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Regioselective Derivatizations of a Tribrominated Atropisomeric Benzamide Scaffold

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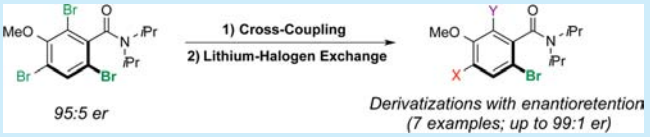
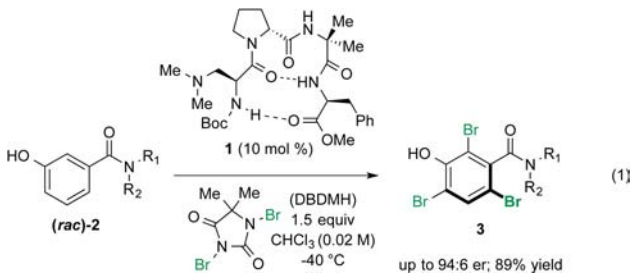
Supporting Information

ABSTRACT: The enantioselective synthesis of atropisomeric, tribrominated benzamides and subsequent regioselective transformations to afford derivatized, axially chiral molecules is reported. The enantioenriched tribromides were carried through sequential Pd-catalyzed cross-coupling and lithium–halogen exchange with high regioselectivity and enantioretention. A variety of complexity-generation functional group installations were performed to create a library of homochiral benzamides. The potential utility of these molecules is demonstrated by using a phosphino benzamide derivative as an asymmetric ligand in a Pd-catalyzed allylic alkylation.



Atropisomers have gained significant attention in the literature for their synthetic utility and are prevalent as asymmetric catalysts and ligands.[1] Additionally, the benzamide subunit is commonly found in pharmaceuticals, and differential biological activity of many enantiopure, axially chiral scaffolds has been recently reported.[2] While biaryls are the most studied atropisomeric system,[3] multiple other scaffolds can also display hindered rotation about a bond, leading to isolable enantiomers such as diaryl ethers,[4] quinazolones,[5] chromenones,[6] and tertiary aromatic amides.[7] In this context, our laboratory has focused on the synthesis of various atropsiomeric scaffolds utilizing small peptides as catalysts to enantioselectively generate axes of chirality.[8] In a recent study, we discovered a small β-turn peptide (**1**) that is capable of converting racemic benzamide **2** to atropisomeric tribromide **3** in the presence of dibromodimethylhydantoin (DBDMH, eq 1).[8b] Because of the low barrier to

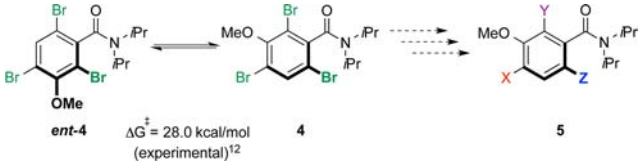


(1)

racemization for *ortho,ortho′* unsubstituted benzamides, substrate **2** readily interconverts between its enantiomeric forms. However, installation of large *o*-bromides promoted by peptide **1** leads to stable, axially chiral compound **3** in high yield and enantiomeric ratio (up to 89% yield; 94:6 er).

The substituents (specifically *ortho*) decorating the aryl ring greatly affect their axial stability,[9] and while this fact has been utilized in the development of methodologies to access axially chiral molecules,[10] the subsequent functionalization of enantioenriched atropisomers must be examined with care due to the potential for racemization.[11] In a previous study, our group reported regioselective functionalizations of an analogous enantioenriched, tribrominated biaryl utilizing cross-coupling.[11] Likewise, using the bromines as convenient handles for derivatization, we hoped the amide scaffold would be amenable to regioselective chemical transformations (Scheme 1). More-

Scheme 1. Experimentally Determined Barrier to Racemization for Atropisomeric, Tribromide 4 and Subsequent Regioselective Derivatizations



over, if regiocontrol of subsequent iterative derivatizations could be achieved, it would be possible to generate a library of enantioenriched and highly functionalized atropisomeric benzamides. Importantly, while tribromide **4** is reasonably stable to racemization, with a barrier to interconversion of 28.0 kcal/mol,[12] the success of this method requires that transformations occur with retention of axial chirality and without subsequent product racemization.

Indeed, various palladium-catalyzed cross-couplings were successful in selectively targeting the least sterically encumbered *para*-position of tribromide **4** (Table 1). Utilizing standard Sukuzi–Miyaura conditions,[13] a phenyl moiety was introduced into the atropisomeric benzamide to provide product **5a** in 67% isolated yield (Table 1, entry 1). Importantly, no erosion of enantioselectivity was observed during the transformation, providing phenyl adduct **5a** in 95:5 er. This material was

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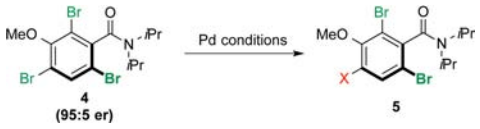
Table 1. Regioselective Pd-Catalyzed *Para*-Functionalizations



entry	Pd conditions	product	yield (%)[a]	pdt er
1	5 mol % $Pd(PPh_3)_4$ 1 equiv phenyl boronic acid 8 equiv K_3PO_4, 50 °C 5:1 THF:H_2O (0.1 M)	 5a	67	95:5
2	5 mol % $Pd(OAc)_2$ 5.5 mol % *rac*-BINAP TMEDA, 1.05 equiv $NaBH_4$ 50 °C, THF (0.1 M)	 5b	71	95:5
3	10 mol % $Pd(OAc)_2$ 10 mol % Xant-Phos 10 equiv NEt_3, CO balloon 60 °C, MeOH (0.05 M), 16 h	 5c	61	95:5
4	5 mol % $Pd_2(dba)_3$ 10 mol % Xant-Phos 1.1 equiv aniline 2.5 equiv NaO*t*Bu, 50 °C THF (0.25 M), 3.5 h	 5d	80	93:7

[a]Reported yields are an average of a 0.5 mmol racemic run and a 0.1 mmol enantioenriched run.

compared to authentic samples, synthesized during development of the bromination methodology,[8b] in order to unambiguously assign the regiochemistry of this transformation. As this process proceeded with very high regioselectivity, the regioisomeric ratios were not conclusively determined. However, it is worth noting that, when observed, the minor regioisomers were easily separated from the desired major component by reversed-phase chromatography.

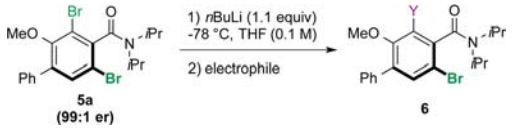
Additionally, dehalogenation conditions employing a hydride source ($NaBH_4$) as the cross-coupling partner[14] yielded dibromide **5b** in 71% yield (Table 1, entry 2), with no observed erosion to the enantioenrichment of the sample. Carbonylation[15] could also be effected at the *para*- position, using slightly higher Pd loading (10 mol % $Pd(OAc)_2$). Interestingly, this transformation proceeded exclusively to ester **5c** in 61% yield (Table 1, entry 3) under a carbon monoxide atmosphere with methanol as solvent. In this case, the reaction stalled at incomplete conversion and starting material could be reisolated.

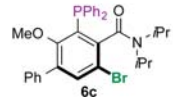
Lastly, Buchwald–Hartwig amination conditions using $Pd_2(dba)_3$ and Xant-Phos[16] provided aniline **5d** (Table 1, entry 4). When the reaction was run at 60 °C with 1.4 equiv of NaO-*t*-Bu using aniline as the coupling partner, **5d** was produced in 90% yield, however, with an 80:20 er. Optimization of reaction temperature and equivalents of NaO-*t*-Bu were important in rectifying excessive loss of enantioselectivity. Thus, performing the coupling at 50 °C with 2.5 equiv of NaO-*t*-Bu afforded **5d** in 80% isolated yield with a slight deterioration of the enantiomeric excess from 95:5 er to 93:7 er. Nonetheless, we were able to derivatize tribromide **4** with little to no enantiomeric erosion in a variety of complexity-generating transformations to install a range of functionalities. All products (**5**) were monitored after 3 weeks in solution and demonstrated no erosion to the enantioselectivities observed.

We next focused on manipulation of the remaining bromides, which reside *ortho* to the amide functional group. Under a range of Pd-catalyzed cross-coupling conditions (standard and modified with respect to temperature, solvent, etc.), we were never successful in developing a highly regioselective process. Multiple complications including low reactivity or double cross-coupling (depending on the conditions), poor regioselectivity, protodehalogenation, and lastly observed erosion to the enantiomeric enrichment proved too challenging to overcome.

Therefore, a new strategy was developed in which a regioselective lithium–halogen exchange was invoked to functionalize the *o*-bromide proximal to the ether moiety[17] (Table 2). By addition of *n*-BuLi at −78 °C, an intermediate

Table 2. Regioselective Lithium–Halogen Exchange



entry	electrophile	product	yield (%)[a]	pdt er
1	MeS-SMe	 6a	87	99:1
2		 6b	80	99:1
3	Cl-PPh_2	 6c	83	99:1[b]

[a]Yields are an average of a 0.2 mmol racemic run and a 0.1 mmol enantioenriched run. [b]Chiral HPLC assay was developed for the phosphine oxide (**6d**).

lithiate was formed which could be trapped by a versatile range of electrophiles.[18] Utilizing dimethyl disulfide and recrystallized **5a** of >99:1 er, sulfide **6a** could be isolated in 87% yield with >99:1 er (Table 2, entry 1). Also, addition to carbonyl-containing compounds, such as benzophenone, could be accomplished to furnish alcoholic products such as **6b** (Table 2, entry 2) in 80% yield. Lastly, chlorodiphenylphosphine afforded phosphine **6c** in 83% yield (Table 2, entry 3). An X-ray crystal structure of phosphine **6c** was obtained for the regioisomeric determination of this transformation.[19] However, in the course of chiral HPLC assay development, the phosphine was observed to slowly convert to phosphine oxide **6d** which was used for enantiomeric determinations of **6c**. Intriguingly, these lithium–halogen exchange reactions proceeded with complete enantioretention, which speaks to the stability of the intermediate at cryogenic temperatures.[7c] In addition, the products (**6**) are also stable in solution (2-propanol/hexanes) for upward of 2 weeks.

While amides are known directing groups of lithiations,[20] in this scaffold we believe this moiety cannot participate due to the orthogonality of the amide's carbonyl and the aryl ring.[21] Thus, we believe that the methyl ether may act as a directing group[22] to achieve such a highly selective lithiation.

With enantioenriched, atropisomeric phosphine (**6c**) in hand, we explored its ability to function as a ligand in organometallic transformations.[23] Containing both a phosphorus atom and the amide functionality, we envisioned that this novel atropisomeric phosphine may display advantageous chelation effects in metal-

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catalyzed processes.[24] Additionally, the axial chirality of this phosphine is in close proximity to the potential metal-binding centers, which could induce high levels of enantioselectivity. Atropisomeric benzamides have been invoked previously to function as bidentate mixed P, O ligands.[25] To assess our benzamides as ligands and to alleviate potential detrimental phosphine oxidation, we chose to complex the atropisomeric phosphine to a metal center for structural analysis (Figure 1). In order to prevent metal insertion into the residual aryl−bromide bond, we chose Au as an appropriate transition metal.

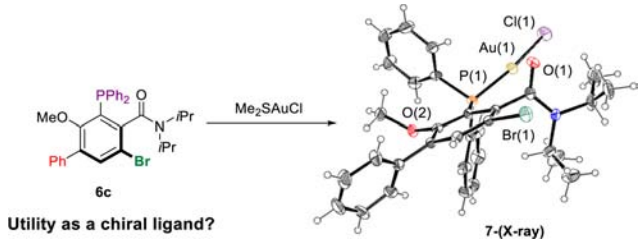
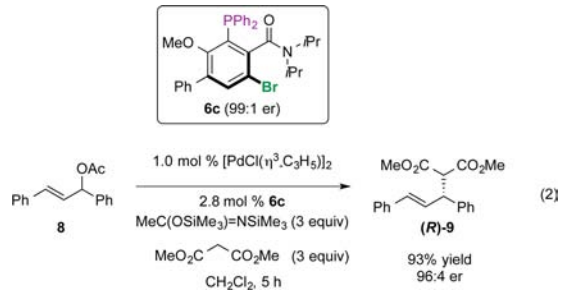


Figure 1. Model system for atropisomeric phosphine **6c** bound to a metal center (P−Au−Cl complex, **7-(X-ray)**).

Thus, complexation of atropisomeric phophine **6c** to Me_2SAuCl, with displacement of volatile dimethyl sulfide, generated a Au−P complex as observed by X-ray crystallography (**7-(X-ray)**). The crystal structure did indeed show the expected linear coordination sphere of Au(I), as well as indicating close proximity of the Au center to the amide moiety (Au−O distance of 3.28 Å). This material also supported our regioisomeric assignments, showing the phenyl ring *para* and phosphine *ortho* to the amide and proximal to the ether. To our knowledge, this is the first report of an atropisomeric, benzamide phosphorus ligand bound to a transition-metal center.

Precedent for axially chiral tertiary aromatic amide P,O ligands in asymmetric organometallic transformations is limited to a few reports showing varied enantioinducing capabilities.[25] Additionally, mixed P,O or P,N bidentate ligands have shown promise in this asymmetric allylic alkylation (AAA) transformation.[26] While we were unsure about the stability of our atropisomeric benzamide under these conditions, we chose Pd-catalyzed AAA as a model system to benchmark our phosphine scaffold in comparison to these analogous studies (eq 2). In the presence of



Pd, 1,3-diphenylpropenyl acetate (**8**) can be alkylated with dimethyl malonate to afford product **9**. To our delight, utilizing 1.0 mol % of allylpalladium dichloride dimer and 2.8 mol % of enantiopure phosphine **6c** furnished the desired alkylated product in 93% yield and 96:4 er in 5 h. In the process of screening, it was identified that premixing the Pd and phosphine ligand provided the highest (and reproducible) enantiomeric ratios of alkylated product **9**. One could conceivably improve the enantioinduction further by manipulating the sterics and electronics of substituents on this modular amide framework.

Utilizing iterative, regioselective cross-coupling and lithium−halogen exchange strategies on tribrominated benzamides, we generated a multitude of heteroatom-rich, axially chiral molecules regioisomerically pure. Coupled together, our peptide-catalyzed bromination followed by regioselective transformations allow for complexity-adding syntheses of unique, atropisomeric scaffolds. As shown by the generation of an enantiopure phosphine ligand for AAA, we hope scaffolds of this type will be useful in both synthetic and biological applications.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures for all experiments and full characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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