Enantioselective α-Arylation of *O*-Carbamates via Sparteine-Mediated Lithiation and Negishi Cross-Coupling

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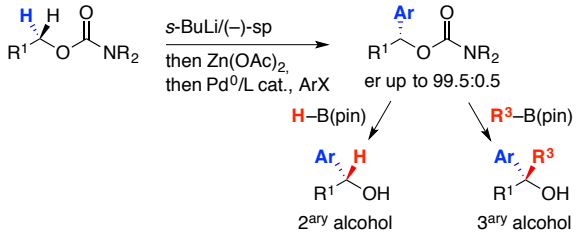
Supporting Information Placeholder



ABSTRACT: A general and highly enantioselective arylation of carbamates derived from primary alcohols was developed by combining Hoppe's sparteine-mediated asymmetric lithiation with Negishi cross-coupling. Coupled with Aggarwal's lithiation-borylation sequence, the current method provides a short and divergent access to a variety of enantioenriched secondary and tertiary benzylic alcohols.

The asymmetric lithiation of carbamates derived from aliphatic alcohols with *s*-BuLi and (–)-sparteine [(–)-sp] has been extensively studied by Hoppe and co-workers (Scheme 1a).[1] Upon trapping the configurationally stable organolithium intermediate with a suitable electrophile, a variety of highly enantioenriched secondary alcohols are accessed. Both enantiomers of sparteine are commercially available or readily prepared from the seeds of Lupinus albus,[2] thereby making this method highly practical and versatile despite the use of stoichiometric chiral reagent. However, to our knowledge the Hoppe method has been limited to nonaromatic electrophiles. On the other hand, Campos and co-workers have been able to combine Beak's asymmetric lithiation of Boc-amines[3] with *s*-BuLi/(–)-sp with stereoretentive Li→Zn transmetalation and Negishi cross-coupling,[4] but high enantioselectivities could be achieved only with Boc-pyrrolidines (Scheme 1b).[5] The current work demonstrates that the combination of Hoppe's asymmetric lithiation with Negishi cross-coupling allows access to α-arylcarbamates with high enantioselectivities (Scheme 1c). These products are precursors of a great variety of enantio-enriched secondary and tertiary benzylic alcohols via Aggarwal's lithiation-borylation method.[6] Both types of alcohols, which are traditionally synthesized by enantioselective reduction, addition of organometallics to carbonyl compounds, or by enzymatic resolution,[7] find widespread use as chiral building blocks for the synthesis of active pharmaceutical ingredients, such as the blockbuster antidepressants Fluoxetine and Escitalopram[8] (Scheme 1, bottom).

Scheme 1. Asymmetric lithiation of carbamates using *s*-BuLi/(–)-sparteine and Negishi arylation: state-of-the-art and current work

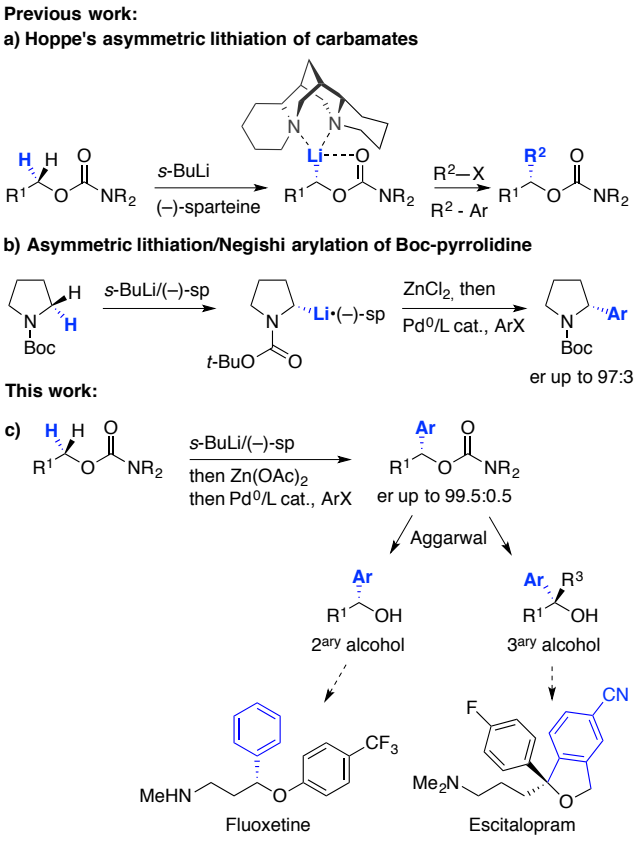
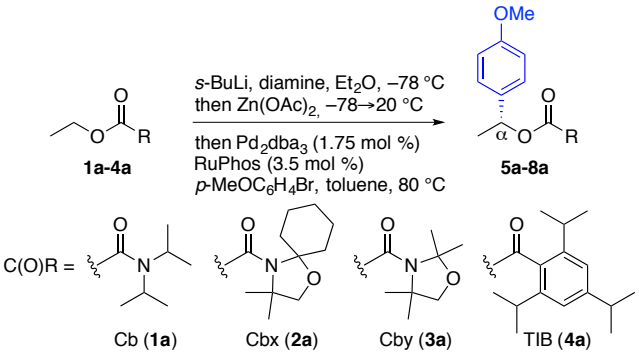
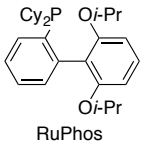


Table 1. Study of the directing group and optimized reaction conditions[a]



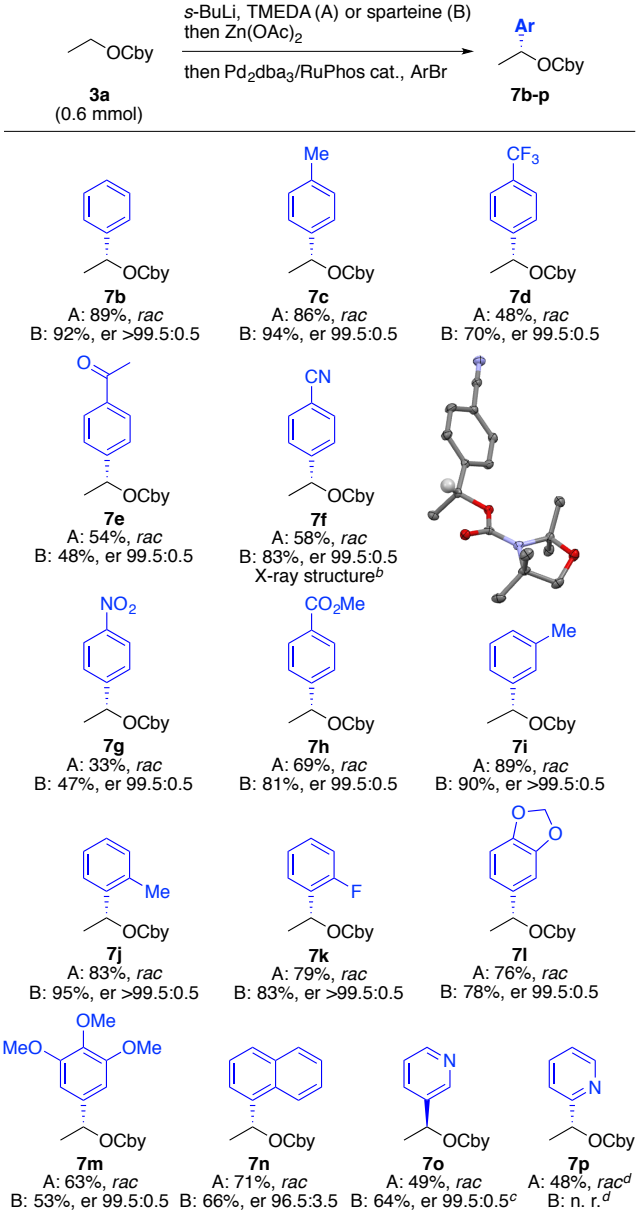
entry	product	C(O)R	TMEDA yield (%)[b]	(–)-sp yield (%)[b]	er[c]
1	**5a**	Cb	71	51	98:2
2	**6a**	Cbx	87	70	99.5:0.5
3	**7a**	Cby	81	86	99.5:0.5
4	**8a**	TIB	47	62	92.5:7.5
5[d]	**7a**	Cby	70	n.d.	n.d.
6[e]	**7a**	Cby	41	n.d.	n.d.
7[f]	**7a**	Cby	7	n.d.	n.d.

[a]Reaction conditions: (i)**1a-4a** (1.0 equiv), *s*-BuLi (1.3 equiv), diamine (1.3 equiv), Et_2O, –78 °C, 1 h (TMEDA) or 5 h [(–)-sp], (ii) $Zn(OAc)_2$ (1.4 equiv), –78 °C, 30 min, then 20 °C, 30 min, then evaporation of volatiles; (iii) *p*-$MeOC_6H_4Br$ (0.7 equiv), Pd_2dba_3 (1.75 mol %), RuPhos (3.5 mol %), toluene, 80 °C, 18 h. [b]Yield of the isolated product. [c]Measured by HPLC using a chiral phase. [d]*p*-$MeOC_6H_4I$ was used as the electrophile. [e]*p*-$MeOC_6H_4OTf$ was used as the electrophile. [f]*p*-$MeOC_6H_4Cl$ was used as the electrophile. TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine.



We set out to explore the α-arylation of diisopropylcarbamate (Cb) **1a** (Table 1). From similar substrates and through trapping with various non-aromatic electrophiles, Nakai, Taylor and co-workers had already reported that, following the lithiation step, the Li→Zn transmetalation occurs with retention of configuration.[9] These, as well as the aforementioned literature reports on *N*-carbamates,[4] provided us with a sound basis for the development of a stereoretentive Negishi coupling of *O*-carbamates, which would involve similar stereoretentive Li→Zn→Pd transmetalations. The method was first optimized in racemic mode using *s*-BuLi/TMEDA for the lithiation step and previously reported conditions as a starting point for the transmetalation and Negishi coupling (Table 1).[4,10,11] For the latter, *p*-bromoanisole was used as the electrophile. The optimal conditions involved deprotonation with *s*-BuLi and TMEDA in diethyl ether at –78 °C, followed by transmetalation with zinc acetate, which proved superior to zinc chloride, and Negishi coupling employing Pd_2dba_3/RuPhos[12] as the catalyst (3.5 mol % vs. the carbamate reactant), and gave rise to (±)-**5a** in 71% yield (entry 1). A 1.4-fold excess of carbamate vs. the aryl bromide was found optimal to achieve good yields. Gratifyingly, the enantioselective arylation, which involved initial deprotonation with (–)-sp for 5 h instead of TMEDA for 1 h, under otherwise identical conditions, furnished compound **5a** in 51% yield and 98:2 er (entry 1). Interestingly, the aminal-derived Cbx (**2a**)[13] and Cby (**3a**)[14] carbamates, which were introduced by Hoppe as efficient and removable directing groups in asymmetric lithiations, gave improved yields and er with both TMEDA and (–)-sp (entries 2-3). In addition to carbamates **1a-3a**, 2,4,6-triisopropylbenzoate (TIB) **4a** proved to be a competent reaction partner with both TMEDA and (–)-sp,[15] albeit with reduced yields and er (entry 4). Finally, the aryl iodide and triflate instead of the corresponding bromide also gave rise to the coupling product, albeit in reduced yields (entries 5-6). Moreover, the reaction of the corresponding aryl chloride was low yielding (entry 7).

Scheme 2. Scope of the racemic and enantioselective α-arylation reactions in aryl bromide[a]

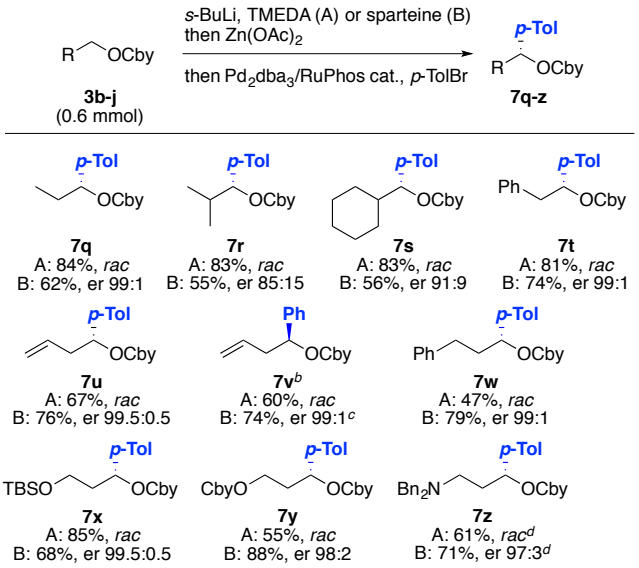


[a]For each product, A shows the yield obtained with TMEDA and

B shows the yield and er obtained with (–)-sp. Reaction conditions: see Table 1. [b]X-ray structure of **7f** showing the absolute configuration (shown with 30% probability ellipsoids, only one H atom is displayed for clarity). [c]Reaction performed with (+)-sp instead of (–)-sp. [d]Reaction performed at 110 °C.

The Cby carbamate and aryl bromides were thus selected as the optimal directing group and electrophiles, respectively, for the study of the reaction scope and limitations (Scheme 2). First, a variety of aryl bromides were found to be compatible with both racemic and enantioselective protocols, including unsubstituted (**7b**), *para*- (**7a**, **7c-h**), *meta*- (**7i**), *ortho*- (**7j-k**), as well as polysubstituted (**7l-n**) arenes. In addition, the Negishi coupling step was mild enough to tolerate sensitive functional groups such as a methyl ketone (**7e**), nitrile (**7f**), nitro (**7g**) and methyl ester (**7h**). Excellent enantioselectivities were achieved in all cases (**7a-n**) with (–)-sp (**7a-n**) as the diamine. In addition to bromoarenes, 3-bromopyridine reacted successfully in both TMEDA and sp-mediated protocols (**7o**). In contrast, the 2-bromo isomer failed to react in the enantioselective reaction (**7p**). Other heteroaryl (e. g., thiophen-2-yl, furan-3-yl), alkenyl or alkynyl electrophiles gave low coupling yields and were not further explored. The absolute configuration of compound **7f** was determined to be (*R*) by X-ray diffraction analysis, and the configurations of other products were ascribed by analogy. This result is consistent with previous work showing that the Li-Zn transmetalation and Pd-catalyzed Negishi coupling are both stereoretentive,[4,9] and that the configuration of the carbamate is fixed in the initial (–)-sp-mediated lithiation.

Scheme 3. Scope of the racemic and enantioselective α-arylation reactions in carbamate[a]

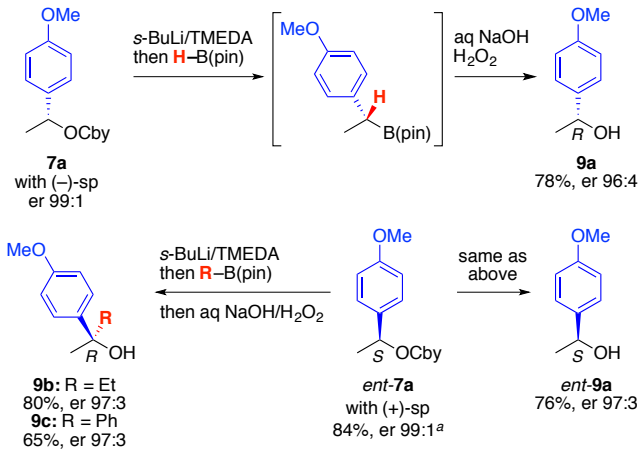


[a]For each product, A shows the yield obtained with TMEDA and B shows the yield and er obtained with (–)-sp. Reaction conditions are identical to those in Table 1, with 1.4 equiv of *s*-BuLi and diamine instead of 1.3 equiv. [b]With PhBr instead of p-TolBr. [c]Reaction performed with (+)-sp instead of (–)-sp on a 3 mmol scale. [d]With 2 equiv s-BuLi/diamine.

Next, the scope with respect to the carbamate reactant was investigated using *p*-bromotoluene as the electrophile (Scheme 3). Moderate-to-very good yields were obtained for both protocols, and excellent er were achieved using (–)-sp for carbamates bearing a secondary carbon at the *β* position (**7q**, **7t-u**, **7w-z**). Lower yields and enantioselectivities were observed with (–)-sp for carbamates containing a more crowded tertiary *β* carbon (**7r-s**). Since the (–)-sp-mediated lithiation of the carbamate precursor of **7r** was reported to occur with er >97.5:2.5,[16] the lower er observed for **7r-s** likely arises from the partial racemization of the corresponding organozinc or organopalladium intermediate. A variety of useful functional groups were tolerated, such as a benzene ring (**7t**, **7w**), an olefin (**7u**), a TBS-protected alcohol (**7x**), and a bis-benzyl-protected amine (**7z**). Interestingly, bis-carbamate **7y**[17] also underwent efficient enantioselective monoarylation. Importantly, as shown with compound **7v**, the reaction could be performed on a fivefold scale (3 mmol, 474 mg of product) and with the (+) enantiomer of sparteine with equally good performance (74% yield, er 99:1).

To demonstrate the versatility and utility of the current arylation method to synthesize scalemic secondary and tertiary alcohol building blocks, a series of reactions were performed from both enantiomers of arylated Cby carbamate **7a**, by adapting the protocols reported by Aggarwal and co-workers with diisopropyl (Cb) carbamates (Scheme 4). A first lithiation/borylation/oxidation sequence was performed with HB(pin)[18] from carbamate (*R*)-**7a**, obtained using (–)-sp, to give 2[ary] alcohol (*R*)-**9a** in good yield and enantiospecificity (*es* 94%).[19] It is important to note that methods described by Hoppe and co-workers to cleave the Cby group by treatment with a metal hydride[1b] or with methanesulfonic acid[14] failed, presumably due to the steric hindrance and acid-sensitivity, respectively, of the current benzylic carbamate. Similarly, the (*S*) enantiomer of **7a** was obtained with 99:1 er using (+)-sp in the asymmetric lithiation/Negishi coupling, which was performed on a 3 mmol scale (542 mg of product). The lithiation/borylation/oxidation of (*S*)-**7a** using HB(pin) furnished (*S*)-**9a** with excellent enantiospecificity (*es* 96%). Alternatively, using organoboronates EtB(pin) and PhB(pin)[20] instead of pinacolborane provided (*R*)-configured 3[ary] alcohols **9b-c** in good yield and excellent preservation of the optical purity (er 97:3, *es* 96%). It is remarkable to notice that the configuration of 2° and 3° alcohols **9a-c** is controlled by the initial sparteine-mediated lithiation of the 1° carbamate **3a**, followed by a sequence of 5 discrete stereospecific steps (Li-Zn transmetalation, Negishi coupling furnishing **7a**, then lithiation, borylation, oxidation).

Scheme 4. Synthesis of enantioenriched secondary and tertiary alcohols via Aggarwal's lithiation-borylation methods



[a]Arylation reaction performed on a 3 mmol scale.

In conclusion, a versatile and highly enantioselective arylation of carbamates derived from primary alcohols was designed by combining Hoppe's sparteine-mediated asymmetric lithiation with Negishi cross-coupling. This method, when coupled to Aggarwal's lithiation/borylation/oxidation sequence, provides a concise and divergent access to enantioenriched secondary and tertiary benzylic alcohols that complements well other enantioselective methods.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at
Full characterization of all new compounds, detailed experimental procedures, copies of NMR spectra, and X-ray crystal structure data (CIF) for compound **7f**.

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Notes

The authors declare no competing financial interest.

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