Intermolecular Asymmetric Arylative Dearomatization of 1-Naphthols

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ABSTRACT: Arylative dearomatization forms all-carbon quaternary stereocenters in cyclic systems with concomitant introduction of an aromatic ring. Pd-catalyzed arylative dearomatization, which uses conditions analogous to cross-coupling, has emerged as a powerful method in an intramolecular context. But translating this from intramolecular cyclizations to an intermolecular process has proven extremely challenging – examples are scarce, and those that exist have not been rendered enantioselective, despite the potential for broad application in medicinal chemistry and natural product synthesis. We describe a strategy that utilizes attractive interactions between ligand and substrate to overcome this challenge and promote intermolecular, highly enantioselective arylative dearomatization of naphthols using a broad range of aryl bromide electrophiles. Crucial to success is the use of the readily accessed, sulfonated chiral phosphine sSPhos, which we believe engages in attractive electrostatic interactions with the substrate. Not only does sSPhos control enantioselectivity, but it also drastically accelerates the reaction, most likely by facilitating the challenging palladation step that initiates dearomatization.

1. INTRODUCTION

Arene or heteroarene dearomatization reactions are powerful complexity-increasing processes.[1] Although the breaking of aromaticity requires significant energy input, versatile three-dimensional, stereocenter-containing products are typically formed, which are poised for further elaboration through the remaining unsaturation.[2] Accordingly, much effort has been placed on developing protocols that induce asymmetry during the dearomatizing event. These have been achieved on a variety of electron-rich arene or heteroarene substrates using various electrophiles; the use of highly reactive electrophiles naturally assists in overcoming the barrier to dearomatization, making the task of rendering the process enantioselective somewhat easier.[3] In this context, arylative dearomatization is particularly challenging due to a paucity of highly electrophilic aryl surrogates. Yet since it results in an aryl group linked to a quaternary stereocentre, a structural feature that is ubiquitous in bioactive small molecules, it remains an important and challenging problem to address in an enantioselective manner.[4] Methods for arylative dearomatization that utilize electrophilic lead,[5] bismuth,[6] and iodine[7] arylating reagents have not translated into enantioselective versions, because most do not operate under the control of a catalyst. The pioneering development by Buchwald and co-workers of palladium-catalyzed arylative dearomatization methods, using aryl bromides as the electrophilic partner, marked a significant step forward.[8] Since then, the protocol has been applied in natural product synthesis and a number of asymmetric examples of this reaction have been reported using chiral ligands for palladium, making it arguably the leading strategy for enantioselective arylative dearomatization (Fig. 1A).[9] One aspect which stands out from surveying the asymmetric examples is that they are all intramolecular. There are very few examples of intermolecular arylative dearomatization using palladium catalysis, and none are enantiocontrolled. The most prominent are those of 1-napthols and 2-napthols, both from You and co-workers,[10] as well as a handful of protocols reported on furans,[11] indoles[12] and pyrroles (Fig. 1B).[13] In fact, there are very few enantioselective examples of intermolecular arylative dearomatization using any kind of catalytic method. One notable example is Zhu and MacMillan's 2012 report of indole dearomatization using iodonium salts and chiral copper catalysis, which was subsequently adapted for total synthesis by Reisman and co-workers,[14] but has not since been further explored in other dearomatization reactions (Fig. 1C, upper).[15] In addition, there are examples of formal arylative dearomatization processes using quinone imides and related aryl-precursor electrophiles under chiral phosphoric acid cataysis, although these are, by their nature, limited to the introduction of very specific arene motifs (Fig. 1C, lower).[16] It is evident that the translation of arylative dearomatization from intramolecular cyclizations to intermolecular couplings is no trivial matter and remains an outstanding challenge. The two pioneering racemic protocols reported by You using palladium catalysis were highly ligand-specific, requiring use of achiral QPhos; no yield was obtained using the other ligands evaluated, a significant barrier to the development of asymmetric variants.[10]

We previously reported the use of sSPhos[17,18] as a general chiral ligand for intramolecular arylative dearomatization and applied it to a range of different scaffolds.[9j] We attribute its efficacy to a key attractive electrostatic interation between the ligand sulfonate group, alkali metal cation and phenolate at the transition state for arene palladation (Fig.

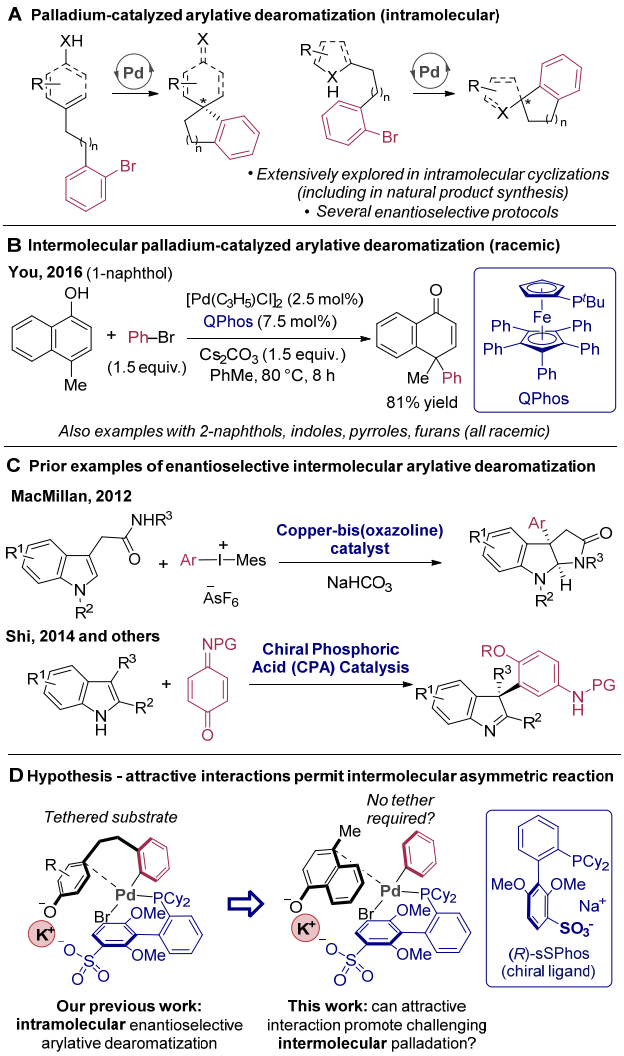


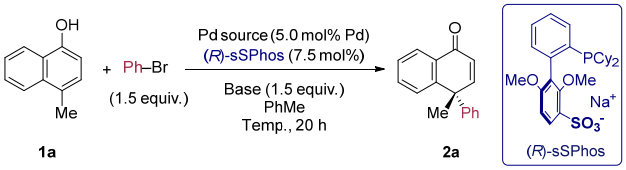
Figure 1: Context for enantioselective intermolecular arylative dearomatization and our hypothesis using sSPhos.

1D, left). This should permit a high degree of organization in the defined chiral environment provided by the ligand.[19] In considering the challenge of intermolecular arylative dearomatization, we speculated as to whether this network of interactions could constitute a key enabling feature, accelerating the challenging palladation step by emulating intramolecularity whilst simultaneously enforcing enantiofacial control (Fig. 1D, right). In this Article, we demonstrate that this is indeed feasible and highly effective. Additionally, we illustrate the versatility of the products in the synthesis of pharmaceutical analogues featuring quaternary stereocenters, as well as an application to natural product synthesis.

2. RESULTS AND DISCUSSION

We commenced with 4-methylnaphthalen-1-ol (**1a**) as the substrate and based our initial conditions on those reported by You and co-workers, with $[PdCl(allyl)]_2$ as the Pd source and Cs_2CO_3 as the base, replacing achiral ligand QPhos with (*R*)-sSPhos (Table 1, entry 1).[10a] While excellent enantioselectivity (98% *ee*) was obtained, the yield was poor. An evaluation of palladium sources (entries 2 and 3) afforded the best result with Pd_2dba_3 (entry 3). Next, the

Table 1: Reaction optimization.



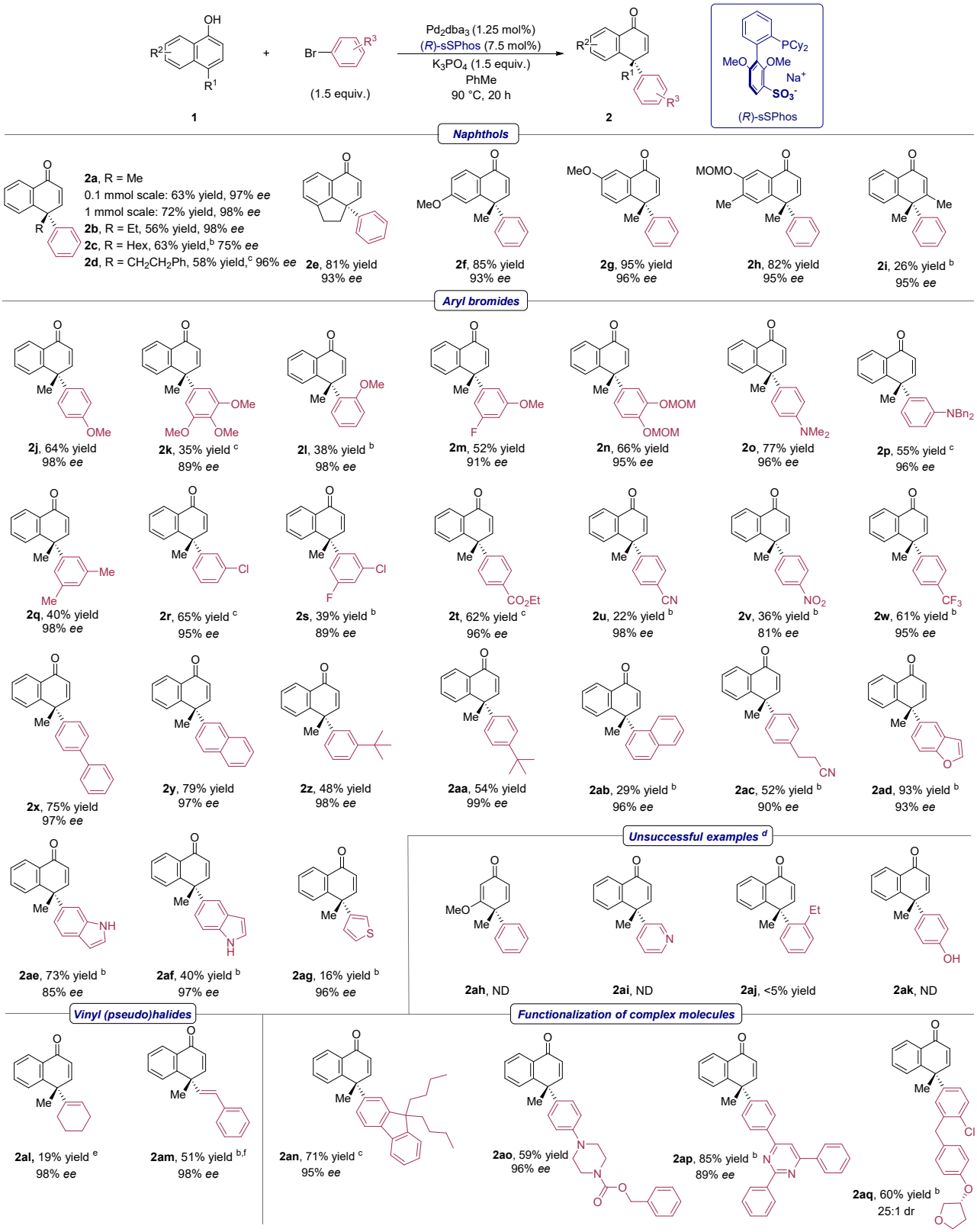
Entry	Pd source	Base	Temp/ °C	Yield /%[a]	ee/%[b]
1	$[PdCl(allyl)]_2$	Cs_2CO_3	90	18	98
2	$Pd(OAc)_2$	Cs_2CO_3	90	trace	N.D.
3	Pd_2dba_3	Cs_2CO_3	90	35	96
4	Pd_2dba_3	K_2CO_3	90	42	83
5	Pd_2dba_3	KOH	90	49	99
6	Pd_2dba_3	NaOH	90	54	99
7	Pd_2dba_3	K_3PO_4	90	61	95
8	Pd_2dba_3	K_3PO_4	70	55	96
9[c]	Pd_2dba_3	K_3PO_4	90	23	96
10[d]	Pd_2dba_3	**K_3PO_4**	**90**	**62 (63)**	**97 (97)**

[a]Yields determined by ^1H NMR with reference to a dibromomethane internal standard. Value in parentheses refers to isolated yield. [b]*ee* determined by SFC analysis of the crude reaction mixture. Value in parentheses refers to *ee* of isolated material. [c] Reaction carried out with 3.75 mol% (*R*)–sSPhos. [d] Reaction carried out with 2.5 mol% Pd.

base was varied (entries 3-7), with optimal yield being obtained with K_3PO_4 (61%) and excellent enantioselectivity maintained.[20] A slight reduction in yield was obtained upon reducing the reaction temperature to 70 °C (entry 8). While halving the ligand loading had a detrimental effect on reactivity (entry 9), reactivity was maintained when the loading of Pd_2dba_3 was halved in entry 10, which formed our final optimized conditions.[21]

With optimized conditions in hand, we established that the reaction could be conducted on a 1 mmol scale, affording very similar results (**Scheme 1**, **2a**, 72% yield, 98% *ee*). Next, the 1-naphthol scope was evaluated. Several different alkyl substituents were tolerated at the C4 position in place of methyl (**2a-2d**). Lower enantioselectivity was obtained with a hexyl substituent (**2c**) but remained high with a similarly large phenethyl substituent (**2d**). Tricyclic (**2e**) and methoxy-substituted naphthols (**2f, 2g**) displayed excellent reactivity as well as enantioselectivity, and a substrate containing a MOM group was tolerated without issue (**2h**). Methyl-substitution at the C3 position (**2i)** impacted reactivity, presumably due to greater steric hindrance and the site of arylation, but the product **2i** was still obtained in excellent enantioselectivity. The aryl bromide component tolerated a wide range of electron-donating substituents (**2j-2q**). Electron-withdrawing substituents also gave excellent selectivity outcomes, although slightly more forcing conditions were required to improve conversion in some cases (**2r-2w**). Even in cases of extremely withdrawing susbtituents such as cyano (**2u**) or nitro (**2v**) which gave low yields, selectivity reamined high. The absolute configuration of chlorine-substituted **2r** was determined by X-ray crystallography, with the stereochemistry of the remaining compounds assigned by analogy. Bulky substituents were tolerated in the *meta* and *para* positions of the aromatic ring (**2x-2aa**)

Scheme 1. Scope of intermolecular arylative phenol dearomatization.

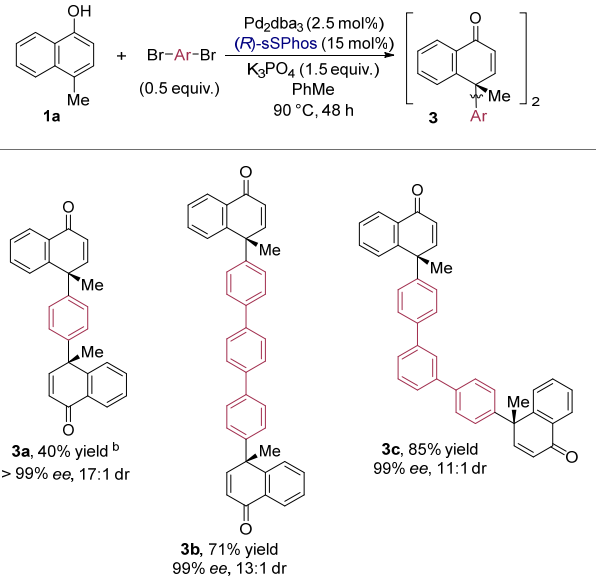


[a] Yields are isolated, *ee* values determined by SFC. [b] 2.5 mol% Pd_2dba_3 and 15 mol% (*R*)-sSPhos for 48 h. [c] 48 h reaction time. [d] Unsuccessful examples were carried out using (*rac*)-sSPhos along with minor variations to the reaction conditions. For full details, see the SI. ND = Not detected. [e] Vinyl triflate used as the electrophile instead of vinyl bromide [f] Product isolated with 11% of an unidentified inseparable impurity

but a naphthyl-based aryl bromide bearing bulk in the *ortho*-position was less reactive (**2ab**) An aryl bromide containing a nitrile group separated from the arene by an aliphatic chain gave good results (**2ac**). We were very pleased to find that electron rich heteroaryl bromides worked very well, including a benzofuran (**2ad**), two different isomers of an unprotected indole (**2ae** and **2af**) and even a thiophene (**2ag**), albeit in low yield. Such excellent tolerance was unexpected given the precedent for electron rich heterocycles to undergo direct arylation reactions under similar Pd-catalyzed conditions.[22] As for the limitations, intermolecular dearomatization of a phenol nucleophile, as opposed to a naphthol, appears too challenging (**2ah**). Regarding unsuccessful aryl bromides, no product was obtained using 3-bromopyridine (**2ai**), *ortho*-ethyl (**2aj**) or a *para*-phenolic (**2ak**) aryl bromide. We discovered that the reaction can extend beyond arylation: a cyclic vinyl triflate (**2al**) and an acyclic, styrenyl bromide (**2am**) were compatible, although further work is required to improve yield. Finally, we applied the arylative dearomatization to more complex aryl bromides in **2an**-**2aq**, demonstrating the tolerance of this methodology to useful and medicinally-relevent functionality.[23] Surprisingly, O/C2-arylation were not generally observed as major byproducts when evaluating the reaction scope; the moderate yields of several scope examples were attributed to the gradual decomposition of 4-methylnaphthalen-1-ol (**1a**) under the reaction conditions (for details, see the Supporting Information).

We were curious to probe whether the catalyst could exert enantiocontrol on the formation of more than one stereocenter in a single reaction, by carrying out the arylative dearomatization using bisbromoarenes (Scheme 2). Gratiflyingly, these doubly functionalized products could be formed with good yields, enantioselectivities, and

Scheme 2. Evaluation of bifunctional electrophiles[a]

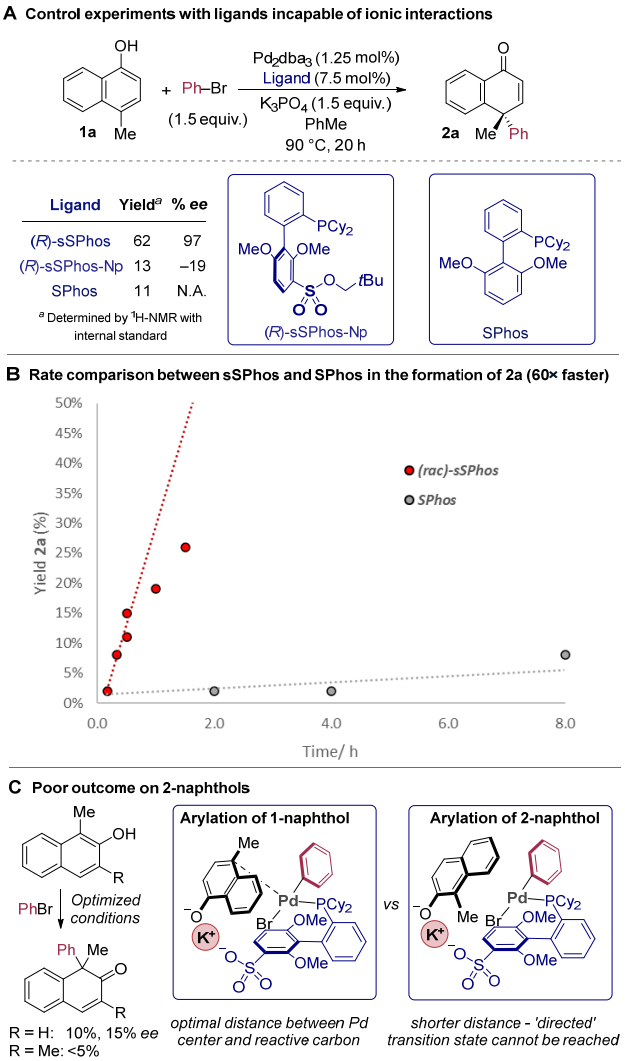


[a] Yields are isolated. Products were isolated as a mixture of diastereomers. *ee* and dr values determined by chiral SFC. [b] Reaction conducted with 0.75 equiv. 1,4-dibromobenzene

diastereoselectivities (**3a-3c**). Diastereomers were inseparable by column chromatography and indistinguishable by NMR: the presence of the minor *meso* diastereomer was only detectable by chiral SFC analysis.

We next carried out control experiments to gain support for the proposed substrate-ligand ionic interaction (Fig. 1D, right). The ligand (*R*)-sSPhos-Np, in which the anionic sulfonate group was converted to a neutral sulfonate ester, was evaluated under the optimized conditions, affording very poor enantioselectivity when compared to (*R*)-sSPhos

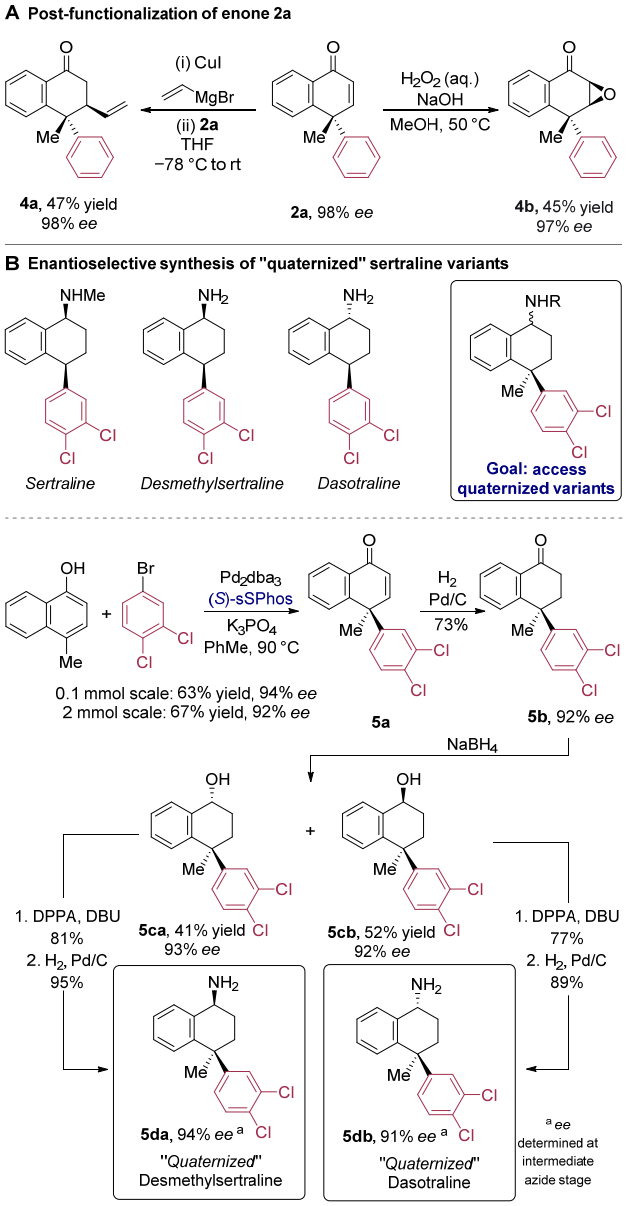
Scheme 3. Experiments to probe electrostatic substrate-ligand interaction



(−19 vs 97% ee, Scheme 3A). Interestingly, the yield was also greatly impacted (13 vs 62%). To further probe this, standard SPhos was also tested, affording almost identically poor yield. These results are consistent with our hypothesis that the ionic interaction is needed to emulate intramolecularity and promote the challenging carbopalladation step. We envisage that the resulting high degree of organization at the transition state permits the steric environment of the chiral ligand scaffold to exert maximum effect in delivering the excellent

enantioselectivities observed in this work. We next compared the rates of the reaction with sSPhos and SPhos and discovered that with sSPhos the reaction proceeds approximately 60 times faster (Scheme 3B). This provides further support that the nucleophilic C4 carbon of the 1-naphthol is ideally situated to interact with the palladium when positioned by the key substrate-ligand interaction. Interestingly, we found two closely related 1-methyl-2-naphthols to be very poor substrates under the optimized conditions (Scheme 3C, left). We speculate that here the reactive site for arylation is too close to the phenolate to fit properly with the ligand (Scheme 3C, right). Low enantioselectivity was also obtained in the cyclization of a suitable 1-substituted-2-naphthol substrate bearing a tethered aryl bromide, suggesting that this trend also applies to the substrates investigated in our earlier intramolecular work (for details, see the Supporting Information).[9j]

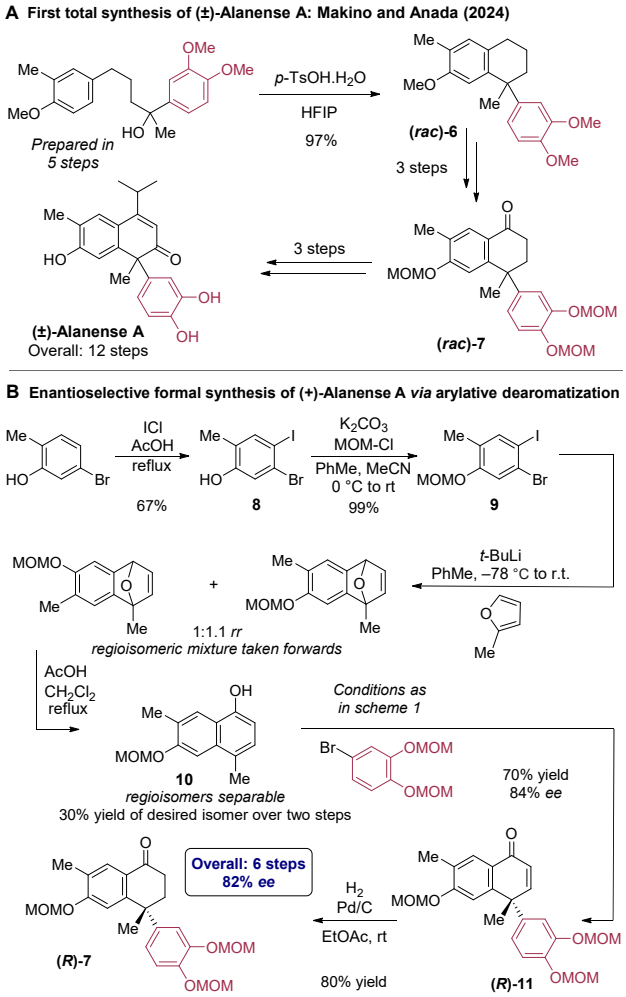
Scheme 4. Post-functionalization and synthesis of quaternized variants of sertraline



The enone motif that remains following dearomatization can be further tranformed in a multitude of ways. We demonstrate two: vinyl cuprate addition to enone **2a** gave a single isolated diastereomer of alkene **4a** (crude NMR indicated a 5:1 d.r.) and nucleophilic epoxidation using basic peroxide formed epoxide **4b** as a single diastereomer (Scheme 4A). We next sought to demonstrate the potential of our method for medicinal chemistry applications. Sertraline is a blockbuster single enantiomer antidepressant drug (Scheme 4B, upper).[24] Desmethylsertraline, an active metabolite of sertraline, has also demonstrated *in vivo* activity as a monoamine uptake inhibitor.[25] Dasotraline, an epimer of desmethylsertraline featuring the opposite configuration at the amine stereocenter, was investigated in clinical trials for the treatment of ADHD in 2015, demonstrating the contemporary relevance of these molecules in drug discovery long after the approval of sertraline by the FDA in 1991.[26] Variants of these molecules containing a quaternary stereocenter arguably present more challenging synthetic

targets, inspiring us to showcase our methodology by accessing "quaternized" analogues of these pharmaceuticals (Scheme 4B, upper right).[27] The arylative

Scheme 5. Application to formal enantioselective synthesis of Alanense A.

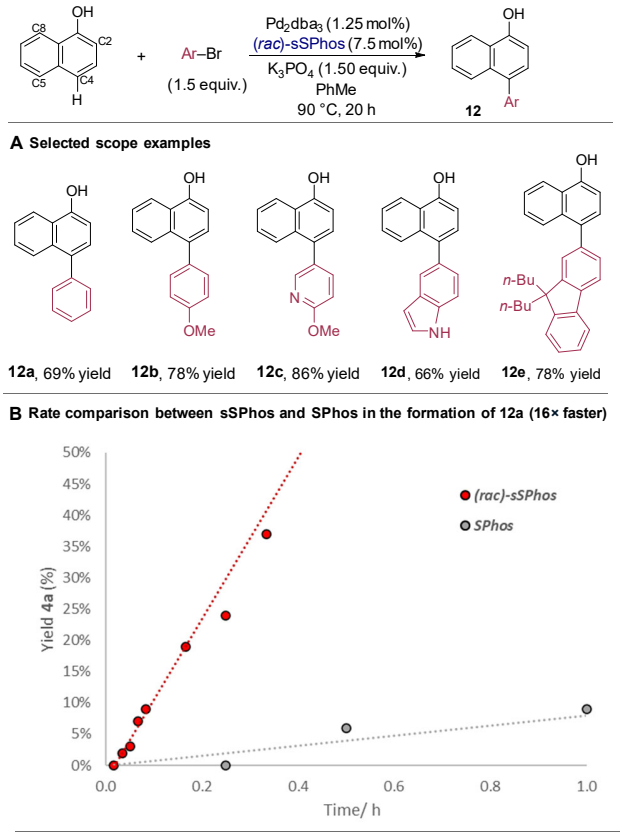


dearomatization, using (*S*)-sSPhos to install the correctly configured stereocenter, delivered enone **5a** in 92% *ee* on a 2 mmol scale, which could be converted to tetralone **5b** following hydrogenation with Pd/C (Scheme 4B, lower). Since both amine configurations are relevant targets, we were pleased to find that the reduction with $NaBH_4$ was unselective, delivering separable alcohol diastereomers **5ca** and **5cb**. These were converted to the corresponding free amines **5da** and **5db** through a Mitsunobu inversion to form the corresponding azide (not shown), followed by hydrogenation.

Alanense A is a cadinane sesquiterpenoid natural product first isolated as a racemate in 2022 by Cao and co-workers (Scheme 5A).[28] In 2024, Makino, Anada and co-workers reported the only total synthesis to date, forming the racemate in which it naturally occurs.[29] Their key step formed the central ring *via* an intramolecular dehydrative Friedel-Crafts alkylation to give *(rac)*-**6**. Three further steps replaced three methoxy substituents for MOM-protected phenols, while oxidizing the unsubstituted benzylic position to afford ketone (*rac*)-**7**. This was converted into (±)-Alanense A in three further steps, constituting a 12-step racemic synthesis. We envisaged that a concise, enantioselective synthesis of intermediate **7** would be feasible using our methodology, which would thereby constitute an enantioselective formal synthesis of Alanense A. Iodination of 5-bromo-2-methylphenol delivered phenol **8** which was MOM-protected to afford benzyne precursor **9** (Scheme 5B). Formation of the corresponding benzyne with *t*-BuLi preceeded [4+2]-cycloaddition with 2-methylfuran to deliver a mixture of regioisomeric 7-oxabenzonorbornadienes. Typical methods to promote the ring opening of these structures rely on either a strong Brønsted acid (such as HCl) or a Lewis acid (such as $Cu(OTf)_2$), both of which were found to be incompatible with the MOM protecting group (for full details, see the Supporting Information).[30] Pleasingly, we found that refluxing with acetic acid in dichloromethane successfully promoted the desired isomerization whilst being sufficiently mild to leave the bis-MOM-protected phenol intact. At this point, the desired naphthol isomer **10** was separable from its undesired regioisomer.[31] The key enantioselective arylative dearomatization delivered enone **11** in 70% yield and 84% *ee*, and this was converted to the intermediate in the prior synthesis, **7**, by hydrogenation with Pd/C. This common intermediate was accessed in highly enantioenriched form in only six steps, compared with the nine steps to form the racemate in the previous synthesis.

According to our mechanistic hypothesis, one might expect that if the alkyl substituent at the 4-position of the napthol were removed, then rearomatization would occur, consituting a C4-selective C-H arylation of naphthalen-1-ol. To the best of our knowledge, such a transformation has generally been reported using specific electrophiles such as quinone monoacetals,[32] *ortho*-nitrobromoarenes[33] or highly electron rich phenols via sulfoxide intermediates.[34] More general aryl halides have been used as electrophiles for C-H arylation of 1-naphthols, but these give rise to the C2 product rather than C4, most likely due to proximity to the oxygen in those particular mechanisms.[35] You and co-workers in their 2016 report showed that 2-methyl-napth-1-ol gave a 1:1 of C4 arylation and diarylation resulting from reaction at C4 and C5 or C8.[10a] We found C4-selective direct arylation to work very effectively with our system on simple naphthalen-1-ol and demonstrate this for several aryl bromides (Scheme 6A, **12a**-**12e**). This was a highly chemoselective transformation, with no competitive *O*-arylation visible, providing a very concise route to these compounds, which have previously been accessed through more lengthy cross-coupling sequences involving protecting group exchange.[36] SPhos also gave similarly high selectivity outcomes, but was a far less reactive ligand than sSPhos – we compared rates using both ligands for the reaction to form arylated product **12a** and observed a 16-fold rate enhancement for sSPhos when compared to SPhos (Scheme 6B). This provides further evidence for the attractive interaction between ligand and substrate when sSPhos is used. Preliminary attempts to form very hindered biaryl bonds and therefore introduce axial chirality using this approach were unsuccessful (see SI for details).

Scheme 6. Direct arylation of 1-naphthols bearing no *para* substituent



3. CONCLUSIONS

In summary, we have developed a highly enantioselective intermolecular arylative dearomatization of 1-naphthols. This consitutes a rare case of palladium-catalyzed arylative dearomatization being carried out asymmetrically in an intermolecular manner (i.e. not as part of a cyclization). We demonstrate applications of this method in the synthesis of medicinally relevent compounds, and in the enantioselective formal synthesis of a natural product. Evidence is provided to support our hypothesis that the sulfonate group on the sSPhos ligand is playing a key role in assembling the reaction components through attractive non-covalent interactions. We anticipate that the demonstration of this principle will lead to further enantioselective variants of this important reaction type.

ASSOCIATED CONTENT

SUPPORTING INFORMATION

Additional optimization, full experimental details, and characterization data for compounds.

ACCESSION CODES

CCDC 2389221 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EW.

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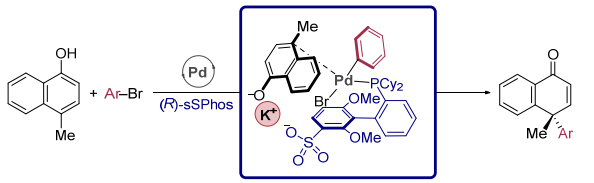

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