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Title: Catalytic Desymmetrization of D\textsubscript{2d}-Symmetric Propochiral Tetrasubstituted Biphenyl Compounds: A Novel Approach to the Synthesis of Axially Chiral C\textsubscript{2} Symmetric Molecules

Abstract approved:

Paul R. Blakemore

Many D\textsubscript{2d}-symmetric 2,2',6,6'-tetrasubstituted biphenyls are readily prepared via net oxidative dimerization of appropriate 1,3-disubstituted benzenes. Conversion of such proprochiral compounds to useful C\textsubscript{2}-symmetric chiral biphenyls requires formal replacement of two substituents on opposing aryl ring units with alternate groups. This under exploited desymmetrization tactic has been demonstrated for the generation of scalemic biaryls using stoichiometric chiral reagent control, but no reports concerning its realization by a (potentially) more efficient asymmetric catalytic approach have appeared. Accordingly, two different possible strategies for achieving a catalytic enantioselective biaryl synthesis based on D\textsubscript{2d} to C\textsubscript{2} desymmetrization were investigated: (a) enzyme catalyzed hydrolysis of tetraester derivatives of 2,2'-biresorcinol, and (b) transition metal catalyzed substitution from 2,2',6,6'-
tetrabromobiphenyl. In pursuit of the first approach, 2,2′-biresorcinol was prepared from 1,3-dimethoxybenzene via n-butyllithium initiated ortho-directed lithiation, followed by iron(III) chloride mediated oxidative coupling of the aryllithium, and then (in a separate step) demethylation of the resulting 2,2′,6,6′-tetramethoxybiphenyl with excess boron tribromide. Tetraacetate and tetravalerate esters of 2,2′-biresorcinol were subsequently synthesized and their hydrolysis with the following four distinct esterases was examined: *Pseudomonas cepacia* lipase (PCL), porcine liver esterase (PLE), *Candida antarctica* lipase B (CAL B), and bovine pancreas acetone powder (a source of bovine cholesterol esterase). Turn-over was not observed in any case; however, a majority of the enzymes studied successfully hydrolyzed model test substrates such as phenyl valerate, phenyl acetate, and mono- and diesters of resorcinol. For the second approach, a significant new one-pot synthesis of 2,2′,6,6′-tetrabromobiphenyl was realized from 1,3-dibromobenzene via lithium diisopropylamide mediated ortholithiation followed again by oxidative coupling with iron(III) chloride (66% yield). Palladium catalyzed cross-coupling reactions (comprising Kumada, Negishi, and Sonogashira subtypes) were evaluated from 2,2′,6,6′-tetrabromobiphenyl and 1,3-dibromobenzene. The latter model substrate revealed that a
degree of control was possible, in that monosubstitution could be readily achieved; however, reactions from the pivotal D2d-symmetric 2,2',6,6'-tetrasubstituted substrate typically gave either no reaction (reflecting the high steric hindrance of the starting material) or else complex intractable mixtures of various polysubstituted products.
Catalytic Desymmetrization of D_2d-Symmetric Prochiral Tetrasubstituted Biphenyl Compounds: A Novel Approach to the Synthesis of Axially Chiral C_2-Symmetric Molecules

By
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I understand that my thesis will become part of the permanent collection of Oregon State University libraries. My signature below authorizes release of my thesis to any reader upon request

Jeremey Tyson Gunderson, Author
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DEDICATION

This work is not only dedicated to the institution and professors that provided me with the means to undertake such a daunting task but also to everyone in my life that has challenged me to learn and grow as an academic and as a person.

To my family and friends: Without your support and guidance, inspiration and challenges I would never have become the man I am today. Thank you for all you have given, that I may now give in return.

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Catalytic Desymmetrization of D_{2d}-Symmetric Proprochiral Tetrasubstituted Biphenyl Compounds: A Novel Approach to the Synthesis of Axially Chiral C_{2}-Symmetric Molecules

1. Proposed Route for the Improvement of Axially Chiral Biaryl Molecule Synthesis

Enantioenriched axially chiral biaryl molecules represent important commodity chemicals and find extensive use as ligands in a wide variety of enantioselective processes,\textsuperscript{1} many of which are conducted on an industrial scale.\textsuperscript{2} Although the reactions controlled by these chiral ligands have reached a high level of sophistication, the biaryl molecules themselves [e.g. 1,1´-binaphth-2-ol (BINOL),\textsuperscript{3} 2,2´-bis-(diphenylphosphanyl)-1,1´-binaphthyl (BINAP),\textsuperscript{4} and 2,2´-bis(diphenylphosphanyl)-6,6´-dimethoxy-1,1´-biphenyl (MeO-BIPHEP)\textsuperscript{5}] are for the most part prepared via lengthy routes and obtained in homochiral form by inefficient classical resolution based protocols (Figure 1).
The objective of the proposed research is to develop an efficient approach to $C_2$-symmetric enantioenriched biaryls (3) based on the catalytic enantioselective desymmetrization of readily obtainable proprochiral $D_{2d}$-symmetric 2,2',6,6'-tetrasubstituted biphenyls (2) (Scheme 1). The desymmetrized products may constitute useful biaryl ligands/materials in their own right, or else provide versatile synthons for the rapid generation of other molecules of interest (e.g. 1,1'-binaphthyls, non-$C_2$-symmetric biaryls, atropisomeric biologically active natural products).
The study will focus on two complementary methods for achieving the desired desymmetrization: (a) transition metal-catalyzed substitution from 2,2’,6,6’-tetrahalobiphenyls (and related species), and (b) acyl transfer processes to/from 2,2’,6,6’-tetrahydroxybiphenyl catalyzed by lipase enzymes. Successful realization of the proposed scheme in either guise will provide entry to useful chiral biaryls via routes which are at once both enantioselective and in many cases shorter than existing syntheses of comparable racemic materials.

1.1 Background and Significance

![Scheme 2. Enantioselective desymmetrization of D_{2d}-symmetric proprochiral biphenyls](image)

Issues of atropoisomerism are increasingly to the forefront of synthetic design and a range of methods are now available for the stereoselective synthesis of biaryl compounds manifesting axial chirality. Despite these advances, important axially chiral commodity chemicals (e.g. MeOBIPHEP, BINAP, etc.) are still for the most part manufactured as racemates and obtained in enantiomerically pure form by classical
resolution. The reason that modern and more sophisticated methods for enantioselective biaryl synthesis have not been widely adopted is due to their multistep nature and intrinsic limitations. For example, the most successful technologies for atroposelective biaryl bond formation require the use of chiral auxiliary groups, while reagent controlled protocols are often non-catalytic and/or have exacting substrate requirements. We seek an efficient and generally applicable enantioselective route to chiral biaryl molecules based on asymmetric catalysis which obviates the need for circuitous manipulations and/or the use of extraneous auxiliary groups to effect stereocontrol en route to the products of ultimate interest. To achieve this objective we propose to employ a new approach to C$_2$-symmetric biphenyls 3 based on the catalytic enantioselective desymmetrization of proprochiral D$_{2d}$-symmetric 2,2',6,6'-tetrasubstituted biphenyl molecules 2 (Scheme 2). The products (3) from such processes may be of direct use themselves, or else represent versatile synthons for straightforward conversion to a plethora of useful (and not necessarily C$_2$-symmetric) axially chiral materials.

Desymmetrization is envisioned by formal replacement of two groups X by two groups Y. The initial "substitution" event, 2 to 5, presents no issue of selectivity; however, in moving forward from the resultant, now prochiral, C$_s$-symmetric intermediate 5, two separate issues of discrimination must be contended with. Specifically, the second X-group to be transformed must lie in the ring previously unperturbed by the
ingress of Y, and of the two enantiotopic X-groups bonded to this arene, the prochirality of one must be selectively recognized over the other. The first issue is essentially a question of regioselectivity and need not present undue difficulties, in principle at least, because the two rings of 5 are potentially electronically differentiated. The second issue, that of enantiotopic group differentiation, has been successfully addressed previously within the context of C₄-symmetric biaryl molecules by both asymmetric transition metal catalysis⁷ and enzyme⁸ based methods (vide infra). An attractive feature of the proposed scheme is the ease with which requisite substrates for desymmetrization studies can be accessed from inexpensive and commercially available 1,3-disubstituted benzene derivatives. Utilization of substituents X which can act as activators during the synthesis of D₂d-symmetric biaryls 2 from "monomer" precursors (1, Scheme 1) and subsequently behave as nucleofugal leaving groups during desymmetrizing substitution will allow for particularly efficient routes to C₂-symmetric biaryl compounds 3.

The D₂d to C₂ desymmetrization approach to enantioenriched biaryl molecules is not without precedent; however, to date this scheme has not been implemented via asymmetric catalysis. Harada and Oku have most extensively explored the concept of interest and described a step-wise method for the overall enantioselective desymmetrization of 2,2’,6,6’-tetrahydroxybiphenyl (6) based on atropodiastereoselective formation of cyclic ketals⁹ and diethers.¹⁰,¹¹ For example, dioxocane 7, representing a
masked synthetic equivalent of 6 in which enantiotopic hydroxyl groups have been expressed and effectively discriminated, is formed with high diastereoselectivity (single isomer) by double alkylation of 6 with a bismesylate (Scheme 3). Adduct 7, and related compounds derived from 6 and other doubly electrophilic chiral addends, can in principle be stereospecifically advanced to a variety of C₂-symmetric biaryl molecules via manipulation of the free hydroxyl groups followed by removal of the chiral tether. Aryl triflates generated from the desymmetrized biphenols (e.g. 8) are ostensibly attractive intermediates for further elaboration; however, successful reports of transition metal catalyzed substitution from such intermediates are limited. Findings from within the Blakemore Research Group suggest that bistriflate 8 is a less than ideal substrate for many useful substitution reactions (Table 1). Notwithstanding the poor reactivity profile of triflate 8, the Harada-Oku desymmetrization approach ultimately lacks efficiency due to its requirement for additional steps to introduce and then subsequently remove the chiral tether.

Scheme 3. Harada-Oku method for the desymmetrization of 2,2’-biresorcinol
An alternative method to effect enantioselective D<sub>2d</sub> to C<sub>2</sub> desymmetrization of proprochiral biphenyls was briefly investigated by Raston and co-workers (Scheme 4).<sup>12</sup> Double metalation of 2,2′,6,6′-tetramethylbiphenyl (14) by a BuLi•(−)-sparteine complex gave dilithio compound 15 which was transformed into diol 16 manifesting 40% ee. While Raston's report clearly indicates that reagent controlled enantioselective desymmetrization of proprochiral biphenyls is possible, the manner in which this was achieved is of narrow scope and would not be applicable for the synthesis of a wider array biaryl molecules.
1.2 Research Objectives

At the onset, variety of efficient catalytic asymmetric methods for enantioselective D$_{2d}$ to C$_2$ desymmetrization of proprochiral biphenyl molecules were to be investigated, including: transition metal catalyzed substitution and acyl transfer processes. In addition, the development of new and efficient syntheses of appropriate substrate molecules \( 2 \) were planned.

Viable concise syntheses of requisite D$_{2d}$-symmetric materials \( 2 \) (\( X = \text{OH, OAc, halogen} \)) can be readily envisioned from inexpensive 1,3-disubstituted benzenes (Scheme 5). The synthesis of 2,2′,6,6′-tetrabromobiphenyl (21) was successfully attempted directly from 1,3-dibromobenzene (20) by employing the nucleofugal halide atoms as activating groups for directed ortho-metalation.$^{14}$
Scheme 5. Proposed syntheses of biaryl substrates

Hayashi and co-workers have reported the enantioselective desymmetrization of prochiral biaryl 2,6-bistriflates, such as 22, by Pd-catalyzed Kumada-type arylation (Scheme 6). High ee’s were generally obtained using (S)-alaphos, although other classes of ligand, including BINAP, also gave non-racemic products. Crucially, it was discovered that the ee of the monosubstituted chiral products increased with the yield of disubstituted adducts (e.g. 24), indicating that kinetic resolution operated in the second (slower) substitution step and favored conversion of the unwanted minor enantiomer.
Scheme 6. Hayashi’s enantioposition-selective arylation\textsuperscript{7}

Hayashi's seminal results reveal that, as may be expected, transition metal catalyzed substitution is faster from arenes possessing two triflate groups than one (i.e. \textbf{22} reacts faster than \textbf{23}). Thus, exposure of a tetrakis(triflate) to Hayashi's protocol would likely proceed from intermediate \textbf{5} (X = OTf, Y = Ar) to regiomer \textbf{3} (X = OTf, Y = Ar) by virtue of intrinsic substrate bias; oxidative addition being faster into more electron deficient Ar-X bonds. Taking Hayashi's protocol as a starting point, we have investigated D\textsubscript{2d} to C\textsubscript{2} desymmetrization of 2,2',6,6'-tetrasubstituted biphenyls with a view to demonstrate the feasibility of such a process and to extend the range of nucleophiles which can be introduced enantioselectively in this manner.\textsuperscript{18}
### Table 2. Scope of proposed transition metal-catalyzed study

Accordingly, the projected study will encompass four different types of transition metal catalyzed substitution reactions (Table 2), some of which have previously been demonstrated in an asymmetric context, i.e. Kumada and Negishi couplings, and others which have not, i.e. Sonogashira coupling and amination.

Efficient enantioselective desymmetrization of prochiral 2-aryl-1,3-diacectoxybenzenes by lipase catalyzed hydrolysis was reported by Matsumoto and co-workers in 2002. These workers achieved greatest success (\%ee \( \geq 97\% \)) with the commercially available purified enzymes *Candida antarctica* lipase (CAL) and *Pseudomonas cepacia* lipase (PCL) (Scheme 7).
Scheme 7. Matsumoto’s lipase catalyzed enantioselective hydrolysis$^8$

Scheme 8. Scope of proposed enzymatic study

We also planned to study similar reactions from proprochiral tetraacetate 19 to chiral diacetate 28 (Scheme 8).

Regioselective acyl donation (6 to 28) is a reasonable expectation since acylation of one hydroxyl group on a given aryl ring of 6 will reduce the nucleophilicity of the remaining free hydroxyl group. Likewise, in the case of deacylation (19 to 28), hydrolysis of a 1,3-diacylated phenyl moiety would occur faster than for a monoacylated resorcinyl unit due to the former being more electron deficient.
2. Proposed Enzymatic Approach for the $D_{2d}$ to $C_2$ Desymmetrization of Tetraacyl Biphenyls

It is well known that the catalytic mechanism of lipases is dependent on the formation of an acyl-enzyme intermediate that facilitates nucleophilic attack and hydrogen transfer.\textsuperscript{30} That being the case, two strategies are available for the deliberate enhancement of acyl-enzyme intermediate formation: 1) the employment of specific substrate structures and/or carbon chain lengths that are well recognized by the wild type enzyme, or 2) the directed evolution of mutant enzymes for the purpose of catalyzing the hydrolysis of specific substrates.\textsuperscript{30} As the later is not an option based on our expertise and available equipment, we have chosen to screen enzymes bearing in mind specific substrate features. Access to the active site of many enzymes is attained through a narrow hydrophobic channel, the length and hydrophobicity of which is supposed to govern the acyl chain length/substrate affinity relationship for esterases.\textsuperscript{31} All three of the selected principal lipases (CAL B, PCL and Porcine Liver Esterase (PLE)) for study present the typical Ser-His-Asp catalytic triad in the active site and so all of the above are perfectly capable of hydrolyzing esters via the same mechanism.\textsuperscript{32-34}
Further, for each of the three enzymes of ultimate interest, there exists literature precedent for both stereoselectivity and tolerance of substrate functionality variation. Although they have never been shown as the sole catalytic means in \( D_{2d} \) to \( C_2 \) desymmetrization, they have been shown to exhibit high levels of stereoselectivity in the esterification/hydrolysis of prochiral biaryl systems (Scheme 3). Further, the enzymes of choice here have been shown to have good substrate affinity for short, medium and long chain acyl groups. Specifically, CAL B demonstrates affinity for acyl groups containing linear chains varying from 1 to 10 carbons and longer. Literature data indicate that the optimum hydrolysis rates are achieved in reactions which employ \( C_{10} \) acyl chains, although acceptable rates of hydrolysis...
and levels of stereospecificity are still available from CAL B where shorter acyl carbon chains are involved.\textsuperscript{30,35}

2.1 Synthesis and Evaluation of Phenylester Test Substrates and Enzyme Candidates

In an effort to confirm the viability of the proposed desymmetrization scheme, a series of test substrates were synthesized for deacylation by exposure to selected lipases for this study. Initial test substrates included a set of esters (31a-d) aimed at the acquisition of data regarding enzyme activity and enzymatic affinity for varying acyl chain length (Table 3). Four different substrates were synthesized in a concise fashion. The drop-wise addition of a slight excess of acyl chloride to the various alcohols necessary dissolved in DCM/Pyr (10:1) followed by sufficient mixing time, readily produced the desired esters in good to excellent yield with purification presenting no significant difficulty.
After purification of the test esters, each was exposed to a series of lipases to determine both the affinity of the enzymes for the test substrates and the activity of the enzymes themselves. Four lipases in total were examined in this research; only three exhibited the desired activity and affinity properties for continued use in this portion of the investigation into \( D_{2d} \) to \( C_2 \) desymmetrization, and so only three are shown here (Table 4).
Table 4. Lipase catalyzed hydrolysis results for monoester test Substrates (hydrolysis results determined by $^1$H NMR)

Under the conditions noted above for each lipase, CAL B, PCL and PLE, showed satisfactory affinity for phenyl acetate and phenyl valerate to continue as lipase candidates. While bovine pancreas acetone powder was shown to be active in the presence of ethyl valerate, it had no affinity for the phenyl esters exposed to it and its candidacy here was discontinued.

2.2 Synthesis of $D_{2d}$-proprochiral Tetraesters of Interest and the Effects of Selected Enzymes on their Hydrolysis

As the synthesis of test phenolic esters was a straightforward and experimentally simple process, so was the synthesis of $D_{2d}$-symmetric 2,2’,6,6’-tetraacyl biphenyl substrates. Beginning with 1,3-dimethoxybenzene (17), using an oxidative ortho-metallation directed oxidative coupling process, the ‘dimerized’ tetraether starting material
(18) was synthesized in a two-step, 1 pot process. Tetraether 18 was subsequently demethylated via exposure to excess BBr₃ in DCM to afford 2,2′-biresorcinol (6). Isolation of the tetrahydroxy biphenyl compound yielded a versatile synthon for the concise and efficient synthesis of D₄-symmetric tetraacyl substrates (Scheme 9).

Scheme 9. Synthesis of compounds 19a and b via the tetraesterification of 2,2′-biresorcinol

While the test substrates showed positive interactions with either CAL B, PCL or PLE, dependant on the acyl group involved, chosen enzymes showed no affinity for any of the tetraacyl compounds (19). Thus no catalytic enzymatic desymmetrization was encountered in this research.
Although no enzyme catalyzed hydrolysis was observed in this study, the reactivity and substitution pattern of the biresorcinol system remained of interest as the explication of the associated substitution motif may provide useful information for the advancement of future work. Since it was not possible to effectively deacylate either of the tetraacyl compounds in a manner that would yield any informative results the non-enzymatic stoichiometric acylation of biresorcinol (6) was investigated (Scheme 12).
Scheme 10. Stoichiometric acylation of biresorcinol

It was found that upon the treatment of biresorcinol (6) with two equivalents of either acetyl or valeryl chloride that the molar ratios of tri- to disubstituted product were 3 : 1 and 31 : 1 respectively. These results lend some information to the reactivity mode of 6 and its mono-, di-, and triacyltated products. One hypothesis to explain the observed results is that there is an intramolecular coordinative effect enhancing the nucleophilicity of free alcohol groups adjacent to acetylated positions. Based on the absence of the 2,6-diacylated products in both the acetyl and the valeryl experiments, this hypothesis presumes that the coordinative effect is operating in both the mono- and diacylated products and the rate conversion to the di- and triacylated products respectively. Statistically the triacylated product would be the major product. Unfortunately, this hypothesis does not explain the absence of the tetraacylated product in both experiments. Steric crowding may be an explanation for the absence of the tetraacyl products, but the addition of excess acyl chloride in both case leads to the quantitative production of the respective tetraesters. Another hypothesis is that the 2,6-diacylated compounds are rapidly converted to the triacylated
compounds as a result of double activation of the previously unperturbed ring and are not observed, leaving the 2,2’-diesters as an observable byproduct.
3. Transition Metal Catalyzed Approach to the Desymmetrization of $D_{2d}$-proprochiral biphenyl Tetrabromide

Several transition metal-catalyzed cross coupling systems are commonly used in organic synthesis today with many advantages and disadvantages to each. However, reactivity profiles for substrates stand as a common factor.

![Diagram of catalytic cycle]

**Figure 3.** General catalytic cycle for Negishi, Kumada and Sonogashira reactions

Herein, Sonogashira, Negishi, and Kumada type couplings were chosen as the Pd-catalyzed reactions of major interest for this study. As for the differences in palladium catalysts and catalytic systems themselves, excluding substrate, the three chosen present distinct
advantages over all others, elevating them to the level of primary interest here. Both the Kumada and Negishi reactions have been noted as highly stereoconservative reactions by virtue of the facile nature of the transmetalation steps involved in each. The expedience of the transmetalation step in transition metal-catalyzed reactions has been noted as an important factor in the configurational stability of intermediates involving 2,2’-dihalobinaphthyl. Enantioenriched dihalobinaphtyls exposed systems, where rapid transmetalation processes are involved, undergo substitution with little to no scrambling of the stereochemistry whereas transition-metal catalyzed processes involving less facile transmetalation steps tend to lead to products with lower ee’s.

Figure 4. Proposed mechanism for stereoconservation/degradation of 2,2’-dihalobinaphthyls.
The Sonogashira reaction was subsequently chosen for its relative experimental ease, high tolerance of both heteroatomic species and dissolved oxygen, and for the lack of steric demand of the incoming alkynes given the highly sterically encumbered substrate. Further, all three cross coupling reactions of interest have the advantage of operating at relatively low temperatures and in the presence of inexpensive bases in most cases. Steric and electronic effects are imposed on these systems by both the ligands and the substrates used. Increasing steric bulk of the phosphine ligands employed is often found to increase the rate of these types of reactions. In 2007 Plenio and co-workers published a study detailing the effect of steric bulk in Sonogashira reactions. It was found that increasing ligand bulk affected reaction rates favorably while increasing steric hindrance of the substrate had an adverse effect on the rate of reaction. Fortunately no degree of substrate hindrance was able to shut down the reaction completely, given the sterically crowded profile of the $D_{2d}$-symmetric proprochiral substrate of interest here. We infer from the above publications that given the proper conditions and ligand systems any of the aforementioned cross coupling reactions of interest are reasonable prospects for the production of $C_2$-symmetric axially chiral compounds.
3.1 Examination of Potential Palladium-Catalyzed Reactions using 1,3-Dibromobenzene as a Test System

As was the case with the investigation of the enzymatic catalysis process, there was also a need to develop a test system for the investigation of viable transition metal catalyzed reactions. Fortunately, in this case, instead of having to synthesize a series of test substrates, only one was needed as the difference in transition metal catalyzed reactions applicable to this project differ in the incoming substrate and reaction conditions, the test substrate need not be altered for each coupling process used. Chosen as the test substrate was 1,3-dibromobenzene (20); the direct precursor to the D<sub>2d</sub>-symmetric tetrabromide (21) used as the main substrate for the transition metal catalyzed desymmetrization studies herein. Conveniently, the aforementioned test substrate/starting material is both commercially available and inexpensive. It was found that 1,3-dibromobenzene is readily mono- and disubstituted by several different palladium catalyzed carbon-carbon coupling reactions including Kumada, Negishi, Sonogashira type reactions as well as several others.\textsuperscript{38,39,40} This investigation looked at both mono- and disubstitution of the test substrate in Negishi, Kumada, and Sonogashira type carbon-carbon coupling reactions (Table 6).
Table 6. Palladium-catalyzed substitutions of 1,3-dibromobenzene

<table>
<thead>
<tr>
<th>Entry</th>
<th>Incoming R (equivalents)</th>
<th>Reaction Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtMgCl (2.0 eq)</td>
<td>PdCl₂(PPh₃)₂, LiCl, Et₂O/Tol, -20 °C</td>
<td>34a : 35a = 13 : 8 (ratio determined by ¹H NMR)</td>
</tr>
<tr>
<td>3</td>
<td>n-BuLi (5.4 eq)</td>
<td>Pd⁹(dppf), THF, ZnCl₂, 65 °C, 24h</td>
<td>34b : 35b = 3 : 2 (ratio determined by ¹H NMR)</td>
</tr>
<tr>
<td>5</td>
<td>OH (1.0 eq)</td>
<td>Pd₂(dba)₃, dppf, ℓPr₂NH (reflux), CuI</td>
<td>34c = 97%</td>
</tr>
<tr>
<td>6</td>
<td>OH (2.0 eq)</td>
<td>Pd₂(dba)₃, dppf, ℓPr₂NH (reflux), CuI</td>
<td>34c : 35c = 13 : 7 (ratio determined by ¹H NMR)</td>
</tr>
</tbody>
</table>

Each of which lend two important sets of data: 1) the test substrate is compatible with the reaction conditions; 2) the second substitution event proceeds more slowly than the first. Assuming that the test substrate (20) behaves with relative similarity to the substrate of interest (21), these results indicate that the biphenyl analog should prove to be a reasonable subject for the study of D₂d to C₂ transition metal catalyzed desymmetrization.

### 3.2 Direct Synthesis of 2,2’,6,6’-Tetrabromobiphenyl from 1,3-Bibromobenzene ‘Monomer’

The synthesis of 2,2’,6,6’-tetrabromobiphenyl in this research has proven to be somewhat significant in its own right. A few syntheses of this particular material had been previously published, two were of note
with respect to this project. In the first paper the first step was an ortholithiation of 1,3-dibromobenzene which was quenched by the addition of excess I$_2$ producing 1,3-dibromo-2-iodobenzene (35). The iodinated product was then subject to a stoichiometric Cu-coupling protocol yielding the desired product in 33\% overall yield (Scheme 13).$^{39}$

![Scheme 11](image-url)

**Scheme 11.** Rajca’s 1996 synthesis of 2,2’,6,6’-tetrabromobiphenyl$^{39}$

The later paper mentioned,$^{40}$ employs a modified Ullmann coupling procedure as a one-pot 3-step procedure from 2-iodo-1,3-dibromobenzene yielding 56\% of the desired D$_{2d}$-symmetric product (Scheme 14). The modification to the procedure of note is the addition of one equivalent of nitrobenzene which emerges from the reaction unchanged and its reduction products are not observed. It is considered that the nitrobenzene acts as a co-solvent facilitating the dissolution of the CuBr$_2$ and subsequent formation of an unstable diaryl copper species by transmetalation of the aryllithium intermediate.
The ortho-coupling process developed here employs LDA generated in situ by $^1$Pr$_2$NH and n-BuLi, FeCl$_3$ and 1,3-dibromobenzene, all of which are commonplace in synthetic laboratories, commercially available and relatively inexpensive. The first step, just as in the first experiment discussed above, produced the aryl lithium intermediate, a process that was checked on numerous occasions for completeness by quenching the aryl lithium intermediate with excess I$_2$, confirming that the lithiation process used here was indeed a quantitative process. After sufficient stirring time was allowed for quantitative lithiation, a suspension of FeCl$_3$ was added to the reaction mixture and the complete solution was given ample time to react and warm to room temperature. The result of the procedure described was a 66% yield of the desired product (Scheme 13).

Scheme 13. Our one-pot, two-step synthesis of tetrabromide 21
Since this reaction was not the focus of the research being conducted, but only a means to the D$_{2d}$-symmetric substrate of ultimate interest, no optimization studies were undertaken. Although, with further optimization this iron-mediated biaryl coupling process could lead to more consistent results, higher yields, more simple work-up procedures, and an overall improvement in the state of the art for the production of this class of materials from available and inexpensive precursors.

3.3 Negishi, Kumada, and Sonogashira Reactions of 2,2’,6,6’-Tetraphenylbiphenyl

The ultimate goal of this portion of the research was to prove that the transition metal-catalyzed desymmetrization of D$_{2d}$-symmetric tetrahalobiphenyl compounds is a viable synthetic approach to C$_2$-symmetric, axially chiral commodity chemicals and other useful synthons.

Scheme 14. Negishi-type butylation of 2,2’,6,6’-tetraphenylbiphenyl
While limited success was achieved, some of our results give hope of the advancement of the proposed route. One of the first attempts at substituting the tetrabromide was made using a Negishi coupling, resulting in a mixture of butylated products intractable by column chromatography, preparative HPLC and chiral HPLC (Scheme 14). This result also showed us that 2,2’,6,6’-tetrabromobiphenyl can in fact be acted upon by palladium-catalyzed carbon-carbon coupling processes. Later attempts for substitution were aimed improving the prospects for successful product discrimination/resolution by using more polar side chains. Using the test system it was shown that Sonogashira coupling, employing various alkynes, was capable of mono- and disubstituting 1,3-dibromobenzene with good to excellent yields (Table 7). In both cases, the products and reaction mixtures were relatively easy to handle and easily separable. A variety of alkynes were used as incoming substituents in the test system to examine the procedural simplicity of their use not only in setting up the reactions but in the elucidation of the products. It was concluded that propargyl alcohol, and 3-butyn-1-ol were both reasonable alkyne candidates based on the results from the coupling of 1,3-dibromobenzene with each (Table 7). The products were easily separated by chromatography, and showed no sign of degradation during work up or short term storage. The Sonogashira coupling proved to be of great interest to us as the technical aspects of the Sonogashira reaction are relatively simple. This reaction is not particularly air
sensitive, it does not call for extreme thermal conditions, and the reagents commonly used in Sonogashira reactions require little to no preparation before their addition to the reaction mixture. Being such an attractive reaction for our purposes, the Sonogashira coupling was examined in detail with respect to this desymmetrization project.

\[
\text{Br} \quad \text{Br} \quad \text{Pd cat} \quad \text{Br} \quad \text{R}
\]

1 equivalent of alkyne

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkyne</th>
<th>Conditions</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[ \text{OH} ]</td>
<td>\text{Pd}_{2}\text{dba}_3, \text{dppf, CuI, ^{i}\text{Pr}_2\text{NH, reflux}}</td>
<td>97%</td>
</tr>
<tr>
<td>2</td>
<td>[ \text{OH} ]</td>
<td>\text{Pd}_{2}\text{dba}<em>3, \text{dppf, ^{i}\text{Pr}</em>\text{NH, reflux}}</td>
<td>96%</td>
</tr>
<tr>
<td>3</td>
<td>[ \text{OH} ]</td>
<td>\text{Pd}_{2}\text{dba}_3, \text{dppf, CuI, Et}_3\text{N, THF, 65 °C}}</td>
<td>No Reaction</td>
</tr>
<tr>
<td>4</td>
<td>[ \text{OH} ]</td>
<td>\text{PdCl}_{2}(\text{PPh}_3)_2, \text{CuI, Et}_3\text{N, DMF, rt}}</td>
<td>93%</td>
</tr>
<tr>
<td>5</td>
<td>[ \text{OH} ]</td>
<td>\text{Pd}_{2}\text{dba}<em>3, \text{dppf, CuI, ^{i}\text{Pr}</em>\text{NH, reflux}}</td>
<td>97%</td>
</tr>
</tbody>
</table>

Table 7. Variations of Sonogashira conditions for the alkyynylation of 1,3-dibromobenzene

Several variations of alkyne (previously discussed), solvent and overall reaction conditions were tested and shown to work very well in the case of 1,3-dibromobenzene. Based on these preliminary results these alkynes, solvent systems and reaction condition sets were each applied to the 2,2’,6,6’-tetrabromobiphenyl system to no avail.
Table 8. Sonogashira reactions of 2,2’,6,6’-tetrabromobiphenyl

While most attempts resulted in the quantitative recovery of the starting material, a few attempts showed that minimal reaction had occurred by $^1$H NMR of the crude mixtures. Unfortunately the resulting reaction mixtures were extremely complex and impossible to extract denying us the ability to definitively isolate any of the desired coupled products for confirmation and analysis purposes.
4. Conclusion

Initial results obtained by way of test substrates in both the enzymatic and transition metal catalyzed approaches to this research lead us to believe that our proposed route to C$_2$-symmetric axially chiral materials is theoretically sound. The test substrates examined for both the enzyme and transition metal-catalyzed cases were readily transformed by the reactions of interest and their products easily isolated implying that the regiochemical outcome of reactions executed on their biphenyl analogs should proceed as proposed. The major failing here being that reactions of the D$_{2d}$-symmetric substrates simply did not proceed. While appropriate test substrates were readily acted upon by the desired reactions, their biphenyl analogs remained unchanged under the same conditions. These results lead to two possible conclusions: 1) the reactivity of the ‘dimerized’ analogs of the test substrates are significantly chemically differentiated from their monomeric counterparts, 2) the biphenyl compounds, while possessing extremely similar electronics to their monomeric counterparts, are simply unable to be acted on under the prescribed conditions due to limitations directly related to their steric and geometric constitutions. One of the major limitations for the investigation of the transition metal-catalyzed desymmetrization route has been the expense and difficulty of compiling a comprehensive ligand library for screening in the work presented here.
Examples of ligands shown to enhance Pd-catalyzed reactions in crowded systems similar to ours include di-adamantyl, and di-tertbutyl phosphines. Polyphosphinyl ligand systems have also been shown to form highly active and efficient catalysts as illustrated in work presented by Doucet and Santelli in 2004. While none of the ligand systems employed here were effective in the substitution of 2,2’,6,6’-tetrabromobiphenyl, many other ligand systems remain uninvestigated despite their apparent potential for affecting the intended process investigated here.

Further work on the enzymatic front of our project may be effective in advancing the understanding and utility of the proposed system. While many purified enzymes are commercially available, only four were investigated here and only three of those four (CAL B, PLE, and PCL) showed reasonable affinity for our test esters. Simply put, the examination of more esterases may prove necessary. In addition to the screening of more enzymes, slight modifications to the tetraesters investigated here in may also prove to be a reasonable course of action. Lengthening of the acyl chains used (e.g. octanoyl vs. valeryl) may provide enhanced substrate recognition or rate of hydrolysis via the formation of more favorable acyl-enzyme intermediates.
5. Experimental

*General techniques:* All reactions requiring anhydrous conditions were conducted in flame-dried glass apparatus under an atmosphere of Argon. THF and Et$_2$O were freshly distilled from sodium benzophenone ketyl prior to use. DMSO and DMF were distilled from CaH$_2$ at 15 mmHg. CH$_2$Cl$_2$ was freshly distilled from CaH$_2$ and PhMe was distilled from molten sodium metal. Anhydrous MeOH was obtained by distillation from its magnesium alkoxide and stored under Argon over activated 4Å molecular sieves. Preparative chromatographic separations were performed on EM Science silica gel 60 (35-75 μm) and reactions followed by TLC analysis using Sigma-Aldrich silica gel 60 plates (2-25 μm) with fluorescent indicator (254 nm) and visualized with UV, phosphomolybdic acid or $p$-anisaldehyde. All commercially available reagents were purchased from Aldrich and were used as received unless otherwise noted.

Melting points were recorded using open capillary tubes on a Griffin melting point apparatus and are uncorrected. Specific optical rotations were measured at ambient temperature (22 °C) from CHCl$_3$ solutions on an Optical Activity AA-1000 polarimeter using a 1 mL cell with 0.2 dm path length. Infra-red spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer using a thin film supported between NaCl plates or KBr discs where stated. $^1$H and $^{13}$C NMR spectra were
recorded in Fourier transform mode at the field strength specified on Bruker Avance FT-NMR spectrometers. Spectra were obtained from the specified deuterated solvents in 5 mm diameter tubes. Chemical shift in ppm is quoted relative to residual solvent signals calibrated as follows:

\[
\begin{align*}
\text{CDCl}_3 & \quad \delta_H (CHCl_3) = 7.26 \text{ ppm}, \quad \delta_C = 77.2 \text{ ppm}; \quad \text{(CD}_3\text{)SO} \quad \delta_H \\
\text{(CD}_3\text{SOCHD}_2) & \quad = 2.50 \text{ ppm}, \quad \delta_C = 39.5 \text{ ppm}; \quad \text{C}_6\text{D}_6 \quad \delta_H (C_6\text{HD}_5) = 7.16 \\
\text{ppm}, \quad \delta_C = 128.0 \text{ ppm}; \quad \text{CD}_3\text{OD} \quad \delta_H (CHD}_2\text{OD}) = 3.31 \text{ ppm}, \quad \delta_C = 49.0 \\
\text{ppm}; \quad \text{(CD}_3\text{)CO} \quad \delta_H (CD}_3\text{COCHD}_2) = 2.05 \text{ ppm}, \quad \delta_C = 29.8 \text{ ppm}.
\end{align*}
\]

Multiplicities in the $^1$H NMR spectra are described as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constants are reported in Hz. Numbers in parentheses following carbon atom chemical shifts refer to the number of attached hydrogen atoms as revealed by the DEPT spectral editing technique. Electron-impact (EI), chemical ionisation (CI), and fast atom bombardment (FAB) mass spectra (MS and HRMS) were obtained with a Micromass VG Autospec spectrometer. Electrospray (ES) mass spectra (MS and HRMS) were obtained with a Micromass LCT spectrometer. Ion mass/charge ($m/z$) ratios are reported as values in atomic mass units.
Laboratory notebook reference: JTG03

2,2',6,6'-Tetramethoxybiphenyl: 1,3-dimethoxy benzene (12.5 mL, d = 1.005, 12.56 g, 90.5 mmol) was added to anhydrous THF (150 mL) at 0 °C under argon by syringe and allowed to stir for 30 min at 0 °C. n-BuLi (39 mL, 2.32 M in hexanes, 90.5 mmol) was added drop-wise over 10 min and stirred for 20 min at 0 °C. Separately, FeCl₃ (15g, 90.5 mmol, dried on high vac 100 °C) was added to anhydrous THF (150 mL) at -78 °C under argon and allowed to stir 1h. The separate solutions were combined via cannula and allowed to stir for 15h, held at -78 °C for 2h then allowed to warm to room temperature. The resulting mixture was then quenched with excess sat. aq. NH₄Cl (300 mL) and the whole biphasic mixture was filtered through celite. Filtrate washed CHCl₃ (3x150 mL) then D.I. H₂O (3x50 mL). Layers were separated and the aqueous layer washed with CHCl₃ (2x100 mL). The organic layer was dried over excess Na₂SO₄ and concentrated on rotovap. The resulting concentrate was then triturated with cold hexanes yielding a colorless crystalline precipitate. The mother liquor was then condensed and recrystalized. 2,2’,6,6’-tetramethoxybiphenyl was obtained as white crystals (4.62 g, 16.8 mmol, 37% yield): mp 174-176 °C (EtOAc); ³¹H
NMR (300 MHz, CDCl$_3$) $\delta$ 7.30 (2H, t, $J = 8.25$ Hz), 6.67 (4H, d, $J = 8.31$ Hz), 3.37 (12H, s) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 158.37 (0), 128.66 (1), 112.53 (0), 104.43 (1), 56.11 (3) ppm. $^1$H and $^{13}$C NMR spectral data in agreement with those previously reported by Sephton.\textsuperscript{ref}

Laboratory notebook reference: JTG07

2,2',6,6'-Tetrahydroxybiphenyl: To a solution of 2,2',6,6'-tetramethoxybiphenyl (5.04 g, 18.4 mmol) in CH$_2$Cl$_2$ (70 mL) at -78 °C under argon allowed to stir for 1h was slowly added a solution of BBr$_3$ (7 mL, FW = 250.5, d = 2.65, 74.2 mmol) in CH$_2$Cl$_2$ (42 mL) under argon via syringe over 15 min. The resulting complete mixture was then allowed to stir for 5h warming to rt H$_2$O (150 mL) was then added to the reaction mixture in a -10 °C bath. The phases were separated and the aqueous phase washed Et$_2$O (2x150 mL), excess brine was added to the aqueous phase and it was extracted again with Et$_2$O (1x150 mL). The organic layer was dried over excess Na$_2$SO$_4$ and condensed in vacuo. 2,2',6,6'-tetrahydroxybiphenyl was collected as colorless crystals (3.21 g, 80% yield): mp 94-98 °C (CH$_2$Cl$_2$); $^1$H NMR
(300 MHz, CDCl₃) δ 7.31 (2H, t, J = 8.23 Hz), 6.70 (4H, d, J = 8.22 Hz) ppm. ¹H NMR data in agreement with those previously reported by Sephton.²²

Laboratory notebook reference: JTG14

2,2′,6,6′-Tetrabromobiphenyl: To a mixture of anhydrous THF (50 mL) and hexanes (16 mL) at -78 °C under argon is added n-BuLi (10 mL, 2.5M in hexanes, 25.0 mmol) slowly by syringe and allowed to stir for 20 min at -78 °C. iPr₂NH (3.5 mL, d = 0.716, 24.8 mmol) was added to the BuLi solution at -78 °C and allowed to stir 20 min. 1,3-Dibromobenzene (3 mL, d = 1.955, 5.86 g, 24.8 mmol) was then added to the solution and allowed to stir 1h at -78 °C under argon. Separately, FeCl₃ (4.46g, 27.5 mmol, dried on high vac 100 °C) was added to anhydrous THF (75 mL) at -78 °C under argon and allowed to stir 1h. The separate solutions are combined via open air transfer and allowed to stir for 15h, held at -78 °C for 2h then allowed to warm to room temperature. The resulting mixture was then quenched with excess sat. aq. NH₄Cl and the whole biphasic mixture was filtered through celite. Filtrate washed CHCl₃ (3x150 mL) then H₂O (3x150 mL). Layers were
separated and the aqueous layer washed CHCl₃ (2x150 mL). The organic layer was dried over excess Na₂SO₄ and concentrated in vacuo. The resulting concentrate was then triturated with cold hexanes yielding a colorless crystalline precipitate. 2,2’,6,6’-tetrabromobiphenyl was obtained as white crystals (4.2 g, 8.3 mmol, 66% yield): mp 214-216 °C (CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 7.66 (4H, d), 7.15 (2H, t) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 142.07 (0), 131.76 (1), 130.76 (1), 124.37 (1) ppm. ¹H and ¹³C NMR were in agreement with those previously reported by Leroux.¹⁴

Laboratory notebook reference: JTG49

\[
\begin{align*}
\text{6} & \quad \text{C}_{12}\text{H}_{10}\text{O}_4 \quad (218.185) \\
\text{19b} & \quad \text{C}_{32}\text{H}_{42}\text{O}_8 \quad (554.68)
\end{align*}
\]

2,2’,6,6’-Tetravaleroxybiphenyl: To a solution of pyridine (1 mL, d = 0.978 g/mL, 0.978 g, 12.4 mmol) in CH₂Cl₂ (10 mL) stirring at room temperature in a flame dried 25 mL round bottom flask under argon was added 2,2’,6,6’-tetrahydroxybiphenyl (0.500 g, FW = 218 g/mol, 2.3 mmol). The resulting solution was allowed to stir for 20 min then valeryl chloride (1.4 mL, FW = 120.6 g/mol, d = 0.995 g/mL, 11.6 mmol) was added dropwise over 30 minutes. The reaction mixture continued
stirring overnight to ensure complete reaction. The reaction mixture was then added to a 125 mL separatory funnel and washed with 1M aqueous NaHCO₃ (1x250 mL) followed by H₂O (2x100 mL). The Et₂O was dried on excess Na₂SO₄ and condensed in vacuo. The product was obtained as a clear yellow oil (1.114 g, 2.01 mmol, 86% yield): IR (thin film) 2959, 2933, 2873, 1766, 1454, 1220, 1135, 1097 cm⁻¹; \(^1\)H NMR (300 MHz, CDCl₃) \(\delta\) 7.40 (2H, t, \(J = 8.2\) Hz), 7.10 (4H, d, \(J = 8.2\) Hz), 2.26 (8H, t, \(J = 7.3\)), 1.43 (8H, m), 1.22 (8H, m), 0.81 (12H, t, \(J = 7.3\) Hz) ppm; \(^1\)C NMR (75 MHz, CDCl₃) \(\delta\) 171.35 (0), 149.40 (0), 128.83 (1), 119.75 (1), 33.69 (2), 26.59 (2), 21.98 (2), 13.67 (3) ppm. MS (TS) \(m/z\) 577.3 (M+H)⁺, 572.7 (M+H)⁺; HRMS (ES) \(m/z\) 555.2958 (calcd. for C₃₂H₄₃O₈: 555.2958).

Laboratory notebook reference: JTG50

\[
\begin{align*}
\text{DCM/Pyr (10:1);} & \quad (2 \text{ eq}) \\
\text{room temp, 2h} &
\end{align*}
\]

2,2'-Dihydroxy-6,6'-divaleroxybiphenyl and 2-hydroxy-2',6,6'trivaleroxybiphenyl: To a solution of pyridine (1 mL, d = 0.978 g/mL, 0.978 g, 12.4 mmol) in CH₂Cl₂ (10 mL) stirring at room temperature in a flame dried 25 mL round bottom flask under argon was
added 2,2',6,6'-tetrahydroxybiphenyl (0.500 g, FW = 218 g/mol, 2.3 mmol). The resulting solution was allowed to stir for 20 min then valeryl chloride (0.4 mL, FW = 120.6 g/mol, d = 0.995 g/mL, 3.3 mmol) was added dropwise over 30 minutes. The reaction mixture continued stirring overnight to ensure complete reaction. The reaction mixture was then added to a 125 mL separatory funnel and washed with 1M aqueous NaHCO₃ (1x250 mL) then H₂O (2x100 mL). The Et₂O layer was dried on excess Na₂SO₄ and condensed in vacuo. The crude residue was further purified by column chromatography (eluting with 33% EtOAc in hexanes) to afford, in order of elution; the trivalerate (180 mg, 0.38 mmol, 23% yield), then the divalerate (5 mg, 0.01 mmol, 0.8% yield) as colorless oils. Divalerate data: IR (thin film) 3415, 2957, 2923, 2852, 1758, 1454, 1145, 1102, 1007 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.36 (2H, t, J = 8.2 Hz), 6.97 (2H, d, J = 8.1 Hz), 6.75 (2H, d, J = 7.85), 2.25 (4H, t, J = 7.4), 1.60-0.77 (14H, m) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 172.96 (0), 155.46 (0), 151.27 (0), 150.14 (0), 131.08 (1), 114.89 (1), 114.79 (1), 33.64 (2), 29.72 (2), 26.73(2), 21.89 (2), 13.65 (2) ppm. MS (TS) m/z 410.3 (M+H)⁺, 409.2 (M+H)⁺; HRMS (ES) m/z 409.1660 (calcd. for C₂₂H₂₆O₆Na : 409.1627). Trivalerate: IR (thin film) 2959, 2932, 2872, 1763, 1454, 1221, 1139, 1100, 1008 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.48 (1H, t, J = 9.0 Hz), 7.27 (1H, q), 6.86 (2H, dd, J = 9.0, 1.5 Hz), 2.25 (6H, q, J = 7.4 Hz), 1.39 (6H, m), 1.18 (6H, m), 0.81 (9H, q, J = 7.1 Hz) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 172.46 (0),
171.51 (0), 155.09 (0), 150.55 (0), 149.18 (0), 130.34 (1), 129.97 (1),
120.63 (1), 115.06 (1), 114.01 (1), 34.03 (2), 33.79 (2), 26.87 (2), 26.77
(2), 22.20 (2), 22.09 (2), 13.81 (3) ppm. MS (TS) m/z 493.5 (M+H)^+;
HRMS (ES) m/z 471.2369 (calcd. for C_{27}H_{35}O_{7}: 471.2383).

Laboratory notebook reference: JTG56

\[
\begin{align*}
6 & \quad \text{C}_{12}\text{H}_{10}\text{O}_{4} & (218.195) \\
19a & \quad \text{C}_{20}\text{H}_{18}\text{O}_{6} & (386.334)
\end{align*}
\]

**2,2',6,6'-Tetraacetoxybiphenyl:** To a solution of pyridine (1 mL, d =
0.978 g/mL, 0.978 g, 12.4 mmol) in CH\(_2\)Cl\(_2\) (10 mL) stirring at room
temperature in a flame dried 25 mL round bottom flask under argon was
added 2,2',6,6'-tetrahydroxybiphenyl (0.494 g, FW = 218 g/mol, 2.27
mmol). The resulting solution was allowed to stir for 20 min then acetyl
chloride (1.4 mL, FW = 78.5 g/mol, d = 1.104 g/mL, 10.2 mmol) was
added dropwise over 30 min. The reaction mixture continued stirring
overnight to ensure complete reaction. The reaction mixture was then
added to a 125 mL separatory funnel and washed with 1M aqueous
NaHCO\(_3\) (1x250 mL) then H\(_2\)O (2x100 mL). The Et\(_2\)O layer was dried
on excess Na\(_2\)SO\(_4\) and condensed in vacuo. The product was obtained as
a colorless semi-crystalline solid in good purity and quantitative yield. A
small sample was recrystallized from a solution of DCM/MeOH (95:5)
to yield colorless needles: mp 192-194 °C (DCM/MeOH); IR (thin film) 1758, 1367, 1190, 1030 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.44 (2H, t, J = 8.2 Hz), 7.13 (4H, d, J = 8.2 Hz), 2.01 (12H, s) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 168.78 (0), 149.24 (0), 129.12 (1), 119.98 (1), 20.66 (3) ppm. MS (TS) m/z 410 (M+H)⁺, 409 (M+H)⁺; HRMS (ES) m/z 409.0893 (calcd. for C₂₀H₁₈O₈Na : 409.0892).

Laboratory notebook reference: JTG57

![Reaction diagram](image)

**2-Hydroxy-2’,6,6’-triacetoxybiphenyl:** To a solution of pyridine (1 mL, d = 0.978g/mL, 0.978 g, 12.4 mmol) in diethyl ether (20 mL) stirring at room temperature in a flame dried 25 mL round bottom flask under argon was added 2,2’,6,6’-tetrahydroxybiphenyl (0.808 g, FW = 218 g/mol, 3.7 mmol). The resulting solution was allowed to stir for 20 min then acetyl chloride (0.53 mL, FW = 78.5 g/mol, d = 1.104 g/mL, 7.4 mmol) was added dropwise over 30 min. The reaction mixture continued stirring overnight to ensure complete reaction. The reaction mixture was then added to a 125 mL separatory funnel and washed with 1M aqueous NaHCO₃ (1x250 mL) then H₂O (2x100 mL). The Et₂O was dried on excess Na₂SO₄ and condensed in vacuo. A 0.711 g mixture of
products was obtained and subject to silica gel chromatography using DCM/MeOH (95:5) the least polar fraction eluted was the triacetate compound (114 mg, 0.3 mmol, 8% yield) isolated as a clear brownish oil: IR (thin film) 3446, 2360, 2340, 1769, 1191, 1028 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.49 (1H, t, \(J = 8.2\) Hz), 7.29 (1H, t, \(J = 8.2\) Hz), 7.14 (2H, d, \(J = 8.2\)), 6.85 (1H, dd, \(J = 8.24, 0.75\)), 6.78 (1H, dd, \(J = 8.1, 0.75\)), 2.0 (9H, s); \(^1^3\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 169.43 (0), 168.95 (0), 154.87 (0), 150.08 (0), 148.85 (0), 130.02 (1), 129.90 (1), 120.48 (1), 114.78 (1), 113.65 (1), 20.69 (3), 20.45 (3) ppm. MS (TS) \(m/z\) 369 (M+H\(^+\)), 367 (M+H\(^+\)); HRMS (ES) \(m/z\) 345.0973 (calcd. for C\(_{18}\)H\(_{17}\)O\(_7\) : 345.0974).

Laboratory notebook reference: JTG08

1,3-Dibromo-2-iodobenzene: To a mixture of anhydrous THF (50 mL) and hexanes (16 mL) at -78 °C under argon is added n-BuLi (10 mL, 2.5M in hexanes, 25.0 mmol) slowly by syringe and allowed to stir for 20 min at -78 °C. \(\text{iPr}_2\)NH (3.5 mL, \(d = 0.716\), 24.8 mmol) was added to the BuLi solution at -78 °C and allowed to stir 20 min. 1,3-Dibromobenzene (3 mL, \(d = 1.955\), 5.86 g, 24.8 mmol) was then added to the solution and allowed to stir 2h at -78 °C under argon. A mixture of
I₂ (6.453 g, 50.9 mmol) in dry THF (15 mL) was prepared in a flame dried 50 mL round bottom flask and cooled to -78 °C under argon. The solutions were then combined by syringe addition of the I₂ solution to the 1,3-dibromobenzene solution. The resultant reaction mixture stirred for 1h at -78 °C under argon and was then allowed to warm slowly to room temperature. The reaction mixture was then condensed in vacuo and dissolved in Et₂O. The Et₂O layer was washed with 10% aq. Na₂S₂O₃ (2x100 mL), dried over excess Na₂SO₄ and condensed again in vacuo. The remaining residue was then dissolved in and recrystallized from EtOH yielding the desired product as colorless crystalline flakes (7.356 g, 20.3 mmol, 81% yield): mp

Laboratory notebook reference: JTG71

Phenyl valerate: To a solution of pyridine (1 mL, d = 0.978 g/mL, 0.978 g, 12.4 mmol) in CH₂Cl₂ (10 mL) stirring at room temperature in a flame dried 25 mL round bottom flask under argon was added phenol (0.562 g, FW = 94.11 g/mol, 5.9 mmol). The resulting solution was allowed to stir for 20 min then valeryl chloride (0.70 mL, FW = 120 g/mol, d = 1.01 g/mL, 5.9 mmol) was added dropwise over 10 min. The reaction mixture continued stirring overnight to ensure complete reaction. The
reaction mixture was then added to a 125 mL separatory funnel to which was added H₂O (20 mL) and EtOAc (20 mL). The resulting emulsion was then acidified using 6M aqueous HCl (4 mL). The layers were separated and the organic layer washed with H₂O (1x10 mL) and dried over excess Na₂SO₄ then condensed in vacuo. The product was obtained as a clear colorless oil (1.043 g, 5.86 mmol, 99% yield): ¹H NMR (300 MHz, CDCl₃) δ 7.38 (2H, dd), 7.22 (1H, t), 7.07 (2H, d), 2.57 (2H, t), 1.75 (2H, m), 1.45 (2H, m), 0.97 (3H, t). CAS # 20115-23-5.

Laboratory notebook reference: JTG105

1-Bromo-3-(propyn-3-ol)-benzene: Combined in a 25 mL round bottom flask were 1,3-dibromobenzene (0.051 mL, d = 1.95, FW = 235.8, 0.42 mmol), propargyl alcohol (0.024 mL, FW = 56.06, d = 0.971, 0.42 mmol), and iPr₂NH (4 mL, FW = 101.19, d = 0.717, 28.3 mmol). The mixture was degassed 1h stirring vigorously under argon at rt. Pd₂(dba)₃ (0.038 g, FW = 915.73, 0.042 mmol), dppf (0.023 g, FW = 554.39, 0.042 mmol) and CuI (1 mg, FW = 190.45, 0.0052 mmol) were then added to the reaction mixture. The complete mixture was heated to 80 °C and allowed to stir for 24h. The reaction mixture was then condensed in vacuo and shaken in a mixture of H₂O (10 mL) and Et₂O
(10 mL). The phases were separated and the aqueous layer washed with Et₂O (3x20 mL). The organic layer was dried over excess Na₂SO₄ and then condensed in vacuo. The product was obtained as a brown oily residue (0.086 g, 0.407 mmol, 97% yield): ¹H NMR (300 MHz, CDCl₃) δ 7.58 (1H, s), 7.45 (1H, d), 7.35 (1H, d), 7.18 (1H, m), 4.49 (2H, s). CAS # 170859-80-0.
6. References


14. In situ generation of 1,3-dibromo-2-lithiobenzene by deprotonation of 1,3-dibromobenzene has been reported, see: (a) "The Aryne Route to Biaryls Featuring Uncommon Substituent Patterns," Leroux, F.; Schlosser, M. Angew. Chem., Int. Ed. 2002, 41, 4272-4274. Oxidative dimerization of 1,3-dibromo-2-lithiobenzene with CuBr₂ to give 2,2′,6,6′-tetrabromobiphenyl is also precedented, see: (b) "Biphenylene Dimer. Molecular Fragment of a Two-Dimensional Carbon Net and Double-Stranded Polymer," Rajca, A.; Safronov, A.; Rajca, S.; Ross, C. R.; Stezowski, J. J. J. Am. Chem. Soc. 1996, 118, 7272-7279.

16. For examples of Cu(I)-catalyzed ArBr to ArI interchange, see: (a) "Copper-Diamine-Catalyzed N-Arylation of Pyrroles, Pyrazoles, Indazoles, and Triazoles," Antilla, J. C.; Baskin, J. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2004**, *69*, 5578-5587. An alternative sequence, ArBr to ArLi to ArI, is also a possibility for this transformation, for an example, see: (b) "Buttressing Effects Rerouting the Deprotonation and Functionalization of 1,3-Dichloro- and 1,3-Dibromobenzene," Heiss, C.; Marzi, E.; Schlosser, M. *Eur. J. Org. Chem.* **2003**, 4625-4629.


18. It is conceivable that products generated in the course of these reactions may themselves constitute effective ligands for the substitution reaction. In such cases (e.g. Nu = Ph$_2$PH), useful autoinduction phenomena may be observed.


27. Asymmetric Heck reactions usually exploit the differentiation of enantiotopic alkenyl groups or else the enantiotopic faces of a prochiral alkene (see ref. 19); however, their achievement via desymmetrization of meso bis-O-sulfonate esters has also been reported, see: "Synthesis of Bis(enolnonaflates) and their 4-exo-trig-Cyclizations by Intramolecular Heck Reactions," Bräse, S. Synlett 1999, 1654.


42. “Synthesis of Novel Ambifunctional Atropisomeric 2,2’,6,6’-Tetrasubstituted Biphenylsand Investigation of Their Properties and Organocatalytic Activity” Sephton, M. A., *Ph. D. thesis*, Oregon State University, **2008**.
Bibliography


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Appendix

$^1$H NMR/$^{13}$C NMR

Compound Spectral Data