Regiodivergent enantioselective C–H functionalization of Boc-1,3-oxazinanes for the synthesis of $\beta^2$- and $\beta^3$-amino acids

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$\beta^2$- and $\beta^3$-amino acids are important chiral building blocks for the design of new pharmaceuticals and peptidomimetics. Here, we report a straightforward regio- and enantiodivergent access to these compounds using a one-pot reaction composed of sparteine-mediated enantioselective lithiation of a Boc-1,3-oxazinane, transmetallation to zinc and direct or migratory Negishi coupling with an organic electrophile. The regioselectivity of the Negishi coupling was highly ligand-controlled and switchable to obtain the C4- or the C5-functionalized product exclusively. High enantioselectivities were achieved on a broad range of examples, and a catalytic version in chiral diaminé was developed using the (−)-sparteine surrogate. Selected C4- and C5-functionalized Boc-1,3-oxazinanes were subsequently converted to highly enantoenriched $\beta^2$- and $\beta^3$-amino acids with the (R) or (S) configuration, depending on the sparteine enantiomer employed in the lithiation step.

$\beta^2$-amino acids substituted at the 2 and 3 positions, named $\beta^2$- and $\beta^3$-amino acids, respectively, are very important chiral substructures found in natural products and active pharmaceutical ingredients (Fig. 1). In particular, the incorporation of $\beta$-amino acids into peptides allows modulation of their secondary structure and increase of their proteolytic stability, hence furnishing peptidomimetics with improved pharmacological value. Although much progress has been made in the enantioselective synthesis of $\beta$-amino acids, more direct and versatile methods are still highly sought after.

Migratory cross-couplings have emerged as interesting new methods to functionalize remote positions of alkyl chains and cyclic systems. In particular, our group has shown that the use of appropriate ligands of palladium-based catalysts allows functionalization of various positions of the same reactant in a regiocontrolled fashion through a Pd migration mechanism. For instance, the Negishi coupling of racemic $\alpha$-zincated Boc-piperidine, generated by Boc-directed $\alpha$-lithiation of Boc-piperidine 1 with $s$-BuLi/$N,N',N''$-tetramethylethylenediamine (TMEDA) and transmetallation to zinc, leads to the C2- and C3-arylated racemic products 2–3 with good positional selectivity in the presence of appropriate phosphine ligands $L^1$–$L^2$ (Fig. 2a). In principle, enantioselective versions of these one-pot reactions may be developed by using a chiral base in the initial lithiation step (selected enantioselective migratory cross-couplings involving carb-o- or hydropalladation of olefins are given in refs. 16–18). Indeed, in a seminal work, Campos and co-workers showed that the enantioselective lithiation of Boc-pyrrroldine 4 in the presence of (−)-sp (sp represents sparteine) 14, followed by one-pot Li–Zn transmetallation and Negishi coupling, furnished C2-arylated products 5 efficiently and with high enantioselectivities, reflecting the enantiospecific nature of the Li–Zn transmetallation and cross-coupling steps (Fig. 2b). However, transposition to N-Boc-piperidine 1 was unsuccessful due to the lack of reactivity of the $s$-BuLi•sp complex towards this substrate. O’Brien and co-workers designed a less hindered surrogate of (−)-sp that provided enhanced reactivity in the lithiation step, but a modest yield and moderate enantioselectivity were observed in the Negishi arylation leading to product 6 (ref. 19). These precedents, together with unsuccessful attempts employing other enantioselective lithiations, discouraged us from developing an enantioselective C3-selective arylation of Boc-piperidine 1. Alternatively, we turned to Boc-1,3-oxazinanes 7, which are protected forms of 3-amino propanol, and hence very appealing substrates that could be used to develop a regiodivergent enantioselective functionalization strategy (Fig. 2c).

The enantioselective lithiation of 7 with (−)-sp, which is currently unknown (the non-enantioselective $\alpha$-lithiation of 2-methyl-Boc-oxazinane with $s$-BuLi/TMEDA was reported in ref. 16), for the enantioselective lithiation of a Boc-piperazine see ref. 19, would furnish $\alpha$-lithiated intermediate A on deprotonation of the pro–S hydrogen atom. Sequential transmetallations with ZnCl$_2$ and the oxidative addition complex generated from Pd$^{II}$/L and an electrophile R–X would afford complex B in a stereoretentive manner. In the presence of a bulky ligand such as $L^1$ (see Fig. 2a), reductive elimination should be favoured to give the C4-functionalized product 8. In the presence of a less bulky and more conformationally flexible ligand such as $L^2$ (refs. 20), stereospecific Pd migration should occur from B, based on previous calculations, via $\beta$-hydride elimination, providing complex C wherein Pd would remain bound to the same face of the molecule. $\pi$-bond rotation and migratory insertion would deliver complex D, which would undergo reductive elimination to give rise to the enantoenriched C5-functionalized product 9.

Isomers 8 and 9 would be simple precursors of $\beta^2$-amino acid 10 and $\beta^3$-amino acid 11, respectively, on aminal cleavage and oxidation. Using (−)-sp (both enantiomers of sparteine are commercially available or readily prepared in micromgram quantities from the seeds of Lupinus albus) instead of (−)-sp in the initial lithiation step would provide access to the enantioenriched end products ent-10 and ent-11 through the same sequence.

Here we show that Boc-oxazinanes are lithiated efficiently and with high enantioselectivity using either stoichiometric or substoichiometric amounts of chiral base, and that the corresponding organozinc compounds obtained on Li–Zn transmetallation...
undergo regiodivergent Negishi cross-coupling with nearly perfect ligand-controlled regioselectivity to give highly enantioenriched C4- and C5-functionalized products. The latter can be converted to valuable β2- and β3-amino acids on aminal cleavage and oxidation.

Results

Optimization of the reaction conditions. We began our studies by investigating the one-pot arylation of Boc-1,3-oxazinanes 7a–d containing various C2 substituents, which were easily synthesized in two steps from 3-aminopropanol and various ketones (Table 1; see also Supplementary Table 1). The lithiation of compound 7a with the achiral s-BuLi•TMEDA complex, followed by transmetalation with ZnCl2 and cross-coupling with bromobenzene in the presence of the very bulky ligand L1, which we recently developed to avoid Pd migration in related Negishi couplings, furnished the C4-arylated product 8aa exclusively in moderate yield (entry 1). Using (+)-sp instead of TMEDA in the lithiation step furnished a promising enantiomeric ratio (e.r.) of 75:25 (entry 2). Gratifyingly, replacing the methyl with ethyl groups on the oxazinane (7b) allowed an increase of the e.r. to 95:5 (entry 3). The less hindered (+)-sp surrogate (according to ref. 22) furnished a lower yield and enantioselectivity (entry 4). Further increasing the size of the Z groups was detrimental to the yield (entry 5). Finally, tuning the conditions by replacing ZnCl2 with Zn(OAc)2, phenyl bromide with phenyl nonaflate, and raising the cross-coupling temperature to 80 °C gave an improved efficiency (61%) and enantioselectivity (e.r. 97:3; entry 6). Then, we switched the ligand of the cross-coupling step to the less hindered and conformationally more flexible phosphine L2, which was previously designed to favour the migratory coupling of Boc-piperidines. Using substrate 7a and TMEDA in the lithiation step, the arylation site selectivity was completely switched to the C5 position, with no trace of C4 isomer (entry 7). This ligand-controlled, total switch of selectivity in favour of the migratory arylation is remarkable, since we always obtained mixtures of isomers during previous studies on migratory couplings using an unbiased electrophile (for example, Fig. 2a). This behaviour might be related to the higher propensity of the 1,3-oxazinane, as compared to the piperidine ring, to reach the twist-boat conformation required for the alignment of the C–Pd and C–H bonds for the β-H elimination step initiating Pd migration. Moreover, the selectivity switch exerted by ligands L2–L4 can be explained by steric factors, that is, the steric environment of the phosphorus atom and the rotation around the C–N axis, according to previous studies. Replacing TMEDA with (+)-sp provided 1,3-oxazinane 9aa with a similar e.r. (77:5.22:5) to the one observed for the C4-arylated product 8aa (75:25, entry 2), showing that the migration occurs with high enantiospecificity. In this case, increasing the bulk of the Z substituents (entries 9, 11 and 12) furnished an optimal yield for n-propyl groups (entry 11), together with a high enantiospecificity. Similar to the C5-selective arylation, the (+)-sp surrogate gave a slightly lower e.r. than (+)-sp (entry 10, compare with entry 9). Parteine was kept for subsequent studies due to its lower price and the higher availability of both enantiomers.

Configuration and deuterium labelling. The absolute configuration of the arylated 1,3-oxazinanes 8ab and 9ac obtained using (+)-sp was determined to be (S) after cleavage of the aminal and comparison of the specific rotations of the corresponding Boc-aminoalcohols with literature data (see Supplementary References). In addition, quenching the organolithium intermediate obtained from 7c and (−)-sp with dimethyl sulfate followed by controlled aminal cleavage led to the known Boc-aminoalcohol possessing the opposite orientation of the methyl group and the (S) configuration (Fig. 3a). This absolute configuration is expected from the parteine-mediated enantioselective lithiations of other Boc-amines, which always give the same induction sense. In addition, the fact that the same sense of enantioselectivity is observed for compounds 12, 8ab and 9ac using a given enantiomer of sp confirms the expected stereoretentive nature of the various elementary steps depicted in Fig. 2c. Deuterium labelling experiments provided complementary insights (Fig. 3b). Performing the lithiation of 7b and 7c with the s-BuLi•(-)-sp complex/trapping with CD3OD twice, as reported by Hoppe, led to the deuterated 1,3-oxazinanes 7b-D and 7c-D with 96% and 98% deuterium incorporation at the C4 position, respectively. Then, lithiating compound 7b-D with the achiral s-BuLi•TMEDA complex and performing the C4-selective arylation under the same conditions as above furnished product 8ab-D with the same (S) absolute configuration as 8ab obtained using (+)-sp, with the same deuterium content as 7b-D and an e.r. of 95:5. The latter matches the theoretical value calculated with an e.r. of 97:3 for the sp-mediated lithiation step and the 96% deuterium incorporation (see Supplementary Fig. 1). These values translate a very large kinetic isotope effect in the TMEDA-mediated lithiation. Similarly large kinetic isotope effects (kD/kH > 30) were already reported by Hoppe and Beak for the lithiation of O- and N-carbamates, respectively, and were ascribed to the tunnel effect. Performing the C5-selective arylation from 7c-D led to a similar outcome, with (S)-9ac-D being produced with a 97% deuterium content and an e.r. of 96:4. These results might be further exploited to synthesize isotopically-labelled β-amino acids.

Scope of the C4 and C5 functionalization using stoichiometric parteine. Using the optimal conditions, the scope of the C4 and C5 functionalization was next examined using (+)-sp as the chiral diamine (Fig. 4; see also Supplementary Fig. 2). The C5 functionalization (Fig. 4b) was found to be more general than the C4 functionalization (Fig. 4a), as the latter was mainly limited to aryl and heteroaryl nonaflates bearing substituents at the para or meta positions. This is probably due to the fact that the C4 position is more sterically hindered than the C5. Nevertheless, this C4 arylation performed satisfyingly with a range of aryl nonaflates containing electronically diverse substituents at the para (8b–f) and meta (8g–i) positions. More substituted aryl groups were also compatible (8j,8k), as well as a naphthyl ring (8l) and diverse heteroaromatic...
Surprisingly, an approximately 3:1 mixture of the C5 and C6 isomers was isolated using 3-bromopyridine (see Fig. 4b). The C6 isomer was n\textsuperscript{a} detected in other cases, and the reason for this singularity is unclear at this point. In addition to (hetero)aryl bromides, alkene hydride elimination products are potential precursors of \( \text{N-Boc} \)-1,3-oxazinanes and application to the synthesis of \( \beta \)-amino acids. Boc, tert-butyloxycarbonyl; \( s-\text{BuLi} \), sec-butyllithium; dba, dibenzylideneacetone; cat., catalytic; NN\textsuperscript{*}, chiral diamine; r.t., room temperature.

Fig. 2 | Lithiation/Negishi coupling of cyclic Boc-amines. a, The Negishi coupling of \( \alpha \)-zincated Boc-piperidine furnish racemic C2 (2) and C3 (3) arylated products with good site selectivity in the presence of appropriate phosphine ligands L\textsuperscript{1}-L\textsuperscript{2}. b, Enantioselective lithiation and direct Negishi coupling is effective for Boc-pyridylidine, but not for Boc-piperidine. c, This work: design of a site- and enantioselective functionalization of Boc-1,3-oxazinanes and application to the synthesis of \( \beta \)-amino acids. Boc, tert-butyloxycarbonyl; \( s-\text{BuLi} \), sec-butyllithium; dba, dibenzylideneacetone; cat., catalytic; NN\textsuperscript{*}, chiral diamine; r.t., room temperature.

As mentioned above, the scope of the C5 functionalization was found to be broader than the C4 functionalization (Fig. 4b). In addition to \( \text{meta} \raiseprocess\text{(9i,9j)} \)- and \( \text{para} \raiseprocess\text{(9b-h)} \)-substituted aryl bromides, \( \text{ortho} \raiseprocess\text{(9k,9l)} \)-substituted aryl bromides could be employed (9k,9l). However, for product 9l bearing a strong electron-withdrawing \( \text{CF}_3 \) group, ligand L\textsuperscript{4} (DavePhos)\textsuperscript{a} afforded an improved efficiency, as previously observed with Boc-piperidines.\textsuperscript{a} Disubstituted arenes (9m,9n), a naphthalene (9o) and heteroarenes (9p-r) could be employed with similar levels of efficiency and enantioselectivity. Surprisingly, an approximately 3:1 mixture of the C5 and C6 isomers was isolated using 3-bromopyridine (see 9p). The C6 isomer was not detected in other cases, and the reason for this singularity is unclear at this point. In addition to (hetero)aryl bromides, alkenyl bromides also reacted successfully, as illustrated with products 9s-v. Once again, good yields and high enantioselectivities (e.r. 92:8 to 96:4) were achieved across all examples, and the corresponding products are potential precursors of \( \beta \raiseprocess\text{2-} \)amino acids containing a range of useful functional groups on further transformation of the alkene. In addition, similar to C4 functionalization, the use of \( \text{(-)} \raiseprocess\text{-sp} \) afforded the \( \text{(R)} \raiseprocess\text{-} \)enantiomers of products 9ac, 9e, 9h, 9j, 9n, 9o, 9r and 9v with similarly good yields and enantioselectivities. Finally, the reaction leading to product \( \text{(R)} \raiseprocess\text{-} \text{9e} \raiseprocess\text{could be conducted on a gram scale with similar efficiency and enantioselectivity. Importantly, a simple aqueous extraction allowed recovery of 85% of the engaged \( \text{(-)} \raiseprocess\text{-sp} \).}

Development of a catalytic enantioselective version. Next, we turned to the development of a catalytic enantioselective version of this method via the diamine exchange method (Fig. 5). Indeed, O’Brien and co-workers reported the enantioselective deprotonation of Boc-pyrrolidine using a combination of substoichiometric \( \text{(-)} \raiseprocess\text{-sp} \raiseprocess\text{or \( \text{(R)} \raiseprocess\text{-} \raiseprocess\text{surrogate and stoichiometric diisopropylbispidine, which is an achiral diamine that reacts slowly in the lithiation with \( s-\text{BuLi} 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satisfaction, electrophiles. The yields and enantioselectivities were applied to both C4- and C5-selective arylations with a few aryl β34 to synthesize both enantiomers of β-amino acids. The deuterium content was measured by high performance liquid chromatography (HPLC) on a chiral stationary phase. Cross-coupling step performed at 60 °C instead of 80 °C.

Table 1 | Effect of selected parameters on the arylation of Boc-1,3-oxazinanes

| Entry | Z | Reactant | Diamine | Ligand | 8/9<sup>+</sup> | Product | Yield (%)<sup>c</sup> | e.r.<sup>d</sup> |
|-------|---|----------|---------|--------|--------------|---------|----------------|--------|
| 1<sup>a</sup> | Me | 7a | TMEDA | L<sup>2</sup> | >98:2 | 8aa | 54 | - |
| 2<sup>b</sup> | Me | 7a | (+)-sp | L<sup>3</sup> | >98:2 | 8aa | 53 | 75:25 |
| 3<sup>b</sup> | Et | 7b | (+)-sp | L<sup>3</sup> | >98:2 | 8ab | 51 | 95:5 |
| 4<sup>a</sup> | Et | 7b | (+)-sp surrogate | L<sup>2</sup> | >98:2 | 8ab | 46 | 91:9 |
| 5<sup>a</sup> | n-Pr | 7c | (+)-sp | L<sup>3</sup> | >98:2 | 8ac | 30 | 94:6 |
| 6<sup>a</sup> | Et | 7b | (+)-sp | L<sup>3</sup> | >98:2 | 8ab | 61 | 97:3 |
| 7 | Me | 7a | TMEDA | L<sup>2</sup> | ≤2:98 | 9aa | 65 | - |
| 9 | Et | 7b | (+)-sp | L<sup>3</sup> | ≤2:98 | 9ab | 48 | 97:3 |
| 10 | Et | 7b | (+)-sp surrogate | L<sup>2</sup> | ≤2:98 | 9ab | 89 | 94:6 |
| 11<sup>g</sup> | n-Pr | 7c | (+)-sp | L<sup>2</sup> | ≤2:98 | 9ac | 72 | 96:5:3:5 |
| 12 | –(CH<sub>2</sub>)<sub>4</sub>– | 7d | (+)-sp | L<sup>2</sup> | ≤2:98 | 9ad | 23 | 85:15 |

Reaction conditions unless otherwise stated: 7 (1.0 equiv.), s-BuLi (1.2 equiv.), diamin (1.2 equiv.), Et<sub>3</sub>O, -78 °C, 8 h, then ZnCl<sub>2</sub>/tetrahydrofuran (THF) (1.2 equiv.), -78 to 20 °C, 1 h, then removal of volatiles, then PhBr (0.7 equiv.), Pd<sub>2</sub>dba<sub>3</sub> (2.5 mol%), ligand (5 mol%), toluene, 80 °C, 17-24 h. *Measured by gas chromatography-mass spectrometry or ¹H nuclear magnetic resonance (NMR) analysis of the crude reaction mixture. Yields of the isolated product. Determined by high performance liquid chromatography (HPLC) on a chiral stationary phase. Cross-coupling step performed at 60 °C instead of 80 °C.

Using Zn(OAc)<sub>2</sub> instead of ZnCl<sub>2</sub> and PhONf instead of PhBr. Conditions employed in Figs. 3–4. Nf, SO<sub>2</sub>(CF<sub>2</sub>)<sub>3</sub>CF<sub>3</sub>.

Application to the synthesis of β<sup>2</sup>- and β<sup>3</sup>-amino acids. To achieve our initial goal, we finally studied the transformation of selected C4- and C5-functionalized 1,3-oxazinanes into β<sup>2</sup>- and β<sup>3</sup>-amino acids (Fig. 6). A simple treatment with trifluoroacetic acid (TFA) in THF effected the cleavage of the aminal group to give the corresponding N-Boc-1,3-aminoalcohols, which are valuable chiral intermediates for asymmetric synthesis in their own right. Then, two one-step procedures were employed for their oxidation to the corresponding β-amino acids. Sharpless’ oxidation was employed for the less sensitive aminoalcohols (method A)<sup>36</sup>, whereas the method employing catalytic 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and stoichiometric (diazetoxiyiodo) benzene (PIDA) was preferred for more sensitive ones (method B)<sup>37</sup>. Selected functionalized oxazinanes 8–9 were hence converted to over 20 valuable β<sup>2</sup>- and β<sup>3</sup>-amino acids 10–11, most of them being new, bearing (hetero)aryl or alkenyl substituents in good yield and excellent enantiospecificity, thereby preserving the enantioselectivity achieved in the initial lithiation step. Notably, the racemization of the more sensitive β<sup>3</sup>-amino acids 11 was not observed under these conditions. Both (R) and (S) enantiomers of the β-amino acids are accessible through this method by simply changing the sparteine enantiomer in the lithiation step of the overall sequence. The X-ray diffraction analysis of product 11a obtained using (+)-sp confirmed the absolute configurations deduced from the comparison of specific rotations of the known β-aminoalcohols (12, precursors of 10c and 10f) and acids (10a, 10c and 11a) synthesized in this study with the corresponding literature values. Of note, compound (R)-10c is a potential.

accessible, and hence this catalytic version can also be applied to synthesize both enantiomers of β-amino acids<sup>41</sup>. These conditions were applied to both C4- and C5-selective arylations with a few aryl electrophiles. The yields and enantioselectivities were satisfying,
precursor of the β1-amino acid found in jasplakinolide (Fig. 1), on cleavage of the methoxy group. Similarly, compound (S)-11e is a potential precursor of the β2-amino acid found in netarsudil on reduction of the carboxylic ester. These two examples further illustrate the interest of the current methodology for the synthesis of bioactive molecules.
Fig. 5 | Development of proof-of-concept catalytic enantioselective C4 and C5 arylation. Reaction conditions: 7 (1.0 equiv.), s-BuLi (1.2 equiv.), (+)-sp surrogate (0.3 equiv.), diisopropylbispindine (1.3 equiv.), Et₂O, -78 °C, 8 h, then Zn(OAc)₂ (1.2 equiv., C4 arylation) or ZnCl₂ (1.2 equiv., C5 arylation), THF, -78→20 °C, 1 h, then removal of volatiles, then R–X (0.7 equiv.), Pd₂dba₃ (2.5 mol%), ligand (5 mol%), toluene, 80 °C, 17 h. aUsing (+)-sp instead of the (+)-sp surrogate.

Fig. 6 | Application to the synthesis of β⁻ and β⁺-amino acids. Reaction conditions: 1. TFA, THF, 20 °C. 2. Method A: RuCl₃ (5 mol%), NaIO₄ (3 equiv.), CH₃CN/H₂O, 20 °C. Method B: TEMPO (20 mol%), PIDA (2 equiv.), CH₂Cl₂/H₂O, 20 °C. (S) enantiomers were obtained with (+)-sp and (R) enantiomers with (-)-sp. Yields in parentheses refer to the overall sequence from Boc-1,3-oxazinanes 7b, 7c. The values of e.r. were determined after derivatization to the corresponding methyl esters. aObtained using method A. bObtained using method B. cThermal ellipsoids shown at 50% probability.
Conclusion
Boc-1,3-oxazinanes are unique platforms for the selective functionalization at the C4 or C5 position using the one-pot directed lithiation, Li–Zn transmetallation and Negishi cross-coupling sequence. The regioselectivity of the cross-coupling step is totally ligand-controlled, and high enantioselectivities can be achieved for both C4 and C5 iso- mers using a chiral diamine in the lithiation step, by taking advantage of the enantiospecific character of the subsequent steps. A simple two- step transformation of the coupling products leads to enantioenriched β2- and β3-amino acids, which are important building blocks for the design of new pharmaceuticals and peptidomimetics.

Data availability
Data supporting the findings of this study are available in the Supplementary Information or from the corresponding author upon request. The Supplementary Information contains full details on the synthesis and characterization of compounds. CCDC 1913804 (compound (R)-11a) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures/.

Received: 17 May 2019; Accepted: 26 July 2019; Published online: 9 September 2019

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Acknowledgements
This work was financially supported by the Swiss National Science Foundation (grant no. 200012_165987) and the University of Basel. We thank A. Prescimone, University of Basel, for X-ray diffraction analysis, D. Haussinger, University of Basel, for NMR experiments, S. Mittelheuser and M. Pfeffer, University of Basel, for mass spectrometry analysis and J. Rotzler and F. Bächle (Solvias AG) for fruitful discussions.

Author contributions
W.L. and K.-F.Z. designed and performed the experiments, analysed the experimental data and prepared the Supplementary Information. O.B. directed the investigations and J. Rotzler and F. Bächle (Solvias AG) for fruitful discussions.

Competing interests
The authors declare no competing interests.