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Regiodivergent enantioselective C–H functionalization of Boc-1,3-oxazinanes and application to the synthesis of β² and β³-amino acids

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Abstract

β[2]- and β[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 diamine was developed using the (+)-sparteine surrogate. Selected C4- and C5-functionalized Boc-1,3-oxazinanes were subsequently converted to highly enantio-enriched β[2]- and β[3]-amino acids with the (*R*) or (*S*) configuration, depending on the sparteine enantiomer employed in the lithiation step.

Introduction

β-Amino acids substituted at the 2- and 3-positions, named β[2]- and β[3]-amino acids, respectively, are very important chiral substructures found in natural products and active pharmaceutical ingredients (Fig. 1).[1–3] In particular, their incorporation into peptides allows modulating the secondary structure of the latter and increasing their proteolytic stability, hence furnishing peptidomimetics with improved pharmacological value.[4–5] Although much

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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 crystallo-graphic 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/.

Author contributions
W.L. and K.-F.Z. designed and performed the experiments, analyzed experimental data and prepared the Supplementary Information. O.B. directed the investigations and prepared the manuscript.

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progress has been made in the enantioselective synthesis of β-amino acids, more direct and versatile methods are still highly sought after.[3]

Migratory cross-couplings have emerged as interesting new methods to functionalize remote positions of alkyl chains and cyclic systems.[6–8] In particular, our group showed 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.[7] For instance, the Negishi coupling of racemic α-zincated Boc-piperidine, generated by Boc-directed α-lithiation of Boc-piperidine **1** with *s*-BuLi/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 $\mathbf{L^1}$-$\mathbf{L^2}$ (Fig. 2a).[9] In principle, enantioselective versions of these one-pot reactions may be developed by using a chiral base in the initial lithiation step.[10–14] Indeed, in a seminal work, Campos and co-workers showed that the enantioselective lithiation of Boc-pyrrolidine **4** in the presence of (–)-sp (sp = sparteine),[15] 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).[16] However, transposition to *N*-Bocpiperidine **1** was unsuccessful due to the lack of reactivity of the *s*-BuLi•sp complex towards this substrate.[17] O'Brien and co-workers designed a less hindered surrogate of (+)-sp which provided enhanced reactivity in the lithiation step, but a modest yield and moderate enantioselectivity were observed in the Negishi arylation leading to product **6**.[18] 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-aminopropanol, and hence very appealing substrates to develop a regiodivergent enantioselective functionalization strategy (Fig. 2c). The enantioselective lithiation of **7** with (–)-sp, which is currently unknown,[19,20] would furnish α-lithiated intermediate **A** upon deprotonation of the pro-*S* hydrogen atom.[15,17] Sequential transmetallations with $ZnCl_2$ and the oxidative addition complex generated from Pd^0/L and an electrophile R–X would afford complex **B** in a stereoretentive manner. In the presence of a bulky ligand such as $\mathbf{L^1}$ (see Fig. 2a), reductive elimination should be favored to give the C4-functionalized product **8**. In the presence of a less bulky and more conformationally flexible ligand such as $\mathbf{L^2}$,[7,9] stereospecific Pd migration should occur from **B**, based on previous calculations,[9] via β-hydride elimination, providing complex **C** wherein Pd would remain bound to the same face of the molecule. π-Bond rotation and migratory insertion would deliver complex **D**, which would undergo reductive elimination to give rise to the enantioenriched C5-functionalized product **9**. Isomers **8** and **9** would be simple precursors of β^3-amino acid **10** and β^2-amino acid **11**, respectively, upon aminal cleavage and oxidation. Using (+)-sp[21] instead of (–)-sp in the initial lithiation step would provide access to the enantiomeric 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 upon 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 β^2- and β^3-amino acids upon 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 transmetallation with $ZnCl_2$ and cross-coupling with bromobenzene in the presence of the very bulky ligand $\mathbf{L^3}$, which we recently developed to avoid Pd migration in related Negishi couplings,[22] furnished the C4-arylated product **8aa** exclusively in moderate yield (entry 1). Using (+)-sp instead of TMEDA in the lithiation step furnished a promising e.r. of 75:25 (entry 2). Gratifyingly, replacing the methyl with ethyl groups on the oxazinane (**7b**) allowed increasing the e.r. to 95:5 (entry 3). The less hindered (+)-sp surrogate[23] 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 $ZnCl_2$ with $Zn(OAc)_2$,[24] phenyl bromide with phenyl nonaflate,[22,25] 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 $\mathbf{L^2}$, which was previously designed to favor the migratory coupling of Boc-piperidines.[9] 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 favor of the migratory arylation is remarkable, since we always obtained mixtures of isomers during previous studies on migratory couplings using an unbiased electrophile (e.g., Fig. 2a).[7,9,26–28] This behavior 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 to align the C–Pd and C–H bonds for the β-H elimination step initiating Pd migration.[9] Moreover, the selectivity switch exerted by ligands $\mathbf{L^2}$-$\mathbf{L^3}$ can be explained by steric factors, i. e. the steric environment of the phosphorus atom and the rotation around the C–N axis, according to previous studies.[9,22,27] 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), thus showing that the migration occurs with high enantiospecificity. In this case, increasing the bulk of the Z substituents (entries 9, 11, 12) furnished an optimal yield for *n*-propyl groups (entry 11), together with a high enantioselectivity. Similar to the C5-selective arylation, the (+)-sp surrogate gave a slightly lower e.r. than with (+)-sp (entry 10, compare with entry 9). Sparteine was kept for subsequent studies due to its lower price and 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 **12** possessing the opposite orientation of the methyl group and the (*S*) configuration (Fig. 3a). This absolute configuration is expected from the sparteine-mediated enantioselective lithiations of other Boc-amines, which always give the same induction sense.[15–18] 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 CD_3OD twice, as reported by Hoppe,[29] 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 Figure 1). These values translate the fact that the TMEDA-mediated lithiation occurs with a very large kinetic isotope effect (KIE). Similarly large KIEs ($k_H/k_D > 30$) were already reported by Hoppe[29] and Beak[30] for the lithiation of *O*- and *N*-carbamates, respectively, and were ascribed to the tunnel effect.[31] 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 sparteine

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 Figure 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-k**), as well as a naphthyl ring (**8l**) and diverse heteroaromatic systems (**8m-p**). In all cases, similar results were obtained, with yields in the range of 45-71% and excellent e.r. values (95:5-97:3) for the (*S*) enantiomers. As expected, simply using (–)-sp instead of (+)-sp in the lithiation step afforded the (*R*) enantiomers of **8c**, **8f**, **8j** and **8l** with similar levels of efficiency and enantioselectivity, hence demonstrating the enantiodivergent character of this method.

As mentioned above, the scope of the C5 functionalization was found to be broader than the C4 functionalization (Fig. 4b). In addition to *para* (**9b-h**) and *meta* (**9i-j**)-substituted aryl bromides, *ortho*-substituted aryl bromides could be employed (**9k-l**). However, for product **9l** bearing a strong electron-withdrawing CF_3 group, ligand $\mathbf{L^4}$ (DavePhos)[32] afforded an improved efficiency, as previously observed with Boc-piperidines.[9] Disubstituted arenes

(**9m-n**), a naphthalene (**9o**) and heteroarenes (**9p-r**) could be employed with similar levels of efficiency and enantioselectivity. Surprisingly, a ca. 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. 92:8-96:4) were achieved across all examples, and the corresponding products are potential precursors of β^2-amino acids containing a range of useful functional groups upon further transformation of the alkene. In addition, similar to C4 functionalization, the use of (–)-sp afforded the (*R*) enantiomers of products **9ac**, **9e**, **9h**, **9j**, **9n**, **9o**, **9r** and **9v** with similarly good yields and enantioselectivities. Finally, the reaction leading to product (*R*)-**9e** could be conducted on gram scale with similar efficiency and enantioselectivity. Importantly, a simple aqueous extraction allowed to recover 85% of the engaged (–)-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 (–)-sp or (+)-sp surrogate and stoichiometric diisopropylbispidine, an achiral diamine which reacts slowly in the lithiation with *s*-BuLi but is able to exchange with the chiral diamine on the lithiated intermediate.[33–34] Different chiral diamines (0.3 equiv) were first tested in combination with diisopropylbispidine (1.3 equiv) in the C5-arylation providing (*S*)-**9c**, and consistent with O'Brien's results the (+)-sp surrogate provided the best yield, together with a satisfying e.r. of 93:7. As a comparison, compound **9c** was obtained in 18% yield, 95:5 e.r. using (+)-sp instead of the (+)-sp surrogate in combination with diisopropylbispidine, which probably indicates that (+)-sp is not easily displaced by diisopropylbispidine, unlike the (+)-sp surrogate. It should be noted that both enantiomers of the sparteine surrogate are in principle accessible, and hence this catalytic version can be also applied to synthesize both enantiomers of β-amino acids.[35] These conditions were applied to both C4- and C5-selective arylations with a few aryl electrophiles. The yields and enantioselectivities were satisfying, although generally lower than those obtained with stoichiometric (+)-sp (compare to Fig. 4). Indeed, the enantioselectivity induced by the (+)-sp surrogate in the lithiation step is lower than (+)-sp (see Table 1). Nevertheless, these results represent a solid proof of concept showing the feasibility of catalytic enantioselective divergent functionalization.

Application to the synthesis of β^2- and β^3-amino acids

To achieve our initial goal, we finally studied the transformation of selected C4- and C5-functionalized 1,3-oxazinanes into β^2- and β^3-amino acids (Fig. 6). A simple treatment with 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.[36] 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),[37] whereas the method employing catalytic TEMPO and stoichiometric PIDA was preferred for more sensitive ones (method B).[38] Selected functionalized oxazinanes **8-9** were hence converted to over twenty valuable β^2- and β^3-

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^2-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-amino alcohols (**12**, precursors of **10c** and **10l**) and acids (**10a**, **10e**, **11a**) synthesized in this study with the corresponding literature values. Of note, compound (*R*)-**10c** is a potential precursor of the β^3-amino acid found in jasplakinolide (Fig. 1), upon cleavage of the methoxy group. Similarly, compound (*S*)-**11e** is a potential precursor of the β^2-amino acid found in netarsudil upon reduction of the carboxylic ester. These two examples further illustrate the interest of the current methodology for the synthesis of bioactive molecules.

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 highly ligand-controlled, and high enantioselectivities can be achieved for both C4- and C5-isomers 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 β^2- and β^3-amino acids, which are important building blocks for the design of new pharmaceuticals and peptidomimetics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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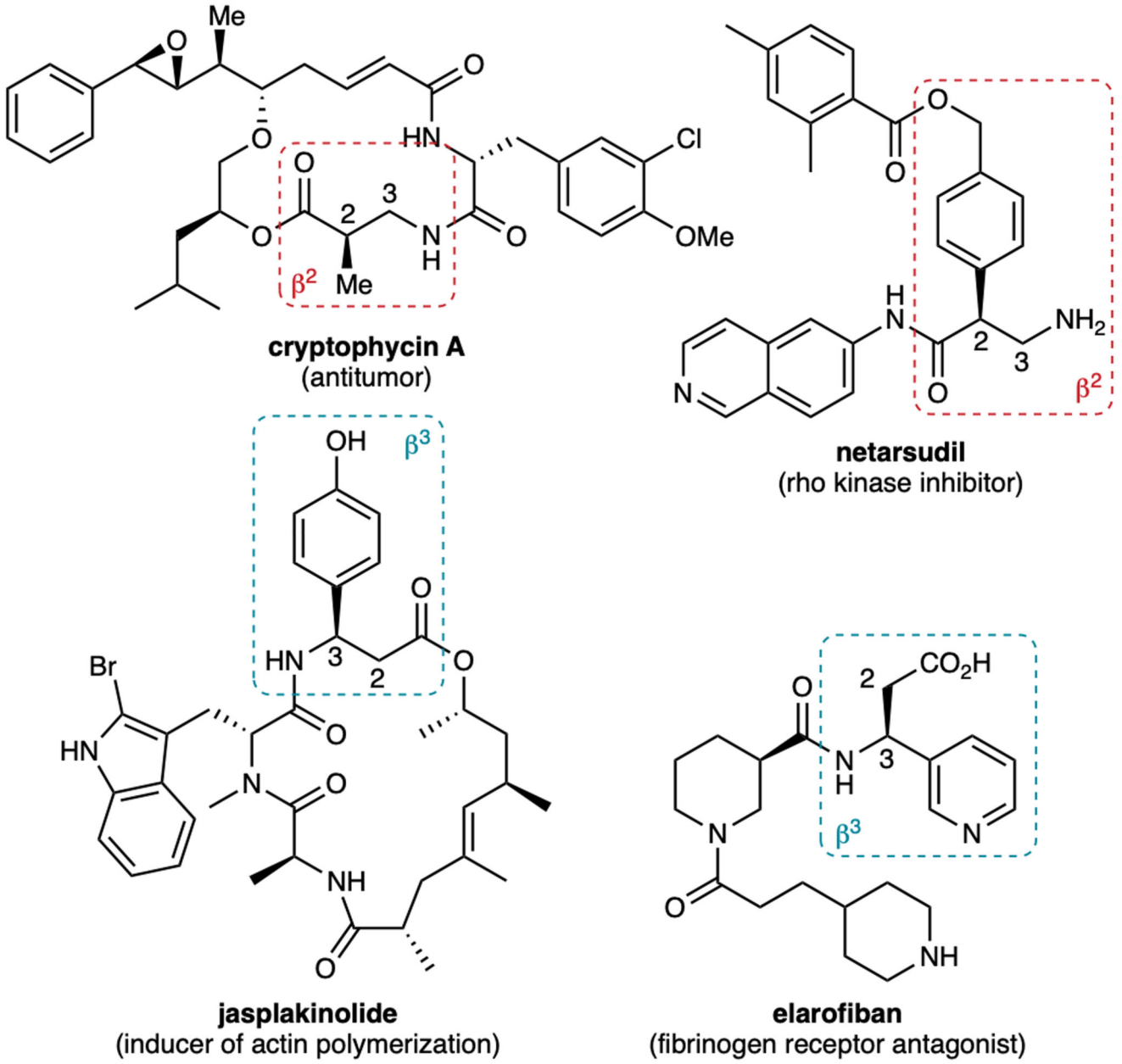

Fig. 1.

Examples of natural products and active pharmaceutical ingredients containing β^2- and β^3-amino acids.

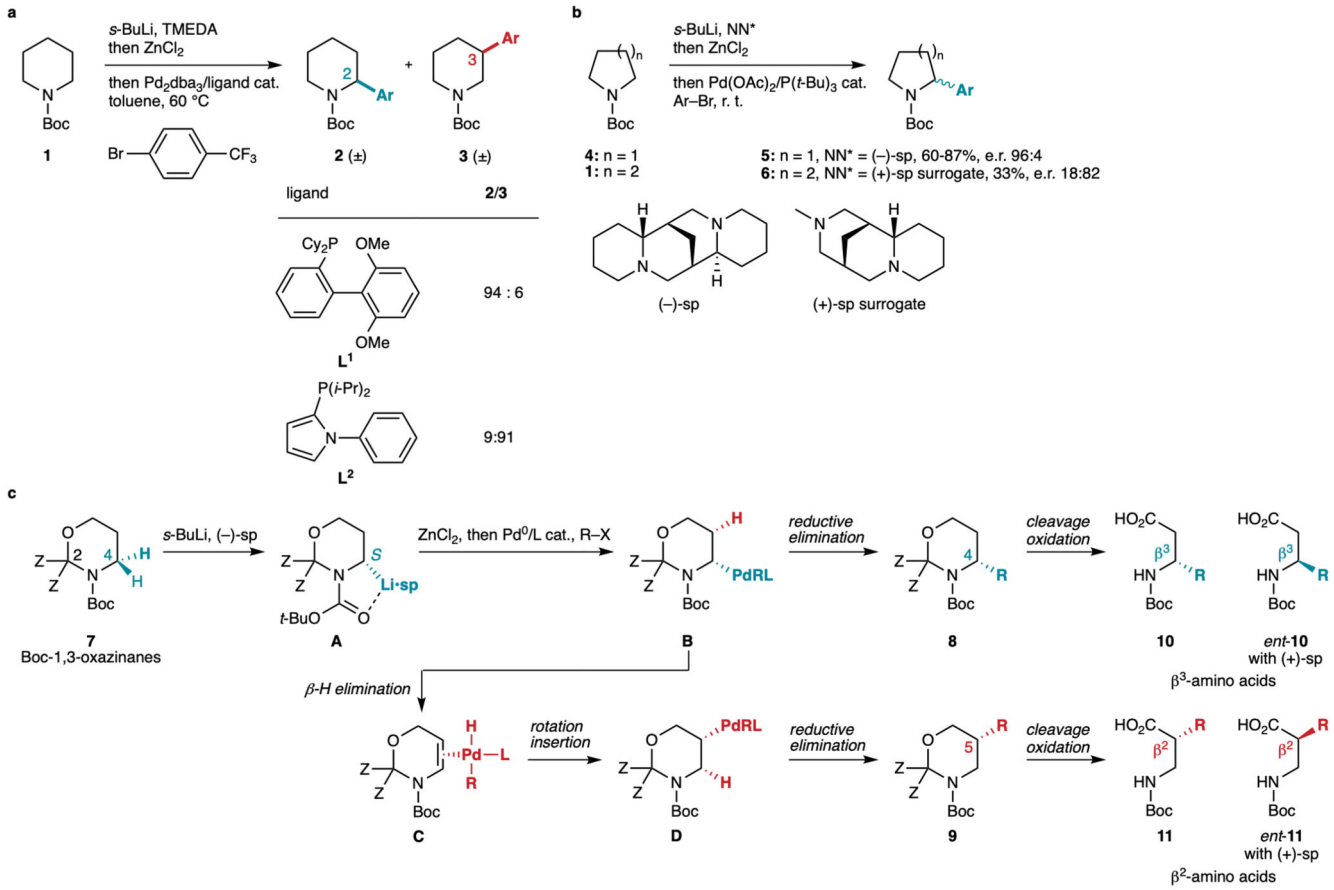

Fig. 2.

Lithiation/Negishi coupling of cyclic Boc-amines. a, The Negishi coupling of α-zincated Boc-piperidine **1** furnishes racemic C-2 (**2**) and C-3 (**3**) arylated products with good site-selectivity in the presence of appropriate phosphine ligands $\mathbf{L^1}$-$\mathbf{L^2}$. **b,** Enantioselective lithiation and direct Negishi coupling is effective for Boc-pyrrolidine, 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 β-amino acids. Boc = *tert*-butyloxycarbonyl; TMEDA = *N,N,N′,N′*-tetramethylethylenediamine; dba = dibenzylideneacetone; NN* = chiral diamine; sp = sparteine.

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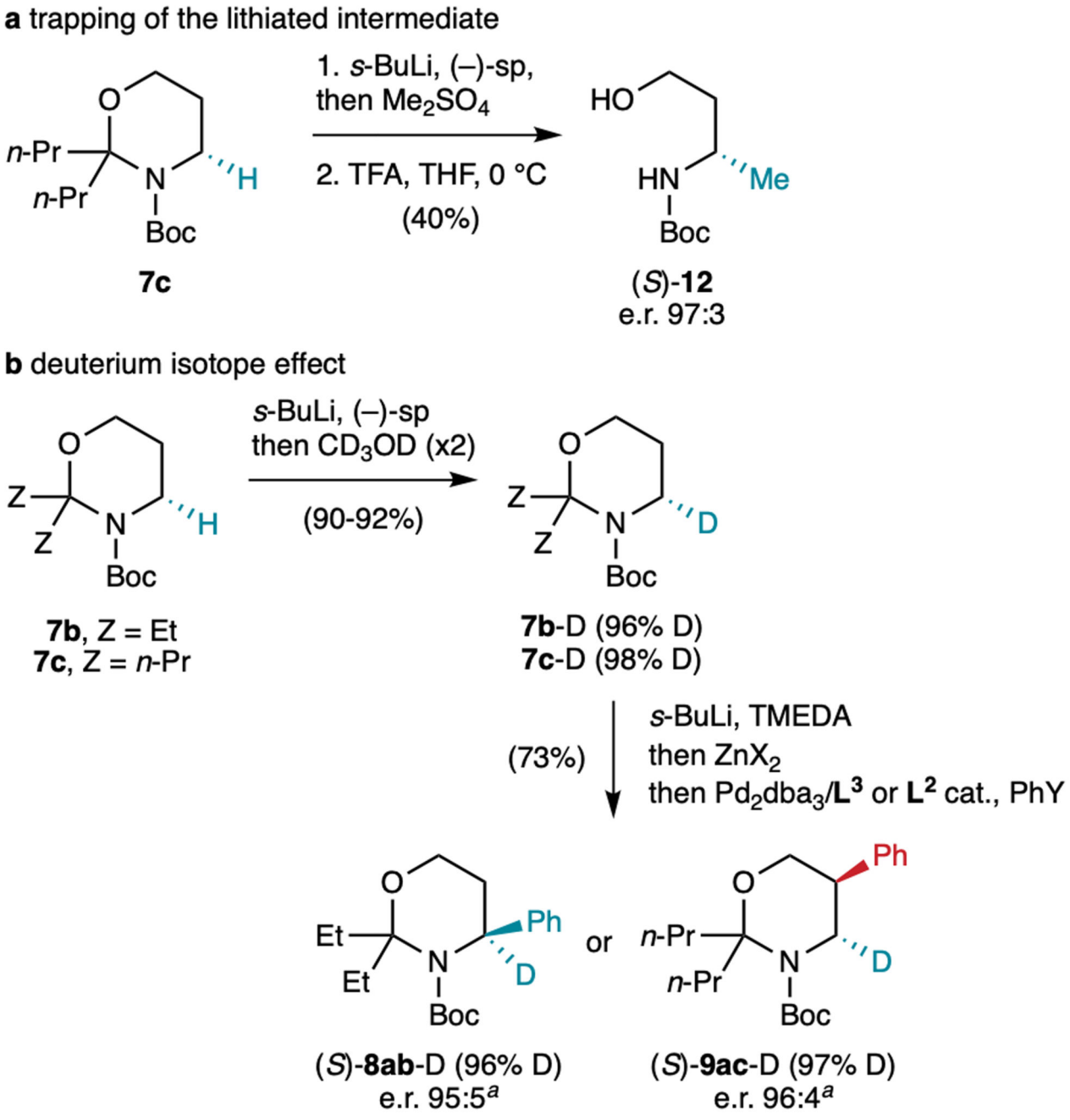

Fig. 3.

Trapping experiments. TFA = trifluoroacetic acid. X = Cl or OAc, Y = Br or ONf (see Table 1). The deuterium contents were measured by ^{1}H NMR. [a] Enantiomeric ratio of the mixtures of isotopomers, determined by HPLC on a chiral stationary phase.

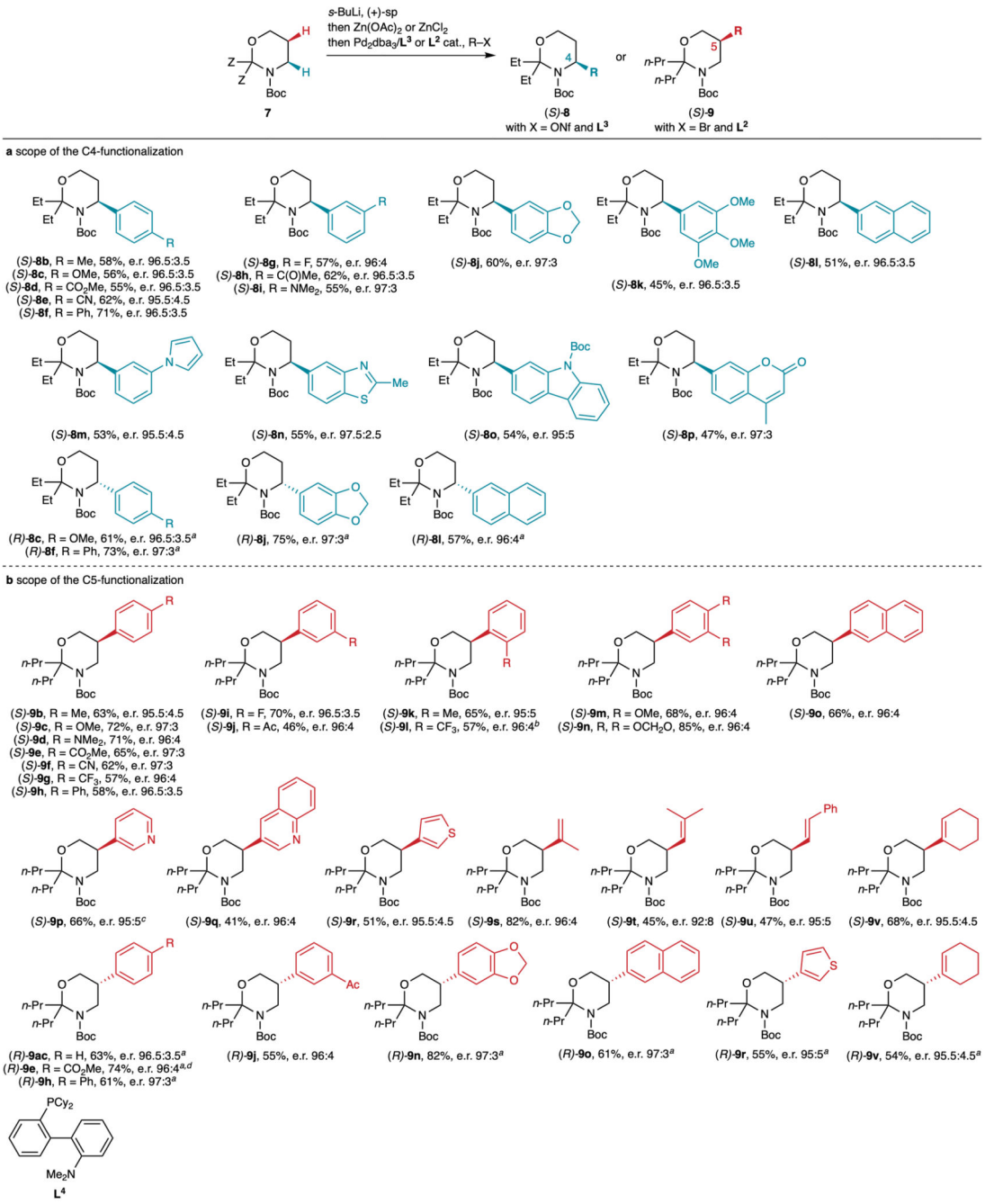

Fig. 4.

Scope of the C4- and C5-functionalization of Boc-1,3-oxazinanes. Reaction conditions: see Table 1, entries 6 (C4-functionalization) and 11 (C5-functionalization). E.r. values were determined by HPLC on a chiral stationary phase, either directly or on the Boc-protected aminoalcohol after cleavage of the aminal. The reference racemic products were synthesized using TMEDA instead of sp. [a] Using (–)-sp instead of (+)-sp. [b] Using **L**^{4} as the ligand. [c] Isolated as an inseparable 77:23 mixture of C5- and C6-isomers. [d] Performed on gram scale; 85% of (–)-sp was recovered.

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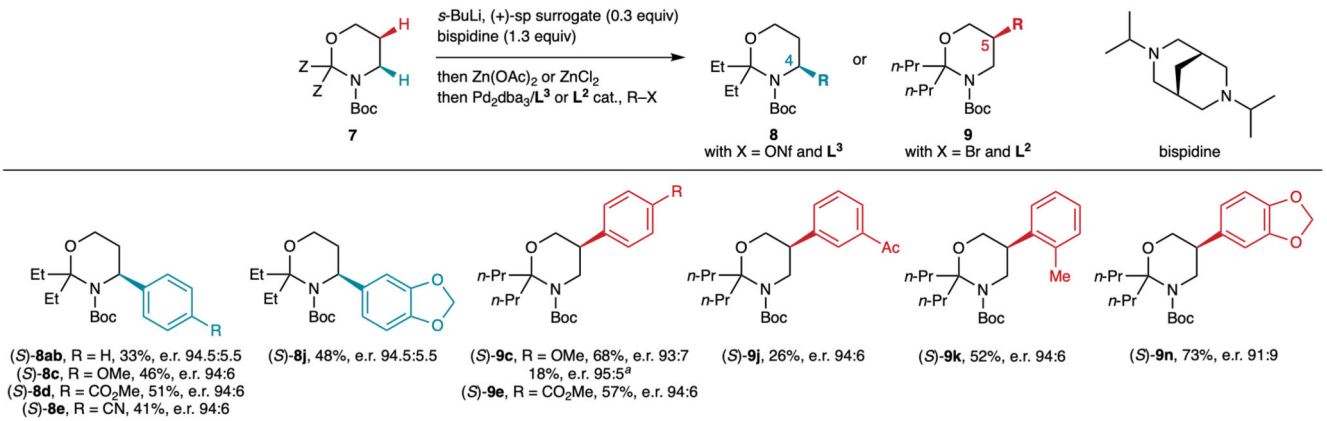

Fig. 5.

Development of proof of concept catalytic enantioselective C4- and C5-arylations.

Reaction conditions: 7 (1.0 equiv), *s*-BuLi (1.2 equiv), (+)-sp surrogate (0.3 equiv), diisopropylbispidine (1.3 equiv), Et_2O, –78 °C, 8 h, then $Zn(OAc)_2$ (C4-arylation) or $ZnCl_2$ (C5-arylation), THF (1.2 equiv), –78→20 °C, 1 h, then removal of volatiles, then PhBr (0.7 equiv), Pd_2dba_3 (2.5 mol%), ligand (5 mol%), toluene, 80 °C, 17 h. [a] Using (+)-sp instead of the (+)-sp surrogate.

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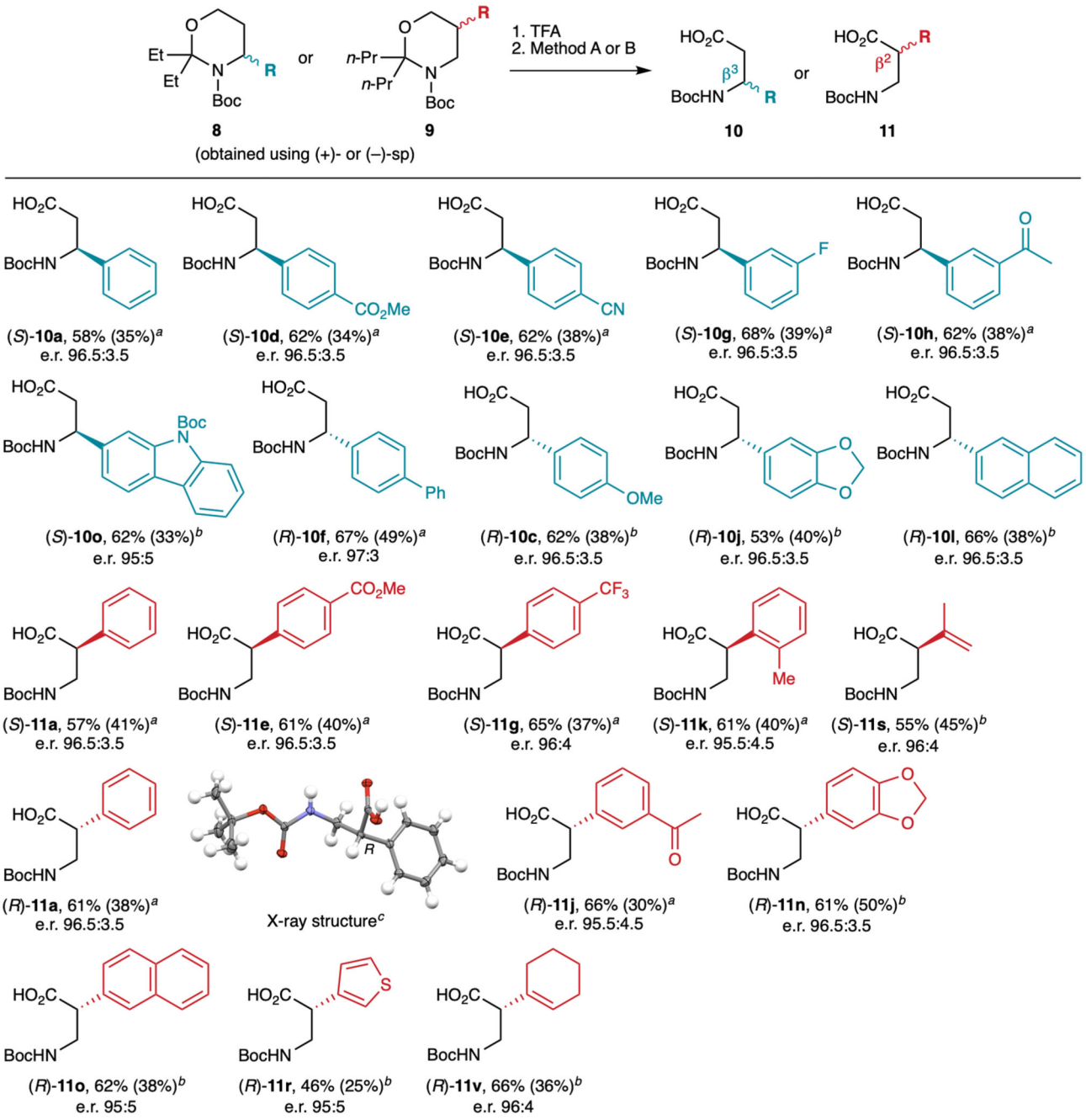

Fig. 6.

Application to the synthesis of β^2- and β^3-amino acids. Reaction conditions: 1. TFA, THF, 20 °C. 2. Method A: $RuCl_3$ (5 mol%), $NaIO_4$ (3 equiv), MeCN/H_2O, 20 °C. Method B: TEMPO (20 mol%), PIDA (2 equiv), CH_2Cl_2/H_2O, 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-c**. The e.r. were determined after derivatization to the corresponding methyl esters. [a] Obtained using method A. [b] Obtained using method B. [c]

Thermal ellipsoids shown at 50 % probability. TEMPO = (2,2,6,6-tetramethylpiperidin-1-yl)oxyl; PIDA = (diacetoxyiodo)benzene.

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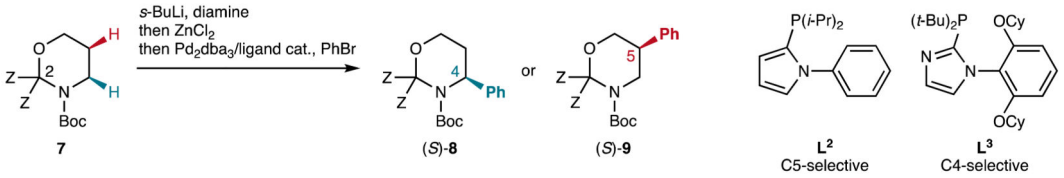
Table 1

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



Entry	Z	Reactant	Diamine	Ligand	8/9[a]	Product	Yield (%)[b]	e.r.[c]
1[d]	Me	**7a**	TMEDA	**L3**	>98:2	**8aa**	54	–
2[d]	Me	**7a**	(+)-sp	**L3**	>98:2	**8aa**	53	75:25
3[d]	Et	**7b**	(+)-sp	**L3**	>98:2	**8ab**	51	95:5
4[d]	Et	**7b**	(+)-sp surrogate	**L3**	>98:2	**8ab**	46	91:9
5[d]	*n*-Pr	**7c**	(+)-sp	**L3**	>98:2	**8ac**	30	94:6
6[e,f]	Et	**7b**	(+)-sp	**L3**	>98:2	**8ab**	61	97:3
7a	Me	**7a**	TMEDA	**L2**	<2:98	**9aa**	65	–
8	Me	**7a**	(+)-sp	**L2**	<2:98	**9aa**	51	77.5:22.5
9	Et	**7b**	(+)-sp	**L2**	<2:98	**9ab**	48	97:3
10	Et	**7b**	(+)-sp surrogate	**L2**	<2:98	**9ab**	89	94:6
11[f]	*n*-Pr	**7c**	(+)-sp	**L2**	<2:98	**9ac**	72	96.5:3.5
12	–$(CH_2)_4$–	**7d**	(+)-sp	**L2**	<2:98	**9ad**	23	85:15

Reaction conditions unless otherwise stated: **7** (1.0 equiv), *s*-BuLi (1.2 equiv), diamine (1.2 equiv), Et_2O, –78 °C, 8 h, then $ZnCl_2$/THF (1.2 equiv), –78→20 °C, 1 h, then removal of volatiles, then PhBr (0.7 equiv), Pd_2dba_3 (2.5 mol%), ligand (5 mol%), toluene, 80 °C, 17-24 h.

[a] Measured by GCMS or ^1H NMR analysis of the crude reaction mixture.

[b] Yield of the isolated product.

[c] Determined by HPLC on a chiral stationary phase.

[d] Cross-coupling step performed at 60 °C instead of 80 °C.

[e] Using $Zn(OAc)_2$ instead of $ZnCl_2$ and PhONf instead of PhBr.

[f] Conditions employed in Fig. 3-4. Nf = $SO_2(CF_2)_3CF_3$.