 1. Deprotection of the pyrroles via ozonolysis and subsequent reductive and basic workup leading to the formamides **15a–g** with retention of configuration.

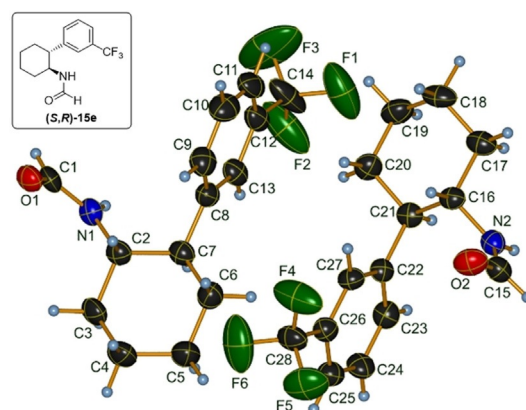| Entry	Functionalized pyrrole	Formamide **15a–15g**
1	**5g**	**15a**, 71% yield
2	(S)-**8c**, 99% ee	(S)-**15b**, 74% yield, 99% ee
3	(S)-**8d**, 99% ee	(S)-**15c**, 65% yield, 99% ee
4	(S)-**11a**, 92% ee	(S)-**15d**, 62% yield, 92% ee
5	(S,R)-**12c**, dr = 99:1, 99% ee	(S,R)-**15e**, 74% yield, dr = 99:1, 99% ee
6	(R,S)-**13f**, dr = 99:1, 99% ee	(R,S)-**15f**, 71% yield, dr = 99:1, 99% ee
7	(S,R)-**14a**, dr = 99:1, 99% ee	(R,S)-**15g**, 76% yield, dr = 99:1, 99% ee

Figure 1. Molecular structure of the deprotected formamide (S,R)-**15e**. Thermal ellipsoids are drawn at 50% probability level. The fluorine atoms of both CF₃ groups are disordered.
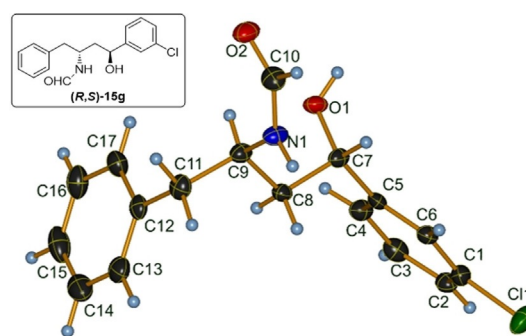
Figure 2. Molecular structure of the deprotected formamide (R,S)-**15g**. Thermal ellipsoids are drawn at 50% probability level.

Conclusions

In conclusion, we have developed a straightforward preparation of pyrrole-protected β-aminoalkylzinc halides starting from optically pure β-amino-alcohols. The pyrrole moiety was a suitable protecting group for the preparation of such organozinc reagents. These β-aminoalkylzinc reagents underwent palladium-catalyzed Negishi cross-coupling reactions and acy-

Chemistry–A European Journal

Full Paper
doi.org/10.1002/chem.202000870

Chemistry
Europe
European Chemical
Societies Publishing

lation reactions with a broad range of functionalized electrophiles providing a range of chiral amino-derivatives. Similarly, secondary cycloalkylzinc halides were prepared from the corresponding iodides. Subsequent cross-coupling and acylation reactions produced various chiral 1,2-cyclohexyl- and cyclopentyl-amines. An amino-ketone prepared via acylation reaction was reduced using an asymmetric CBS-reduction providing optically pure 1,3-substituted *N*-pyrrolyl-alcohols. A deprotection procedure was also developed involving an ozonolysis with subsequent reductive work-up. This allowed to convert these pyrrole derivatives into diastereomerically and enantiomerically enriched formamides.

Experimental Section

Typical procedure for the preparation of *N*-pyrrolyl-alcohols of type 2 from amino-alcohols of type 1: Preparation of (*S*)-3-phenyl-2-(1*H*-pyrrol-1-yl)propan-1-ol ((*S*)-2d)

(*S*)-2-Amino-3-phenyl-1-propanol (*S*)-1d (3.8 g, 25 mmol, 1.0 equiv) and NaOAc·3H₂O (3.4 g, 25 mmol,1.0 equiv) were dissolved in a DCE/water mixture (1:1, 75 mL) and glacial acetic acid (12.5 mL). 2,5-Dimethoxytetrahydrofuran (*cis/trans* mixture, 3.3 g, 25 mmol, 1.0 equiv) was added and the two-phase mixture was refluxed at 90 °C under vigorous stirring for 16 h. The organic phase was separated, the aqueous phase was extracted three times with EtOAc and the combined organic phases were neutralized with sat. aq. NaHCO₃ solution, washed with brine and dried over MgSO₄. After evaporation of solvents, the residue was purified by flash column chromatography (*i*-hexanes/ethyl acetate 8:2 + 1 vol% Et₃N) and the corresponding pyrrol-1-yl-alcohol (*S*)-2d (4.3 g, 21 mmol, 85% yield) was obtained.

Typical procedure for the preparation of alkyl iodides of type 3: Preparation of (*S*)-1-(1-iodo-3-phenylpropan-2-yl)-1*H*-pyrrole ((*S*)-3d)

In a dry Schlenk flask, PPh₃ (6.1 g, 23 mmol, 1.1 equiv) and imidazole (1.6 g, 23 mmol, 1.1 equiv) were dissolved in dry DCM (44 mL) and cooled to 0 °C. Iodine (5.9 g, 23 mmol, 1.1 equiv) was added in three portions over a period of 10 min. The corresponding pyrrol-1-yl-alcohol (*S*)-2d (4.3 g, 21 mmol, 1.0 equiv) dissolved in dry DCM (40 mL) was added dropwise to the reaction mixture at 0 °C over a period of 30 min. The mixture was stirred for 30 min at this temperature and then warmed to 25 °C and stirred additionally for 1 h. After quenching with sat. aq. Na₂S₂O₃ solution, the organic phase was separated and the aqueous phase extracted three times with DCM. The combined organic phases were dried over CaCl₂ and solvents were evaporated. Purification by flash column chromatography (*i*-hexanes/ethyl acetate 99:1) afforded the corresponding alkyl iodide (*S*)-3d (5.5 g, 18 mmol, 84% yield, 99% *ee*).

Typical procedure for the zinc insertion into pyrrole-containing alkyl iodides: Preparation of (*S*)-(3-phenyl-2-(1*H*-pyrrol-1-yl)propyl)zinc(II) iodide ((*S*)-4d)

In a Schlenk flask, LiCl (340 mg, 8.0 mmol 1.0 equiv) and zinc dust (785 mg, 12 mmol, 1.5 equiv) were dried in vacuo. Under argon atmosphere, freshly distilled dry THF (12 mL) was added and the zinc dust was activated using 1,2-dibromoethane (35 µl, 5 mol%) and Me₃SiCl (50 µL, 5 mol%). The suspension was slightly heated with a

heat-gun until a gas formation started. Afterwards, the alkyl iodide (*S*)-3d (2.5 g, 8.0 mmol, 1.0 equiv) was added slowly and the mixture stirred at 25 °C. The reaction progress was monitored by gas chromatographic analysis of small aliquots quenched with sat. aq. NH₄Cl solution. After 10 min, the solution was passed through a syringe filter and the concentration of the organozinc reagent (*S*)-4d was determined by titration against iodine (13 mL, 0.47 M, 6.5 mmol, 82% yield).[7]

Typical procedure for palladium-catalyzed cross-coupling reactions: Preparation of ethyl (*S*)-4-(3-phenyl-2-(1*H*-pyrrol-1-yl)propyl)benzoate ((*S*)-8c)

In a dry Schlenk flask, Pd(OAc)₂ (2.3 mg, 10 µmol, 2 mol%) and SPhos (8.2 mg, 20 µmol, 4 mol%) were dissolved in freshly distilled dry THF (1 mL) and stirred for 10 min at 25 °C. Ethyl 4-iodobenzoate (140 mg, 0.5 mmol, 1.0 equiv) was added and to this mixture, the alkylzinc reagent (*S*)-4d in THF (1.3 mL, 0.47 M, 0.6 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred for 16 h at 25 °C and then quenched with sat. aq. NH₄Cl solution (1 mL). The mixture was extracted three times with EtOAc, the combined organic phases were dried over MgSO₄ and solvents were evaporated. Purification via flash column chromatography (*i*-hexanes/ethyl acetate 95:5) provided the cross-coupling product (*S*)-8c (162 mg, 0.49 mmol, 96% yield, 99% *ee*).

Typical procedure for palladium-catalyzed acylation reactions: Preparation of (*S*)-1-(3-chlorophenyl)-4-phenyl-3-(1*H*-pyrrol-1-yl)butan-1-one ((*S*)-8f)

In a dry Schlenk flask, Pd(PPh₃)₄ (23 mg, 20 µmol, 4 mol%) was dissolved in freshly distilled dry THF (1 mL) and 3-chlorobenzoyl chloride (88 mg, 0.5 mmol, 1.0 equiv) was added. To this mixture, the alkylzinc reagent (*S*)-4d in THF (1.3 mL, 0.47 M, 0.6 mmol, 1.2 equiv) was added dropwise. The reaction mixture was stirred for 16 h at 50 °C and then quenched with sat. aq. NH₄Cl solution (1 mL). The mixture was extracted three times with EtOAc, the combined organic phases were dried over MgSO₄ and solvents were evaporated. Purification via flash column chromatography (*i*-hexanes/ethyl acetate 95:5) provided the acylation product (*S*)-8f (138 mg, 0.43 mmol, 85% yield, 99% *ee*).

Typical procedure for deprotection of the pyrrole-group: Preparation of ethyl (*S*)-4-(2-formamido-3-phenylpropyl)benzoate ((*S*)-15b)

In a Schlenk flask, (*S*)-8c (334 mg, 1.0 mmol, 1.0 equiv) was dissolved in DCM (8 mL) and methanol (2 mL) and then cooled to −78 °C. Ozone was passed through the solution for 5 min and afterwards flushed with nitrogen for 10 min. Dimethyl sulfide (621 mg, 10 mmol, 10 equiv) was added and the reaction mixture stirred for 4 h at 25 °C. After evaporation of the solvents, the residue was stirred for 1 h in 10 mL KOH in ethanol (0.1 M) and afterwards ethanol was removed under reduced pressure. The crude product was purified by via flash column chromatographic purification (*i*-hexanes/ethyl acetate 1:1) and formamide derivative (*S*)-15b (230 mg, 0.74 mmol, 74% yield, 99% *ee*) was obtained.

Conflict of interest

The authors declare no conflict of interest.

[1] a) T. C. Nugent, M. El-Shazly, *Adv. Synth. Catal.* **2010**, *352*, 753; b) T. C. Nugent, *Chiral Amine Synthesis* Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim **2010**; c) M. Breuer, K. Ditrich, T. Habicher, B. Hauer, M. Kesseler, R. Stürmer, T. Zelinski, *Angew. Chem. Int. Ed.* **2004**, *43*, 788; *Angew. Chem.* **2004**, *116*, 806.

[2] a) G. Dagousset, C. François, T. León, R. Blanc, E. Sansiaume-Dagousset, P. Knochel, *Synthesis* **2014**, *46*, 3133; b) J.-M. Bégouin, C. Gosmini, *J. Org. Chem.* **2009**, *74*, 3221; c) A. Krasovskiy, V. Malakhov, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; *Angew. Chem.* **2006**, *118*, 6186; d) M.-C. Lacasse, C. Poulard, A. B. Charette, *J. Am. Chem. Soc.* **2005**, *127*, 12440; e) C. Gosmini, Y. Rollin, J. Y. Nedelec, J. Perichon, *J. Org. Chem.* **2000**, *65*, 6024; f) A. B. Charette, A. Beauchemin, J.-F. Marcoux, *J. Am. Chem. Soc.* **1998**, *120*, 5114; g) P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117.

[3] a) A. J. Ross, F. Dreiocker, M. Schäfer, J. Oomens, A. J. H. M. Meijer, B. T. Pickup, R. F. W. Jackson, *J. Org. Chem.* **2011**, *76*, 1727; b) A. J. Ross, H. L. Lang, R. F. W. Jackson, *J. Org. Chem.* **2010**, *75*, 245; c) T. Carrillo-Marquez, L. Caggiano, R. F. W. Jackson, U. Grabowska, A. Rae, M. J. Tozer, *Org. Biomol. Chem.* **2005**, *3*, 4117; d) H. J. C. Deboves, U. Grabowska, A. Rizzo, R. F. W. Jackson, *J. Chem. Soc. Perkin Trans. 1* **2000**, 4284; e) R. F. W. Jackson, K. James, M. J. Wythes, A. Wood, *J. Chem. Soc. Chem. Commun.* **1989**, 644.

[4] R. Duddu, M. Eckhardt, M. Furlong, H. P. Knoess, S. Berger, P. Knochel, *Tetrahedron* **1994**, *50*, 2415.

[5] a) C. M. L. Goddard, A. R. Massah, R. F. W. Jackson, *Tetrahedron* **2010**, *66*, 9175; b) S. Tang, S. Li, D. Zhou, H. Zeng, N. Wang, *Sci. China Chem.* **2013**, *56*, 1293.

[6] An exception to this is the electron-withdrawing protecting group TFA which has been reported to stabilize the resulting organozinc compound (see Reference [5a]).

[7] A. Krasovskiy, P. Knochel, *Synthesis* **2006**, *5*, 0890.

[8] D. A. Dickman, A. I. Meyers, G. A. Smith, R. E. Gawley, *Org. Synth.* **1985**, *63*, 136.

[9] a) B. S. Gourlay, P. P. Molesworth, J. H. Ryan, J. A. Smith, *Tetrahedron Lett.* **2006**, *47*, 799; b) C. W. Jefford, F. de Villedon de Naide, K. Sienkiewicz, *Tetrahedron: Asymmetry* **1996**, *7*, 1069.

[10] a) V. Morozova, J. Skotnitzki, K. Moriya, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 5516; *Angew. Chem.* **2018**, *130*, 5614; b) G. L. Lange, C. Gottardo, *Synth. Commun.* **1990**, *20*, 1473; c) P. J. Garegg, B. Samuelsson, *J. Chem. Soc. Perkin Trans. 1* **1980**, 2866; d) R. Appel, *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 801; *Angew. Chem.* **1975**, *87*, 863.

[11] a) T. D. Blümke, F. M. Piller, P. Knochel, *Chem. Commun.* **2010**, *46*, 4082; b) C. Feng, Q. T. Easter, S. A. Blum, *Organometallics* **2017**, *36*, 2389; c) C. Feng, D. W. Cunningham, Q. T. Easter, S. A. Blum, *J. Am. Chem. Soc.* **2016**, *138*, 11156; d) K. Jess, K. Kitagawa, T. K. S. Tagawa, S. A. Blum, *J. Am. Chem. Soc.* **2019**, *141*, 9879.

[12] a) E. Negishi, L. F. Valente, M. Kobayashi, *J. Am. Chem. Soc.* **1980**, *102*, 3298; b) E. Negishi, *Acc. Chem. Res.* **1982**, *15*, 340; c) N. Hadei, E. A. B. Kantchev, C. J. O'Brie, M. G. Organ, *Org. Lett.* **2005**, *7*, 3805; d) C. Valente, M. E. Belowich, N. Hadei, M. G. Organ, *Eur. J. Org. Chem.* **2010**, 4343; e) D. Haas, J. M. Hammann, R. Greiner, P. Knochel, *ACS Catal.* **2016**, *6*, 1540.

[13] a) T. E. Barder, S. D. Walker, J. R. Martinelli, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 4685; b) Y. Yang, N. J. Oldenhuis, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2013**, *52*, 615; *Angew. Chem.* **2013**, *125*, 643.

[14] a) R. D. Rieke, S.-H. Kim, *Tetrahedron Lett.* **2011**, *52*, 3094; b) E. Negishi, V. Bagheri, S. Chatterjee, F.-T. Luo, J. A. Miller, A. T. Stoll, *Tetrahedron Lett.* **1983**, *24*, 5181.

[15] a) H.-S. Jung, S.-H. Kim, *Tetrahedron Lett.* **2015**, *56*, 1004; b) E. Nakamura, I. Kuwajima, *J. Am. Chem. Soc.* **1984**, *106*, 3368.

[16] A. R. Massah, F. Dreiocker, R. F. W. Jackson, B. T. Pickup, J. Oomens, A. J. H. M. Meijer, M. Schäfer, *Phys. Chem. Chem. Phys.* **2011**, *13*, 13255.

[17] For the experimental procedure, see Supporting Information.

[18] H. P. Knoess, M. T. Furlong, M. J. Rozema, P. Knochel, *J. Org. Chem.* **1991**, *56*, 5974.

[19] T. Thaler, B. Haag, A. Gavryushin, K. Schober, E. Hartmann, R. M. Gschwind, H. Zipse, P. Mayer, P. Knochel, *Nat. Chem.* **2010**, *2*, 125.

[20] Structure and configuration was determined by single-crystal *x*-ray analysis; see Supporting Information.

[21] a) E. J. Corey, C. J. Helal, *Angew. Chem. Int. Ed.* **1998**, *37*, 1986; *Angew. Chem.* **1998**, *110*, 2092; b) E. J. Corey, S. Shibata, R. K. Bakshi, *J. Org. Chem.* **1988**, *53*, 2861.

[22] a) T. R. Hoye, C. S. Jeffrey, F. Shao, *Nat. Protoc.* **2007**, *2*, 2451; b) J. M. Seco, E. Quiñoá, R. Riguera, *Chem. Rev.* **2004**, *104*, 17.

[23] a) E. Tokumaru, A. Tengeiji, T. Nakahara, I. Shiina, *Chem. Lett.* **2015**, *44*, 1768; b) C. Kashima, T. Maruyama, Y. Fujioka, K. Harada, *J. Chem. Soc. Perkin Trans. 1* **1989**, 1041.

[24] a) H. Yinglin, H. Hongwen, *Synthesis* **1990**, 615; b) F. Wüst, M. B. Skaddan, P. Leibnitz, H. Spies, J. A. Katzenellenbogen, B. Johannsen, *Bioorg. Med. Chem.* **1999**, *7*, 1827.