SYNTHETIC STUDIES TOWARDS HOMOTYROSINOL SULFONAMIDE DERIVATIVES VIA HECK-MIZOROKI COUPLING REACTIONS

by

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Abstract

Homotyrosine, as a nonproteinogenic α-amino acid, is present as a component of diverse natural products that have important biological activities. Therefore, homotyrosine and its derivatives are important precursors for the total synthesis of some natural products. However, up to now, there was no report concerning a reliable synthetic route towards the synthesis of homotyrosine or its derivatives in a preparative scale.

In this thesis, a robust method was developed for the preparation of homotyrosinol derivatives and related intermediates through a Mizoroki-Heck coupling reaction between an aryl iodide and appropriate amino acid-derived olefins in the presence of N-phenylurea as the ligand. In addition, a preparative scale protocol for the oxidative cyclization of the homotyrosinol sulfonamide derivative was established. These results are essential for various synthetic efforts towards more complicated natural products ongoing in our laboratory.
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<td>N,N-dimethylacetamide</td>
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<td>N, N-dimethylformamide</td>
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<tr>
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<tr>
<td>M</td>
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<td>quantitative</td>
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<td>room temperature</td>
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<tr>
<td>s</td>
<td>secondary</td>
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<td>s</td>
<td>singlet</td>
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<td>sat.</td>
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<td>Full Name/Description</td>
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</tr>
<tr>
<td>$t$</td>
<td>tertiary</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetra-$n$-butylammonium fluoride</td>
</tr>
<tr>
<td>TBAB</td>
<td>tetrabutylammonium bromide</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butyl-diphenylsilyl</td>
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<tr>
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Chapter 1: Introduction

As their name implies, the so-called nonproteinogenic α-amino acids are α-amino acids that are not commonly found in proteins, even though they may be observed as components of diverse natural products and drug molecules. Examples include homophenylalanine, 1.1, α-aminobutyric acid, 1.2, homotyrosine, 1.3, 3-hydroxy-N-methylvaline, 1.4, piperazic acids, 1.5, and so on. For instance, a number of angiotensin-converting enzyme (ACE) inhibitors, which are used for the treatment of hypertension and congestive heart failure,4,5 incorporate L-homophenylalanine (1.1). Examples include Benazepril (1.6) and Enalapril (1.7), which are widely used in clinical practice.

![Nonproteinogenic Amino Acids](image)

**Figure 1.1: Nonproteinogenic Amino Acids**
Figure 1.2: ACE inhibitors Incorporating Homophenylalanine

The aminoacid, N-methyl-3-hydroxyvaline is found, e.g., in luzopeptins, peptide natural products that exhibit potent antiretroviral activity. These substances also display piperazic acid residues, which are widespread among natural products.

Figure 1.3: Luzopeptin E2: Natural Products Containing N-Methyl-3-Hydroxyvaline and Piperazic Acid
Homotyrosine can be found in a variety of natural products, especially cyclic peptides isolated from cyanobacteria. Notable examples are the microcystins (MC, Figure 1.4), a class of toxic cyclic heptapeptides produced by organisms of the genera *Anabaena*, *Microcystis*, and *Oscillatoria (Planktothrix)* and *Nostoc*. Homotyrosine is present in MCs such as oscillamide Y (1.10), cyanopeptolins 880 (1.11) and anabaenopeptins 915 (1.12).

![Figure 1.4: Microcystins](image)

**1.10 Oscillamide Y**

**1.11 Cyanopeptolins 880**

**1.12 Anabaenopeptins 915**
Homotyrosine is also present as a component of lyngbyastatin 4 (1.13), a depsipeptide isolated from the marine cyanobacterium *Lyngbya confervoides*. This natural product is a highly selective inhibitor of elastase\textsuperscript{13} and chymotrypsin,\textsuperscript{14} with IC\textsubscript{50} values of 0.03 and 0.30 μM, respectively, while it is essentially inactive toward other serine protease such as trypsin and thrombin.

The synthesis of nonproteinogenic α-amino acids and their derivatives continues to attract the interest of the synthetic community\textsuperscript{15} on account of their considerable potential as building blocks in natural product and medicinal chemistry. In addition, a number of these compounds have important biological functions.\textsuperscript{16}

1.1 Homotyrosine as an important precursor for total synthesis of natural products

Homotyrosine and its derivatives are also useful as chiral intermediates for the synthesis of medicinal agents and natural products. For example, the Melillo synthesis
of \((R, R)\)-4-propyl-9-hydroxynaphthoxazine \([(+)-PHNO, 1.18]\), a dopamine agonist with therapeutic potential in the treatment of Parkinson’s disease,\(^{18}\) started from D-homotyrosine. As seen in Scheme 1.1, this amino acid undergoes Friedel-Crafts cyclization to 1.15, which is elaborated into the final 1.18 in a straightforward manner. The pharmacologically active \(R, R\) enantiomer is thus obtained directly.

(a) Oxalyl chloride/\(\text{CH}_2\text{Cl}_2/\text{DMF}\); (b) \(\text{TiCl}_4/\text{CH}_2\text{Cl}_2/\text{H}_3\text{O}^+\); silica gel; (c) \(\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2/t-\text{BuOMe/tol}\); (d) \(\text{KOH/MeOH/H}_2\text{O}\); (e) \((\text{EtCO})_2\text{O}\); (f) \(\text{BH}_3\text{Me}_2\text{S/THF};\) NaOH/\(\text{H}_2\text{O}\); (g) \(\text{ClCH}_2\text{COCl/Na}_2\text{CO}_3/\text{H}_2\text{O/tol}\); (h) NaOH/\(\text{H}_2\text{O/tol/n-Bu}_4\text{NCl}\); (i) \(\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2/\text{tol};\) NaOH/\(\text{H}_2\text{O};\) (j) HCl; (k) \(\text{MeSO}_3\text{H/methionine}\).

**Scheme 1.1: Synthesis of (+)-PHNO from L-homotyrosine derivative**

The Ciufolini synthesis of (-)-cylindricine C (1.20) and (-)-2-epicylindricine C (1.21)\(^{19}\) illustrates an application of homotyrosine in natural product chemistry. Cylindricines are structurally unique alkaloids produced by the ascidian, *Clavelina*
They have elicited considerable interest in the synthetic arena due to their unusual architecture and moderate cytotoxic activity. A key sequence in the Ciufolini synthesis of the common precursor 1.26 was the oxidative cyclization of derivative 1.22 of D-homotyrosine (Scheme 1.2).

(a) SOCl₂/MeOH; (b) MsCl/TEA (excess), CH₂Cl₂, 0°C, 91% over two steps; (c) NaBH₄/EtOH/THF, 94%; (d) NaOH/dioxane, 80°C, 90%; (e) PhI(OAc)₂, (CF₃)₂CHOH, room temperature; (f) tBuPh₂SiCl, imidazole, DMF, room temperature, 82% over two steps; (g) KHMDS, THF, -100°C, 89% (d.r.=7:1); (h) PhSH, BF₃OEt₂ (cat.), CH₂Cl₂, 0°C, 77%; (i) Raney Ni, EtOH/THF, 77%; (j) tBuLi, THF, -78°C, (+/-)-1-octene oxide,
BF$_3$OEt$_2$; (k) DMP, CH$_2$Cl$_2$, room temperature, 88% over two steps; (l) 1. DBU, DMF; 2. bis(pinacolyl)diboronate, CuCl, KOAc, room temperature, 86%.

**Scheme 1.2: Synthetic Route to (-)-Cylindrinicine Precursor**

An ongoing effort in these laboratories aims to achieve the synthesis of (-)-lepadiformine (1.27). This substance was isolated in 1994 by Biard et al. from the tunicate, *Clavelina lepadiformis*,  and it was subsequently found to possess moderate cytotoxicity against KB and non-small-cell lung carcinoma cells. In addition, it was also found to be a cardiac K$^+$-channel blocker.

![Figure 1.6: Structure of (-)-Lepadiformine](image)

**Figure 1.6: Structure of (-)-Lepadiformine**

Structurally and biosynthetically, lepadiformine is related to the cylindricines (1.20 and 1.21). Accordingly, our group’s strategy for the synthesis of 1.27 also rests on the oxidative amidation of homotyrosine derivative 1.32 to generate the nitrogen-containing spirocyclic unit of the molecule, as outlined in Scheme 1.3.

Either enantiomeric form of homotyrosine and of various derivatives is article of commerce; however, they are expensive ($500 for 5 g). Given their central role in
ongoing efforts in our laboratory, we decided to develop a practical synthesis from readily available intermediates. Indeed, the objective of this study was to establish a reliable avenue to homotyrosinol, which is the starting point of a number of our current synthetic efforts.

**Scheme 1.3: Retrosynthetic Logic for (-)-Lepadiformine**

1.2. Previous syntheses of homotyrosine and its derivatives

Past asymmetric syntheses of homotyrosine have relied primarily on Noyori-type asymmetric catalytic hydrogenation to create the $N$-bearing stereogenic center, or on Negishi or Suzuki coupling reactions of a chiral organometallic agent with an appropriate aryl building block. Alternative approaches have involved Friedel-Crafts reaction of an aromatic substrate with an aminoacid-derived acylating agent, Michael additions of $\alpha$-methylbenzylamine to appropriate unsaturated dicarbonyl compounds, and 1,3-dipolar
cycloadditions of chiral nitrones to styrenes. The following paragraphs illustrate representative syntheses of homotyrosine and derivatives using these technologies.

1.2.1 Catalytic enantioselective hydrogenation route

Meliolo et al. achieved the catalytic asymmetric hydrogenation of acrylate derivative 1.39 with chiral rhodium catalysts (Scheme 1.4).\textsuperscript{17} Thus, condensation of 1.34 with methyl carbamate in the presence of a catalytic amount of $p$-toluenesulfonic acid (toluene, 80 °C) provided a mixture of (Z)-olefin 1.35, (E)-olefin 1.36 and dicarbamate adduct 1.37 in a ratio of 3:3:4. Treatment of this mixture with gaseous HCl induced both the elimination of one molecule of methyl carbamate from 1.37 to form the acrylate-type product, as well as the isomerization of 1.36 to 1.35. Stereochemically pure 1.35 was then subjected to Rh-catalyzed asymmetric hydrogenation. Depending on the nature of the ligand utilized in the latter step, either enantiomer of the desired product could be obtained in 80-90% ee. To illustrate, a complex obtained through the interaction of [Rh(NBD)$_2$]ClO$_4$ with 1 equivalent of (R,R)-DIPAMP afforded (S)-1.39 of 90% ee, while the use of (S,S)-Chiralphos provided (R)-1.38 of 82% ee. The structures of the rhodium complex and the ligands appear in the scheme 1.4.
Scheme 1.4: Enantioselective Hydrogenation

(a) Mg/THF; (b) (EtO₂C)₂, H₃O⁺; (c) HOAc: 10% aq. H₂SO₄=1:1, 80% over three steps;
(d) H₂NCO₂Me/ p-TSA/tol/reflux/-H₂O; (e) HCl/tol/80 °C, 90% over two steps; (f) H₂/[Rh(NBD)-(S,S)-chiraphos)]ClO₄, MeOH, 80%; (g) H₂/[Rh(NBD)₂-((R,R)-DIPAMP)]ClO₄, MeOH, 90%.
Jiang et al. extended the study of this asymmetric hydrogenation and applied it to the enantioselective synthesis of L-homophenylalanine 1.44,24 which is structurally similar to homotyrosine. Best results in this reaction were obtained by the use of a complex of Rh(I) with ligand 1.43 (DPAMPP; Scheme 1.5).

The DPAMPP ligand was introduced by Chan et al., who also produced monodentate ligands such as H8-MonoPhos (1.38). Rhodium complexes of the latter proved to be effective catalysts in asymmetric hydrogenation.25,26 Thus, enantioselectivities as high as 98.4% e.e. were observed in the hydrogenation of the substrates shown in Scheme 1.6, at a catalyst loading as low as 0.01 mol %.
Scheme 1.6: \( \text{H}_2\)-MonoPhos Catalyzed Enantioselective Hydrogenation

1.2.2 Organometallic routes

Much progress has been made in the use of functionalized zinc reagents in the organic synthesis in the past two decades. Such organometallics are now readily prepared under mild conditions by the direct insertion of activated zinc into carbon-halogen bonds.\(^{27}\) For instance, functionalized zinc reagent 1.52, derived from protected L-iodoalanine 1.51, can be prepared as detailed in Scheme 1.7. This material undergoes efficient Negishi-type coupling with benzoyl chloride to afford enantiopure ketone 1.53. The latter may be smoothly hydrogenated to furnish homotyrosine derivative 1.54 in a quantitative yield. The sequence proceeded with no erosion of optical purity.
(a) Zn/ Cu in benzene-dimethylacetamide at 60 °C; (b) 4-methoxy-benzoyl chloride, 6 mol% (Ph₃P)₂PdCl₂, 63%; (c) H₂, Pd/C, quant.

Scheme 1.7: Synthesis of Homotyrosine Derivative from Organozinc Reagent

Organozinc reagent 1.51 (Scheme 1.7) has found widespread use in the preparation of enantiopure, nonproteinogenic amino acids. However, it suffers from limitations such as a restricted range of compatible electrophiles, low reactivity in the absence of palladium or copper catalysts and poor nucleophilicity toward simple aldehydes and ketones. To palliate these difficulties, Taylor et al. investigated organolithium reagent 1.59 (Scheme 1.8), which added efficiently to aldehydes (e.g., benzaldehyde) and ketones, including cyclohexanone and cyclobutanone, in yields ranging from 75 to 98%. These workers did not demonstrate a synthesis of homotyrosine using 1.59; however, they did describe the preparation of homophenylalanine.
Scheme 1.8: Synthesis of Homophenylalanine from Organolithium Reagent

Jackson et al. developed organozinc reagent 1.63 that behaves as a carrier of an amino acid γ-anion synthon (Scheme 1.9). Negishi coupling with aryl iodides proceeded as expected to give homotyrosine or homophenylalanine derivatives 1.66 in high optical purity. However, chemical yields were moderate. A major side reaction was protonolysis, resulting in formation of variable quantities of 1.67.
Scheme 1.9: Example of Organozinc Reagent and by-product in the Synthetic Path

1.2.3 Hydroboration-Suzuki cross coupling route

The Suzuki cross-coupling reaction\(^{30}\) constitutes an efficient and mild method for the synthesis of unnatural \(\alpha\)-amino acids through union of an organoborane derivative of an amino acid with an appropriate vinyl or aryl halide. This chemistry has been largely developed by Taylor, \textit{et al.},\(^ {31}\) and Johnson \textit{et al.}\(^ {32}\).

The Taylor technology involves the elaboration of the Garner aldehyde, \textbf{1.70},\(^ {33}\) into vinyl derivative \textbf{1.71}, which subsequently undergoes hydroboration to produce \textbf{1.72}. 

(a) activated Zn, r.t, 4-12h, 90%; (b) ArI, Pd\(_2\)(dba)\(_3\) (0.625 mol%), P(\text{o-tol})\(_3\) (2.5 mol%), THF, 50\(^\circ\)C, 1h, 26-65%; (c) LiOMe (1 equiv.), MeOH, -10\(^\circ\)C, 1h, 90%; (d) Et\(_3\)SiH, Boc\(_2\)O, Et\(_3\)N, EtOH, 60 \(^\circ\)C, 7d.
(Scheme 1.10). In this connection, Taylor also devised an improved procedure for the preparation of 1.70 via LAH reduction of Weinreb amide 1.69.

(Scheme 1.10). The Taylor Synthesis of Garner Aldehyde and the Derived Organoborane

The coupling of organoborane 1.72 with aryl halides provides rapid access to homotyrosine and homophenylalanine derivatives. However, the reaction with 4-iodoanisole leading to homotyrosine precursor 1.73 was moderate yielding and kinetically slow, overshadowing the application of the method for preparative purposes.
(a) 4-iodoanisole, PdCl₂(dppf).CHCl₃, DMF, 16h, 71%; (b) Jones’ Oxidation; (c) CH₂N₂ or TMSCHN₂, 64% over two steps.

**Scheme 1.11: Homotyrosine Precursor Synthesis with Cbz-borane**

It should be noted that a Boc-protected analog of 1.75 was also prepared and studied.³¹ This borane proved to be inferior as a building block for amino acid synthesis in that the oxidation of 1.76 to 1.77 under Jones conditions³⁵ promoted release of the Boc group (recall, the Jones reagent is strongly acidic). The premature liberation of the primary amino function during Jones oxidation resulted in diminished yields of 1.78. On the other hand, two N-Cbz and N-Boc versions of the borane underwent coupling in identical yield (71% and 72%, respectively).
(a) Ph$_3$PCH$_3$Br, KHMDS, THF, -78 °C to r.t, 2h, 80%; (b) 9-BBN-H, THF, 0 °C to r.t, 2h;
(c) 4-iodoanisole, PdCl$_2$(dpdf),CHCl$_3$, DMF, 16h, 72% over two steps; (d) Jones’
Oxidation; (e) CH$_2$N$_2$ or TMSCHN$_2$, 54% over two steps; (f) 6M aq. HCl, anisole, 70 °C,
5h, 88%.

Scheme 1.12: Synthesis of Homotyrosine Derivative using Suzuki Coupling

Johnson et al. devised an alternative route to either enantiomer of building block
1.85 through lipase-catalyzed kinetic resolution of alcohol 1.82.$^{32}$ The preparation of the
latter started with an Overman-type$^{36}$ rearrangement of bis-trichloroimidate derivative
1.80 of cis-2-butene-1,4-diol. In the present case, the rearrangement occurred under Pd-
catalyst. The key step, the enantioselective acylation of (S)-1.82 promoted by Amano PS-
30 lipase, afforded 1.83 in 48% chemical yield and 96% ee, plus unreacted (R)-1.82,
denoted in the scheme below as compound 1.84, in 46% chemical yield and 97% ee. It is
(a) CCl₃CN, KH, 90-93%; (b) PdCl₂(CH₃CN)₂, THF, 85%; (c) 6N HCl; (d) Boc₂O, 60%
over two steps; (e) PS-30 lipase, isopropenyl acetate, 48% for 1.83, 46% for 1.84; (f)
KCN, MeOH, 93%; (g) 2,2-dimethoxypropane, acetone, BF₃-Et₂O, quant.

**Scheme 1.13: Preparation and Kinetic Resolution of Alcohol 1.82**

worthy of note that the resolution step was less efficient with an analog of 1.82 in which a
Cbz group was present in lieu of a Boc protecting group.

Johnson also reported that the hydroboration of 1.86 with 9-BBN was
considerably more efficient when carried out in toluene instead of THF, as indicated
earlier by Taylor. The resultant 1.87 underwent smooth coupling with p-bromoanisole as
well with a variety of other aryl halides and triflates. Two examples are shown in Scheme
Scheme 1.14: Synthesis of Organoborone and Suzuki Coupling Reaction

1.14. The conversion of 1.89 into homotyrosine derivative 1.91 proceeded in excellent overall yield via Dess–Martin oxidation of 1.90 to an aldehyde and subsequent Pinnick oxidation of the latter to a carboxylic acid (Scheme 1.15).34

Scheme 1.15: Synthetic Steps towards 1.91

(a) HCl, MeOH, r.t, over night, 80%; (b) i. Dess-Martin/THF; ii. NaClO₂, NaH₂PO₄; (c) H₂, Pd/C, 81% over three steps.
1.2.4. Friedel-Crafts acylation route

The potent dopamine agonist, 2-amino-6,7-dihydoxy-1,2,3,4-tetrahydronaphthalene (ADTN, 1.96) is of interest as a potential treatment for Parkinson’s disease. An asymmetric synthesis of this material by Nordlander et al. started with the creation of homotyrosine derivative 1.95 through the Friedel-Crafts acylation of 1,2-dimethoxybenzene 1.92 with aspartic acid-derived anhydride 1.93. The reaction occurred regioselectively at the carbonyl group farther removed from the nitrogenous functionality. Ketone 1.94 was thus obtained as a single isomer in 55% yield after recrystallization.

Scheme 1.16: The Nordlander Synthesis of a Homotyrosine Derivative

A later paper by Melillo et al. described the application of the same chemistry to the synthesis of homotyrosine methyl ether, 1.101. In accord with Nordlander, these workers observed that the Friedel-Crafts acylation of anisole with anhydride 1.102

(a) AlCl₃, CH₂Cl₂, r.t, 80h, then HCl, 20min, 55%; (b) Et₃SiH, CF₃CO₂H, reflux, 2h, 72%.
occurred selectively at the carbonyl group away from the NCOOMe group; however, the \textit{ortho-para} selectivity with respect to the aromatic substrate was poor (ca. 2:1 in favor of the desired isomer). The problem was corrected by engaging chloroanisole 1.98 in the reaction, whereupon only product 1.99 \((X = \text{Cl})\) was obtained. Hydrogenolysis of the aryl ketone and of the chloro substituent took place simultaneously when 1.99 \((X = \text{Cl})\) was hydrogenated in the presence of Pd(C).

\[
\begin{align*}
1.97 \ (X = \text{H}) & \quad \text{HCO}_2 \text{Me} \quad \text{NHCO}_2 \text{Me} \\
1.98 \ (X = \text{Cl}) & \quad \text{HCO}_2 \text{Me} \quad \text{NHCO}_2 \text{Me} \\
1.99 \ (X = \text{Cl}) & \quad \text{HCO}_2 \text{Me} \quad \text{NHCO}_2 \text{Me}
\end{align*}
\]

(a) AlCl₃, CH₂Cl₂, MeNO₂; H₃O⁺; 94%; (b) H₂ (3 atm)/i-PrOH/Pd-C; 94%

\textbf{Scheme 1.17: The Melillo Synthesis of Homotyrosine Methyl Ether}

In the course of studies directed toward the synthesis of homophenylalanine, Hashimoto \textit{et al.} encountered difficulties in the acylation of benzene (less reactive than anisole derivatives) with the above aspartic-acid-derived anhydrides under Nordlander or Melillo conditions (AlCl₃ as the catalyst). To correct the problem, they investigated the
use of strong Bronsted acids as promoters. Neat trifluoromethane sulfonic acid induced formation of a mixture of 1.102 and 1.103, which were isolated in 54% and 3% yield, respectively. When acid chloride 1.104 was employed in lieu of the anhydride, the desired 1.102 emerged in 98% yield; however, the transposition of these results to the homotyrosine series gave disappointing results, affording a 5:4 mixture of regioisomers 1.105 and 1.106.\textsuperscript{39}

(a) PhH, neat TfOH, 0 °C, 1h, 54% for 1.102, 3% for 1.103; (b) anisole, neat TfOH, 0 °C, 1h, 97% combined yield.

\textbf{Scheme 1.18: The Hashimoto Approach to Homotyrosine Derivatives}
1.2.5. Michael addition route

The observation that compounds of the type 1.109 may be efficiently hydrogenated to yield homotyrosine derivatives induced Yamada et al. to explore a route to 1.110 involving the addition of a chiral nitrogen nucleophile to intermediate 1.108.\textsuperscript{40} The latter substance is readily prepared by Friedel-Crafts acylation of anisole with maleic anhydride. Furthermore, the more electrophilic keto carbonyl directs subsequent 1, 4-additions. Accordingly, reaction of 1.108 with (S)-\(\alpha\)-methylbenzylamine afforded 1.109 in 90% yield and 97% d.e. Subsequent hydrogenolysis delivered 110.

\[ \text{1.107} \xrightarrow{a} \text{1.108} \xrightarrow{b} \text{1.109} \]

(a) Anisole (yields and selectivity was not mentioned in the paper); (b) 1.1 eq. (S)-\(\alpha\)-methylbenzylamine, 60 °C, 16h, 90%, 97% d.e.; (c) 10% Pd/C, H\(_2\), EtOH, r.t, 24h, 90%.

Scheme 1.19: the Yamada Synthesis of Homotyrosine using Michael Addition

24
1.2.6. 1, 3-dipolar cycloaddition route

Baldwin et al. have utilized nitrone 1.112 as a chiral glycine template for the synthesis of non natural α-amino acids. The substance may be prepared in 70-80% yield by oxidation of lactone 1.111 with the urea-hydrogen peroxide complex in the presence of a catalytic amount of methyltrioxorhenium, according to the procedure of Goti and Murray. Nitrone 1.112 undergoes the anticipated 1,3-dipolar cycloaddition with various olefins; in particular, with styrenes. While the faciality of the process with respect to nitrone is excellent (exclusive attack anti to the phenyl substituent), the topological control in the reaction is moderate, at least with styrenes.

(a) H$_2$NCONH$_2$, H$_2$O$_2$, MeReO$_3$ (cat); (b) Ph$_3$P, CHCl$_3$, reflux, 3h, 84%, 5:1=exo: endo;
(c) H$_2$, Pd(OH)$_2$/C, dioxane/TFA, 45%

Scheme 1.20: Synthesis of Homotyrosine using 1, 3-dipolar Cycloaddition
For instance, a 5:1 mixture of *exo* (major) and *endo* cycloadducts were obtained in the reaction of 1.112 with 1.113. Fortunately, this was immaterial in the context of a synthesis of homotyrosine. Indeed, catalytic hydrogenation of the mixture of 1.113 (*exo* and *endo*) affords the same end product 1.117. Two aspects of the final step merit comment. First, the authors uncovered evidence that the reaction proceeded through an initial cleavage of the N-O bond, followed by rapid translactonization to give γ-lactone 1.116. This was followed by hydrogenolysis of the benzylic C-O and C-N bonds. Second, the phenolic acetyl protecting group was lost during the reaction, providing the desired homotyrosine directly (Scheme 1.20).
Chapter 2: Results and Discussions

2.1 Objectives and approach

As indicated in the Introduction (p. 8), the objective of this study was to devise a practical synthesis of homotyrosinol. Specifically, we required an entry to sulfonamide derivatives of homotyrosinol, because those are the actual substrates for oxidative cyclization of interest to us (Scheme 1.2). To that end, we focused on three approaches (Scheme 2.1): a Suzuki coupling reaction of boranes 2.2 in a manner reminiscent of Taylor (Scheme 1.11) and Johnson (Scheme 1.14), an alkene metathesis reaction between 2.4 and a styrene, and a Heck reaction of 2.4 with an aryl halide. Because borane 2.2 would be prepared by hydroboration of 2.4, our first concern became the preparation of the latter intermediate, which is recognized as a derivative of vinylglycinol.

Scheme 2.1: Strategies for the synthesis of homotyrosinol sulfonamides explored in the course of this study
2.2. Synthesis of vinyl glycinol derivatives

Vinylglycinol derivatives can be easily synthesized from L-methionine by thermal elimination of the corresponding sulfoxide.\textsuperscript{44,45} We presumed that the literature methods devised to access carbamate derivatives of 2.15-2.17 could be adapted to the sulfonamide series, even though the CAS database records no occurrences of compound 2.6, 2.7 or 2.8. This proved to be the case. Reaction of L-methionine methyl ester hydrochloride 2.5 with CH$_3$SO$_2$Cl afforded the expected 2.6 in virtually quantitative yield. Reduction with LiAlH$_4$ provided 2.7, which was converted into three different O-protected derivatives, 2.9-2.10. Sulfoxide formation from the latter occurred smoothly upon reaction with

\[
\begin{align*}
\text{S} & \quad \text{O} \\
\text{NH}_2 & \quad \text{HCl} \\
\text{NHMs} & \quad \text{2.5} \\
\text{O} & \quad \text{Me} \\
\text{a} & \quad \text{b} & \quad \text{c} \\
\text{S} & \quad \text{O} & \quad \text{NHMs} \\
\text{NHMs} & \quad \text{2.6} \\
\text{S} & \quad \text{O} & \quad \text{NHMs} \\
\text{NHMs} & \quad \text{2.7} \\
\text{S} & \quad \text{OPG} & \quad \text{NHMs} \\
\text{d} & \quad \text{e} \\
\text{S} & \quad \text{OPG} & \quad \text{NHMs} \\
\text{NHMs} & \quad \text{2.8} \\
\text{S} & \quad \text{OPG} & \quad \text{NHMs} \\
\text{NHMs} & \quad \text{2.9} \\
\text{S} & \quad \text{OPG} & \quad \text{NHMs} \\
\text{NHMs} & \quad \text{2.10} \\
\text{S} & \quad \text{OPG} & \quad \text{NHMs} \\
\text{NHMs} & \quad \text{2.11} \\
\text{S} & \quad \text{OPG} & \quad \text{NHMs} \\
\text{NHMs} & \quad \text{2.12} \\
\text{S} & \quad \text{OPG} & \quad \text{NHMs} \\
\text{NHMs} & \quad \text{2.13} \\
\text{S} & \quad \text{OPG} & \quad \text{NHMs} \\
\text{NHMs} & \quad \text{2.14} \\
\text{S} & \quad \text{OPG} & \quad \text{NHMs} \\
\text{NHMs} & \quad \text{2.15} \\
\text{S} & \quad \text{OPG} & \quad \text{NHMs} \\
\text{NHMs} & \quad \text{2.16} \\
\text{S} & \quad \text{OPG} & \quad \text{NHMs} \\
\text{NHMs} & \quad \text{2.17} \\
\end{align*}
\]

(a) MsCl, Et$_3$N, CH$_2$Cl$_2$, 0°C to RT (99%); (b) LiAlH$_4$, THF, 0°C to RT (90%); (c) TBDPSCI/TBSCI/Ag$_2$O, Imidazole, DMF, RT; 2.9: 95%; 2.10: 90%; 2.11: 98%; (d); NaIO$_4$, MeOH, H$_2$O, RT; (e); Na$_2$CO$_3$, 1,2-dichlorobenzene, 180°C; 2.15: 72%; 2.16: 85%; 2.17: 70-83%.

Scheme 2.2: Synthesis of vinyl glycinol derivatives
NaIO₄, and thermolysis of the products in refluxing 1, 2-dichlorobenzene afforded vinylglycinol derivatives 2.15-2.17 in excellent overall yield (Scheme 2.2). It is noted that the sulfoxide thermolysis was carried out in the presence of Na₂CO₃ as the base. An experiment in which K₂CO₃ was employed instead of Na₂CO₃ during the thermolysis of sulfoxide 2.14 produced the desired 2.17 in significantly lower yield (30%-40% instead of 83%). Consequently, all other such reactions were only carried out with Na₂CO₃. The overall sequence appeared to be robust: large-scale reactions starting with 30 mmol of methionine ester 2.5 proceeded in 70% yield over 5 steps.

2.3 Study on the alkene metathesis approach

The work described in this section was carried out by Dr. Huan (Steven) Liang, of our group.

Olefin metathesis is a reaction between a pair of alkenes, which undergo formal double bond cleavage and statistical redistribution of alkylidene fragments (Scheme 2.3). Pioneering work by Schrock⁴⁶,⁴⁷, and especially Grubbs⁴⁸, has rendered this transformation as central to modern synthetic practice as the more classical reactions of organic chemistry. The transformation is promoted by a variety of metal-carbene complexes; i.e., organometallic compounds containing the functional group Mt=C (Mt = Ti, Ni, Mo, Rh, Ru …).

\[
\begin{align*}
\text{R}^1\text{R}^3 + \text{R}^5\text{R}^7 & \xrightleftharpoons[\text{catalyst}]{\text{catalyst}} \text{R}^1\text{R}^7 + \text{R}^5\text{R}^3 \\
\end{align*}
\]

Scheme 2.3: General Alkene Metathesis
However, the majority of metathesis reactions of interest in synthetic organic chemistry rely on the so-called Grubbs catalysts and their Hoveyda variants. These ruthenium complexes possess the structures shown in Figure 2.1. Their popularity derives from their good stability, excellent tolerance of spectator functionality (carbonyls, amides, carbamates, alcohol, ether, borane, silane), applicability in a broad range of solvents, and from the high yields that they generally afford.

Initial experiments aiming to induce cross-metathesis between styrene 2.21 and 2.22 in the presence of the Grubbs first generation complex 2.17 produced disappointing results. The choice of catalyst was dictated by its greater air stability relative to its congeners, which makes handling very convenient, as well as its lower cost. These
advantages are offset by a lower activity relative to other catalysts. In our case, heating a mixture of 2.21 and 2.22 at 100 °C for 24 h in the presence of variable amounts of

![Reaction conditions: catalyst (5 mol %), vinyl moiety (0.5 mmol), styrene moiety (0.6 mmol), CH2Cl2, room temperature or 100 °C (in sealed tube).](image)

Scheme 2.4: Alkene Metathesis

catalyst as much as 100 mol% – resulted at most in a modest 15% conversion (NMR) and in 8% isolated yield of desired 2.23. This was clearly unacceptable. Unfortunately, the use of more active second-generation catalysts did not cure the problem. As seen in the table below, the highest yield of 2.23 ever recorded was 20% at 40% conversion. These

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Conversion</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grubbs I</td>
<td>15%</td>
<td>8%</td>
</tr>
<tr>
<td>Grubbs II</td>
<td>40%</td>
<td>20%</td>
</tr>
<tr>
<td>Hoveyda I</td>
<td>25%</td>
<td>11%</td>
</tr>
<tr>
<td>Hoveyda II</td>
<td>35%</td>
<td>21%</td>
</tr>
</tbody>
</table>

Table 2.1: Conversion and Yields by different Catalysts
setbacks induced us to abandon the metathesis approach.

2.4. The Suzuki coupling route

In order to proceed the Suzuki coupling reaction, first should convert \( \text{2.22} \) into a borane suitable for the conduct of a Suzuki-type reaction according to Taylor and Johnson. Regrettably, the hydroboration of \( \text{2.22} \) failed. Thus, the substrate was immune to the action of 9-BBN, catecholborane, or pinacolborane, either alone or in conjunction with the Wilkinson catalyst.\(^4\) At room temperature, no reaction took place; at higher temperatures, the substrate decomposed. Recall that the hydroboration of a carbamate derivative of vinylglycinol was achieved without incident (Scheme 1.11). Evidently, this reaction is intolerant of secondary sulfonamide functionality. While the reasons for this behavior were escaped from us, it is possible that the significant acidity of the N-H bond in \( \text{2.22} \) (pKa of similar sulfonamides = 10-12, according to Evans’ pKa table) induced

![Scheme 2.5: Boron Derivatives Synthesis](image)
protonolysis of the borane and formation of an N-boryl derivative of the substrate (cf. 2.25). The resulting steric congestion engendered around the vinyl group could well suppress any further reaction.

2.5. The Heck coupling route

The above failures induced us to refocus our attention on a Heck reaction of 2.22 to the formation of 2.26 (Scheme 2.6).

![Scheme 2.6: Approach to 1.32 by a Heck reaction](image)

Since R. F. Heck’s publication of a landmark 1972 paper entitled “Palladium-catalyzed vinylic hydrogen substitution reactions with aryl, benzyl, and styryl halides,” what is now known as the Heck-Mizoroki, or more simply the Heck, reaction has become one of the premier methods for the arylation of olefins. New ligands and palladium catalysts developed over the years have greatly expanded the scope and efficiency of the reaction, which, through the important work of Overman has even been extended to the intramolecular regime.

Mechanistically, the process is believed to start with an oxidative addition of a Pd(0) complex into the aryl-X (or vinyl-X) bond. In cases where the Pd catalyst is introduced as a Pd(II) compound, preliminary reduction of the metal to the zerovalent
oxidation state is believed to occur. The resultant arylpalladium(II) halide complex may then promote carbonpalladation of an appropriate olefin, resulting in the formation of a putative arylpalladium(II) alkyl intermediate. The presence of a β-H atom in the latter permits the occurrence of a β-H elimination of a halopalladium(II)hydride complex, which ultimately undergoes reductive elimination of a Pd(0) complex and concomitant formation of a molecule of H-X. The reaction is therefore carried out in the presence of an appropriate base to absorb the H-X thus produced. This sequence of events is exemplified in Scheme 2.7. Notable stereochemical aspects of the reaction are the syn course of both the carbopalladation (cf. \( \text{2.29} \rightarrow \text{2.30} \)) and the β-H elimination (cf. \( \text{2.30} \rightarrow \text{2.32} \)) steps.
Our initial attempts to produce compound \textbf{2.35} through the union of \textbf{2.22} and \textbf{2.33} employed a widely used catalytic system composed of Pd(OAc)$_2$ and triphenylphosphine in a 1:2 molar ratio.\textsuperscript{56} As shown by Amatore,\textsuperscript{57-59} the interaction of these two agents induces reduction of Pd(II) to Pd(0). Specifically, the two combine to produce a Pd(0) complex plus one equivalent each of triphenylphosphine oxide and acetic anhydride (Scheme 2.8). The reaction was carried out in DMF, a common solvent for this transformation, in the presence of K$_2$CO$_3$ as the base and at a temperature of 105 °C. Again, these are common literature conditions.\textsuperscript{60} The conversion of the starting materials into the product was monitored by NMR, which showed that the reaction was complete in four and a half hours. As seen in Scheme 2.8, two products were thus obtained: the anticipated \textbf{2.34} and the corresponding deacetylated analogue \textbf{2.35}. While both products

\begin{equation}
\text{Pd(OAc)}_2 + n \text{Ph}_3\text{P} \rightarrow \text{[Ph}_3\text{P}]_{n-1}\text{Pd(0)} + \text{Ph}_3\text{P}=\text{O} + \text{Ac}_2\text{O} \quad (2 \leq n \leq 5)
\end{equation}

**Scheme 2.8: Reduction of Pd(II) to Pd(0) according to Amatore**

Conditions: Pd (OAc)$_2$ (20 mol %), Ph$_3$P (40 mol %), 1.2 equiv. K$_2$CO$_3$, de-gassed DMF ([C] = 0.35 /vinyl moiety), 105 °C, vinyl moiety (0.5 mmol), phenol (0.6 mmol).
are useful, inasmuch as they both can be advanced to desired 1.32, the total yield of the two was only around 40%, which was unacceptably low for our purposes. The balance of the olefinic substrate was converted to polymeric materials that we were unable to characterize. These observations validated the Heck approach, but they also signaled that the conditions employed in these test experiments were inappropriate. Consequently, we carried out a screen of ligands, sources of metal, bases, and protecting groups on both aryl and vinyl components in order to optimize the reaction.

2.5.1 Ligand screening

A total of ten ligands were examined in a reaction carried out under the following standard conditions: 0.5 mmol (200 mg) of vinyl component 2.22, 1.5 mL of degassed DMF (substrate concentration = 0.3 M), 0.6 mmol (1.2 equiv.) of aryl moiety 2.33, Pd(OAc)$_2$ (20 mol % relative to 2.22), Ph$_3$P (40 mol % relative to 2.22, 2 equiv. relative to Pd(OAc)$_2$), 0.6 mmol (1.2 equiv.) of K$_2$CO$_3$, 105 °C, NMR monitoring, reported yields refer to chromatographically purified products. The results of experiments that employed Ph$_3$P, $n$-Bu$_3$P, trifurylphosphine, JohnPhos, cyclohexyl JohnPhos, XPhos, DavePhos, and an unnamed phosphine as ligands are summarized in Table 2.2. Among these eight ligands, only tributylphosphine and XPhos afforded good (> 80%) yields. Reactions run with $n$-Bu$_3$P were more selective, in that only the acetylated product 2.35 was obtained, while XPhos consistently furnished an approximately 2:1 mixture of acetylated and deacetylated materials. Recall, this is not a major concern, because the acetyl group is destined to be released anyway. Trifurylphosphine and the JohnPhos ligands performed especially poorly, while reactions run in the presence of DavePhos stalled at about 70%
\[
\begin{align*}
\text{AcO-} & \text{Ph-} \text{I} + \text{NMe-} \text{CH-} \text{OTBDPS} \\
& \rightarrow \text{RO-} \text{Ph-} \text{CH-} \text{OTBDPS}
\end{align*}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>reaction time</th>
<th>isolated yield of 2.34</th>
<th>isolated yield of 2.35</th>
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<tr>
<td>a</td>
<td>Ph₃P</td>
<td>4.5</td>
<td>31</td>
<td>9</td>
</tr>
<tr>
<td>b</td>
<td>n-Bu₃P</td>
<td>4</td>
<td>87 (0.5 mmol scale)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>58 (6.7 mmol scale)</td>
<td>0</td>
</tr>
<tr>
<td>c</td>
<td>(cyclohexyl JohnPhos) (P(tert-Bu)_2)</td>
<td>7</td>
<td>&lt; 10</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>d</td>
<td>(JohnPhos)</td>
<td>9</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>e</td>
<td>(cyclohexyl JohnPhos) (PCy_2)</td>
<td>9</td>
<td>22</td>
<td>0</td>
</tr>
<tr>
<td>f</td>
<td>(XPhos) (PCy_2) (i-Pr) (i-Pr)</td>
<td>4</td>
<td>58</td>
<td>24</td>
</tr>
<tr>
<td>g</td>
<td>(O-i-Pr) (i-PrO) (PCy_2) (Me_2N) (PCy_2)</td>
<td>4</td>
<td>55</td>
<td>5</td>
</tr>
<tr>
<td>h</td>
<td>(DavePhos) (PCy_2) (Me_2N)</td>
<td>5 (72% \text{ conv.})</td>
<td>24</td>
<td>20</td>
</tr>
</tbody>
</table>

Table 2.2: Ligands Screen with \(\text{Pd(OAc)}_2\) in Heck Coupling Reaction
conversion to form a 1:1 mixture of \textbf{2.34} and \textbf{2.35}.

The good results observed with Bu$_3$P induced us to scale up the reaction by an order of magnitude. Unfortunately, the yield of product dropped significantly when 6.7 mmol of \textbf{2.22} were thus processed (58% vs. 87%), all other reaction parameters being equal. No attempts were made to scale up the reaction involving XPhos on accounts of the considerable cost of this substance.

Besides proceeding in unsatisfactory yield, the above reactions also required a large quantity of palladium (20 mol%) to proceed reasonably rapidly. In our continuing search for an improved procedure that would afford high yields and require a diminished quantity of precious metal, we evaluated the use of SPhos and the recently described phenylurea as ligands.

Results of reactions that employed SPhos are summarized in Table 2.3. These experiments were carried out as described earlier: 0.5 mmol (200 mg) of vinyl component \textbf{2.22}, 1.5 mL of degassed DMF (substrate concentration = 0.3 M), 0.6 mmol (1.2 equiv.) of aryl moiety \textbf{2.33}, 0.6 mmol (1.2 equiv.) of K$_2$CO$_3$, 105 °C, NMR monitoring, reported yields refer to chromatographically purified products. However, the source and amount of metal, as well as the ratio of metal to ligand was varied as indicated. It should be noted that the reactions tended to stall when run at temperatures lower than 100-105 °C.

The use Pd(OAc)$_2$ as the source of metal afforded the highest conversions and yields. Furthermore, yields remained essentially constant regardless of the metal / ligand ratio or, more importantly, the quantity of metal used, down to a metal loading around 3%. Below this level, yields dropped. A reaction carried out with 4.7 grams (11.7 mmol) of \textbf{2.22} afforded a 1.5:1 mixture of \textbf{2.34} and \textbf{2.35} in 86% total yield, indicating that the
\[
\begin{align*}
\text{AcO-} & \text{I} + \text{OTBDPS-} \text{NHMs} \\
\end{align*}
\]

\[2.33 \quad 2.22 \]

\[
\begin{align*}
\text{RO-} & \text{OTBDPS-} \text{NHMs} \\
\end{align*}
\]

\[2.34 \quad 2.35 \quad R=\text{Ac} \quad R=\text{H} \]

\[
\begin{array}{cccccc}
\text{entry} & \text{ligand} & \text{source of Pd} & \text{mol\% of Pd} & \text{mol ratio Pd / ligand} & \text{isolated yield of 2.34} & \text{isolated yield of 2.35} \\
\hline
a & \text{MeO} & \text{Pd(OAc)}_2 & 20 & 1 : 2 & 91 & 0 \\
\quad & \text{MeO} & \text{PCy}_2 & \text{SPhos} & & & \\
b & " & " & 20 & 1 : 2 & 52 & 34 \\
\quad & & & & (11.7 \text{ mmol scale}) & & \\
c & " & " & 10 & 1 : 2 & 73 & 11 \\
d & " & \text{Pd}_2(\text{dba})_3 & 10 & 1 : 2 & 40 & 0 \\
\quad & & & & (80\% \text{ conv. after 4h}) & & \\
e & " & \text{Pd(PPh}_3)_4 & 10 & 1 : 2 & 9 & 0 \\
\quad & & & & (30\% \text{ conv. after 4h}) & & \\
f & " & \text{PdCl}_2(\text{PPh}_3)_2 & 10 & 1 : 2 & 49 & 0 \\
\quad & & & & (65\% \text{ conv. after 4h}) & & \\
g & " & \text{Pd(OAc)}_2 & 10 & 1 : 1 & 21 & 62 \\
h & " & " & 5 & 1 : 2 & 43 & 40 \\
i & " & " & 3 & 1 : 1 & 34 & 52 \\
j & " & " & 1 & 1 : 2 & 31 & 21 \\
\quad & & & & (70\% \text{ conv. after 9h}) & & \\
\end{array}
\]

**Table 2.3: Reactions using SPhos as Ligand**

reaction was probably scalable.
2.5.2 Substrates scope

The foregoing observations encouraged us to examine the coupling of variously

\[
R-O\text{-}\begin{array}{l}X\end{array} + \text{OP}^+\text{NHMs} \rightarrow \text{RO}\text{-}\begin{array}{l}\text{NHMs}\end{array}
\]

<table>
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<tr>
<th>entry</th>
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<th>2.37</th>
<th>isolated yield of 2.38, R = Ac</th>
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<tr>
<td>a</td>
<td>AcO-</td>
<td></td>
<td>73</td>
<td>11</td>
</tr>
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<td>b</td>
<td>AcO-</td>
<td></td>
<td>0</td>
<td>21</td>
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<tr>
<td>c</td>
<td>AcO-</td>
<td></td>
<td>41</td>
<td>0</td>
</tr>
<tr>
<td>d</td>
<td>HO-</td>
<td></td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>e</td>
<td>HO-</td>
<td></td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>f</td>
<td>AcO-</td>
<td>Br</td>
<td>15</td>
<td>0</td>
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Table 2.4: Substrate Scope for Pd(OAc)$_2$ Catalyzed Heck Coupling Reaction
protected substrates under the catalytic influence of the Pd – SPhos system. These experiments were motivated by a desire to avoid the use of a costly TBDPS protecting group on the vinyl component. Table 2.4 summarizes the results of reactions carried out under the following standard conditions: 0.5 mmol of vinyl component, 1.5 mL of degassed DMF ([2.37] = 0.35 M), 10 mol % Pd(OAc)$_2$, 20 mol% SPhos, 0.6 mmol of aryl moiety, 0.6 mmol K$_2$CO$_3$, 105 °C, 4 h, NMR monitoring, yields of chromatographically purified products. It is apparent from the data shown that the reaction proceeded best with TBDPS-protected 2.37 and the acetate ester of 4-iodophenol (entry a). As seen previously in Table 2.3, this reaction afforded a ca. 7: 1 mixture of acetylated and deacetylated product. Recall, reactions run with a 20% load of Pd complex afforded no deacylated product. However, deacetylated material was the only product observed in entry b.

2.5.3 The base

(a) 0.5 mmol of 2.22, 1.5 mL of degassed DMF ([2.22] = 0.35 M), 10 mol % Pd(OAc)$_2$, 20 mol% SPhos, 0.6 mmol of 2.33, 0.6 mmol NaHCO$_3$, 105 °C, 4 h, NMR monitoring, yields of chromatographically purified products.

Scheme 2.10: Heck Coupling Reaction with Base NaHCO$_3$
As mentioned above, the formation of mixtures of acetylated and deacetylated products is inconsequential. However, we questioned whether replacing the stronger base, K₂CO₃, with a weaker one could improve product selectivity even further. It was found that the use of NaHCO₃ in lieu of K₂CO₃ greatly reduced the extent of deacetylation (Scheme 2.10).

2.5.4. The breakthrough: N-Phenylurea as ligand

A recent report by Guo, et al., described the use of inexpensive N-phenylurea as an effective ligand for Pd.⁶¹ In the context of a Heck reaction, the use of this ligand resulted in a 99% yield (determined by GC) of stilbene through the coupling of bromobenzene with styrene.

When 0.5 mmol of 2.22 in 1.5 mL of degassed DMF ([2.22] = 0.35 M) containing 10 mol % Pd(OAc)₂, 20 mol% N-phenylurea, 0.6 mmol of 2.33, and 0.6 mmol K₂CO₃ was heated at 105 °C (NMR monitoring), complete consumption of 2.22 was detected after about 2h. Chromatographic purification of the crude product delivered 2.34 in 38% yield and 2.35 in 48% yield (86% overall entry a). Replacing the base with the milder NaHCO₃ resulted in exclusive formation of 2.34 in an 84% yield after chromatography. Clearly, this inexpensive alternative to the costly SPhos afforded even better results. Table 2.5 summarizes a brief study of reaction conditions. The new ligand permitted the use of only 5 mol % of Pd(OAc)₂ even on substantial scales (entry e). For preparative purposes (entry f), we utilized the conditions of entry e: 5 mol% of metal, 10 mol% ligand, K₂CO₃ as the base, 2 h reaction time, affording in 83% chromatographed yield a mixture of 2.34 (63% by NMR) and 2.35 (20% by NMR).
The degree of enantiomeric purity of product 2.42 was determined by the Mosher method. Accordingly, the TBDPS group in 2.34 was released (TBAF) and the resulting alcohol 2.42 was esterified with (R)-MTPA chloride (Scheme 2.11). The emerging ester 2.44 was assayed by $^{19}$F-NMR spectroscopy, whereupon only one signal was detected.
(Figure 2.2). This established that the optical integrity of the molecule had been preserved during the coupling reaction.

Et₃N, HOBT, EDCI, CH₂Cl₂, 0 °C to r.t. 70%.

**Scheme 2.11: Optical Purity of Heck Coupling Product**

**Figure 2.2: **¹⁹F-NMR Spectrum of 2.44
2.5.6 Literature procedure

At this juncture of our research, a publication from the laboratories of Gobel appeared, which disclosed a similar Heck route to non-natural aromatic amino acids through the coupling of aryl bromides with Cbz-protected vinylglycinol 2.45 in aqueous DMF and in the presence of K$_2$CO$_3$. A noteworthy aspect of the Gobel reaction is the use of a ligand-free catalytic system that comprises Pd(OAc)$_2$ and a phase-transfer agent, such as Bu$_4$N$^+$·OTf. Representative examples are shown in Figure 2.3.

The transposition of this alternative methodology to the methanesulfonamide derivative of vinylglycinol as the substrate revealed three major drawbacks. First, the reaction had to be carefully monitored to avoid degradation of the product by the catalytic

![Chemical structures and yields for the Gobel synthesis of compounds 2.46 by Heck reaction.](image)

**Figure 2.3: The Gobel Synthesis of Compounds 2.46 by Heck Reaction**
system. Prolonged heating of reaction mixtures beyond the time at which complete
disappearance of the vinyl component had occurred (about 4 h, $^1$H NMR) caused an
unacceptable loss of product to polymerization. Variable amounts of polymeric materials
were evident in the spectra of crude products even if the reaction was stopped
immediately upon disappearance of $2.22$. The problem was especially acute when
operating with more than 1 mmol of substrate, whereupon the separation of desired

(a) Reaction conditions: DMF: H$_2$O= 20:1, $[2.22]= 0.07$M, phenol/vinyl ration=1.2:1,
10 mol % Pd (OAc)$_2$, 12 mol % Bu$_4$NOTf (1.2 equiv. vs. Pd(OAc)$_2$), K$_2$CO$_3$ (2.4
equiv. vs. $2.22$), 100 °C, 4 h ($^1$H NMR monitoring). Yields refer to
chromatographically purified products.

Table 2.6: Heck Reaction of $2.22$ with $2.33$ under Gobel Conditions
product from polymeric material (column chromatography) became very troublesome. Secondly, the Gobel procedure prescribes a concentration of vinylglycine substrate equal to 0.07 M. Such a degree of dilution is entirely impractical for the conduct of preparative work. Third, 10 mol % of Pd(OAc)$_2$ were required instead of 5%. Two examples of reactions carried out under Gobel conditions are provided in Table 2.6. The yield of a preparative run of the reaction was about half of that obtained by our optimized procedure.

2.6 Synthesis of N-mesyl-O-silyl homotyrosinol

Having established a robust preparative route to 2.34, we turned our attention to its conversion into the desired 2.48. This transformation entails the hydrogenation of the olefin and the release of the protecting groups. The proper order of these steps was determined through experiment. Thus, hydrogenation of a mixture of 2.34 and 2.35 over Pd(C) in MeOH containing suspended K$_2$CO$_3$ afforded compound 2.47 in 95% yield (Scheme 2.12). The K$_2$CO$_3$ utilized in this step served to promote the cleavage of the phenolic acetate. The desilylation of the primary alcohol occurred significantly more efficiently in the presence of 70% HF in pyridine (80% yield after chromatography) relative to the customary TBAF (ca. 70% yield). The use of HF in pyridine also facilitated the purification of the final 2.48, which was obtained in 76% overall yield. An improvement in overall efficiency obtained when the desylation was carried out prior to hydrogenation. Treatment of a mixture of 2.34 and 2.35 with suspended K$_2$CO$_3$ in MeOH (release of the phenolic acetate) then with HF – pyridine, followed by hydrogenation over Pd(C) afforded compound 2.48 in 90% overall yield after chromatography. In summary,
the desired 2.48 was now available in four steps from 2.17 and 2.33 (Heck reaction, HF-pyr, H2/Pd(C)/MeOH/K2CO3) in 4.5 g batches with an overall yield of 77%.

Scheme 2.12: Synthesis of L-Homotyrosine Derivative

2.7 Synthesis of other analogues using a similar approach

The optimized three-step sequence thus devised was extended to the preparation of other intermediates of current interest in our laboratory. Table 2.7 provides four such examples. The substrates for this study, compounds 2.50a – d, were prepared by Dr. H. Liang, of our group. The successful preparation of 2.51d merits comment. This molecule and its vinyl precursor 2.50d incorporate a dialkyl sulfide functionality. The presence of
Conditions: $[\text{PdCl}(\text{CH}_2\text{CH}=\text{CH}_2)]_2$/Tedicyp (1:2) (0.01 mmol), aryl halide (1 mmol), ethyl vinyl sulfide (2 mmol), base (2 mmol), 130 °C, 20h, argon, isolated yield.

**Scheme 2.13: Tetradentate Phosphine Ligand used in Pd-catalyzed Heck Reactions of Vinyl Sulfide Derivatives**

Conditions: 2-methylene-1,3-dithiane 1-oxide (0.5 mmol), aryl iodide (1.2eq), palladium acetate (5mol%), DPPE (5mol%), potassium carbonate (1.2eq), TBAB (1.2eq), DMF (2.0ml), argon, isolated yield.

**Scheme 2.14: Bidentate Phosphine Ligand used in Pd-catalyzed Heck Reactions of Vinyl Sulfide Derivatives**
such sulfur centers may hamper the progress of transition metal-mediated reactions. In some cases, special tetradentate phosphine ligands (Scheme 2.13) had to be employed to circumvent the problem,\textsuperscript{63} but in others, a more common bidentate phosphine proved to

\[
\text{AcO} - \text{I} + \text{R} - \text{NHMs} \rightarrow \text{a - c} \rightarrow \text{R} - \text{NHMs} - \text{OH}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
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<tbody>
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<td>a</td>
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</tr>
<tr>
<td>b</td>
<td>Me</td>
<td>84</td>
</tr>
<tr>
<td>c</td>
<td>Ph-CH₂</td>
<td>66</td>
</tr>
<tr>
<td>d</td>
<td>MeS-CH₂-CH₂</td>
<td>44</td>
</tr>
</tbody>
</table>

(a) 0.4 – 0.5 mmol of \textbf{2.50}, DMF, [\textbf{2.50}] = 0.35 M, phenol/vinyl ration=1.2:1, 5 mol \% Pd (OAc)\textsubscript{2}, 10 mol \% PhNHCONH\textsubscript{2}, (2 equiv. vs. Pd(OAc)\textsubscript{2}), K\textsubscript{2}CO\textsubscript{3} (1.2 equiv. vs. \textbf{2.50}), 100-105 °C, 2 h (\textsuperscript{1}H NMR monitoring). (b) MeOH, 1.2 equiv. K\textsubscript{2}CO\textsubscript{3}, rt, 1h. (c) H\textsubscript{2}, Pd(C), overnight. Yields refer to chromatographically purified products.

\textbf{Table 2.7: Heck Reaction of 2.33 with 2.50 with a Pd - Pheny lurea Complex}
be quite effective (Scheme 2.14).\textsuperscript{50} In the case of 2.50d, the Heck coupling proceeded in about 45-50\% yield. Indeed, the overall yield of 2.51d, 44\%, reflects substantially the efficiency of the Heck step, in that the subsequent hydrogenation reaction was essentially quantitative.\textsuperscript{64}

2.8 Oxidative cyclization of homotyrosinol derivative 2.48.

As discussed in the introductory section, our interest in a synthesis of homotyrosinol derivatives was motivated by their importance as substrates for an oxidative cyclization that converts them into dienones 2.53 (Scheme 2.15). In its original format,\textsuperscript{65} the reaction involved the use of iodobenzene diacetate ("DIB") as the oxidant and of very costly 1,1,1,3,3,3-hexafluoro-2-propanol as the solvent. This chemistry is central to a total synthesis of cylindricine C.\textsuperscript{19} More recently, Dr. Liang from our laboratory discovered that the reaction may be carried out in inexpensive trifluoroacetic acid with excellent results.\textsuperscript{66}

Mechanistically, the reaction is believed to involve a Bronsted acid catalyzed exchange of an acetoxy ligand on DIB with the phenolic substrate. The resultant 2.58

Scheme 2.15: Oxidative Cyclization of Sulfonamide Derivatives of Homotyrosinol
subsequently undergoes acid-catalyzed dissociation to a presumed cationic intermediate 2.61, which is then captured by the sulfonamide (Scheme 2.16).

A final aspect of the research described here centered on the exploration of conditions suitable for the conduct of the oxidative cyclization of 2.57 on preparative scales. The choice of 2.63 as the substrate was dictated by its importance as an intermediate for an ongoing synthesis of (-)-lepadifomine.

Slow dropwise addition of a 0.16 M solution of 2.63 (0.3 mmol) in TFA to a 0.16 M solution of DIB also in TFA (final concentration of reactants = 0.08 M), at room temperature, induced a virtually instantaneous reaction that produced dienone 2.64 in 95% yield. The reaction was clearly quite efficient; however, from a preparative standpoint, it was impractical to operate at such a high dilution during large scale
reactions. Experiment revealed that there was no need for high dilution. Indeed, reactions run at a final concentration of 0.3 M of substrate (2.63) were also as high-yielding as 95%. A semipreparative run with 3.8 mmol (1 g) of substrate afforded 2.64 in a 75% yield (Scheme 2.17). The structure of 2.64 was ascertained by X-ray diffractometry.

![Scheme 2.17: Oxidative Cyclization of 2.63](image)

Reaction conditions: 1.05 eq. DIB, TFA, [C] = 0.3 M, yield 75%

![Figure 2.4: The Molecular Structure of Compound 2.64](image)
In summary, this research defined a robust method for the preparation of homotyrosinol derivatives and related intermediates through a Mizoroki-Heck coupling between an aryl iodide and appropriate aminoacid-derived olefins. A key aspect of the work is the use of inexpensive \(N\)-phenylurea as the ligand for Pd during Heck reaction. In addition, a preparative scale procedure for the oxidative cyclization of the methanesulfonamide derivative of homotyrosinol was established. The results obtained in the course of these studies are essential to the progress of various synthetic efforts ongoing in our laboratory.
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Appendix: Experimental Section

Unless otherwise indicated, $^1$H and $^{13}$C NMR spectra were recorded at room temperature on Bruker models AV-300 (300 MHz for $^1$H and 75.5 MHz for $^{13}$C) from CDCl$_3$ solutions. Chemical shifts are reported in parts per million (ppm) on the $\delta$ scale and coupling constants, $J$, are in hertz (Hz). Multiplicities are described as “s” (singlet), “d” (doublet), “t” (triplet), “q” (quartet), “dd” (doublet of doublets), “dt” (doublet of triplets), “m” (multiplet), “br” (broad). Infrared (IR) spectra (cm$^{-1}$) were recorded on Nicolet 4700 Fourier transform spectrophotometer from neat films of analyte deposited on NaCl plates. Low-resolution mass spectra (m/z) were obtained in the electrospray (ESI) and atmospheric pressure chemical (APCI) mode on a Waters Micromass ZQ mass spectrometer. High-resolution mass spectra (m/z) were recorded in the electrospray (ESI) mode on a Micromass LCT mass spectrometer by the UBC Mass Spectrometry laboratory. Melting points (uncorrected) were measured on a Mel-Temp apparatus.

All reagents and solvents were commercial products and used without further purification except THF (freshly distilled from Na/benzophenone under argon) and CH$_2$Cl$_2$ (freshly distilled from CaH$_2$ under argon). Flash chromatography was performed on Silicycle 230 – 400 mesh silica gel. Analytic and preparative TLC was carried out with Merck silica gel 60 plates with fluorescent indicator. Spots were visualized with UV light or KMnO$_4$. All reactions were performed under dry Ar in oven-dried flasks equipped with Teflon$^\text{TM}$ stirbars. All flasks were fitted with rubber septa for the introduction of substrates, reagents, and solvents via syringe.
**Preparation of 2.6**

![Structure of 2.6](attachment:image.png)

To a solution of L-Methionine methyl ester hydrochloride (10 g, 50.3 mmol) and triethylamine (13.9 ml, 100 mmol) in DCM (150 ml) at 0°C, methanesulfonyl chloride (5.8 ml, 75 mmol) was drop-wise added over a period of 10 minutes. At the end of the addition, the solution turned to yellow. The reaction mixture was warmed up to room temperature and stirred over night. The mixture was quenched by aq. Sat. NH₄Cl (50 ml) and extracted with EtOAc (3* 75 ml). The combined extracts were sequentially washed with aq. sat. NH₄Cl (3* 50 ml), aq. sat. NaCl (50 ml), dried over MgSO₄ and concentrated to afford 12.1 g (49.8 mmol, 99%) product as a colorless solid.

\[ ^1H \text{ NMR} (\text{CDCl}_3): \ 5.40 \ (d, \ J=9, \ 1H); \ 4.31-4.21 \ (m, \ 1H); \ 3.77 \ (s, \ 3H); \ 2.96 \ (s, \ 3H); \ 2.61 \ (br, \ 2H); \ 2.08 \ (s, \ 3H); \ 2.19-1.86 \ (m, \ 2H) \]

\[ ^13C \text{ NMR} (\text{CDCl}_3): \ 172.6; \ 54.7; \ 52.9; \ 41.2; \ 32.1; \ 29.7; \ 15.2 \]

IR:

3278; 1740l; 1317; 1109

HRMS:

calcd. for \( \text{C}_7\text{H}_{15}\text{NO}_4\text{S}_2 \): \ 264.0340 \ [M+Na]^+ \]

found: \ 264.0338 \ [M+Na]^+ \]

M.P. 41-42°C

\([\alpha]_{D}^{23} \ -19.2 \degree \ (\text{CHCl}_3, \ c= 0.85)\)
Figure A.1: $^1$H NMR spectrum of 2.6

Figure A.2: $^{13}$C NMR spectrum of 2.6
Figure A.3: IR spectrum of 2.6
Preparation of 2.7

To a stirring solution of 2.6 (12.1 g, 49.8 mmol) in THF (150 ml) in an ice bath, lithium aluminum hydride powder (2.55 g, 67.2 mmol) was slowly added over a period of 30 minutes. Then reaction mixture was warmed up to room temperature and stirred over night under Argon protection. Upon the completion of the reaction, the mixture was cooled down to 0 °C. First, H₂O (2.55 ml) was added to quench the reaction. Then 30 minutes later, 15% NaOH solution (2.55 ml), H₂O (7.65 ml) and 5 tps of drying reagent (MgSO₄) was sequentially added in the interval of half an hour with vigorous stirring. The suspension solution was filtered through Celite using acetone. The crude light yellow colored solution was evaporated to afford 9.54 g (44.8 mmol, 90%) product as orange colored oil which was used without further purification.

¹H NMR (CDCl₃): 5.34 (br, 1H); 3.79-3.70 (m, 1H); 3.65-3.53 (m, 2H); 3.05 (s, 3H); 3.00 (br, 1H); 2.68-2.52 (m, 2H); 2.09 (s, 3H); 1.87-1.74 (m, 2H).

¹³C NMR (CDCl₃): 64.9; 54.6; 41.5; 30.9; 30.3; 15.3

IR: 3285; 1308; 1100

HRMS: calcd. for C₆H₁₅NO₃S₂: 236.0391 [M+Na]⁺
found: 236.0393 [M+Na]⁺

[α]D²⁰ -34.5° (CH₂Cl₂, c= 1.13)
Figure A.4: $^1$H NMR spectrum of 2.7

Figure A.5: $^{13}$C NMR spectrum of 2.7
Figure A.6: IR spectrum of 2.7
**Preparation of 2.11**

To a solution of 2.7 (9.54 g 44.8 mmol) and imidazole (6.1 g, 89.6 mmol) in DCM (100 ml) at 0°C, TBDPSCl (15.4 ml, 58.24 mmol) was drop-wise added over a period of 10 minutes. Then the reaction mixture was warmed up to room temperature and stirred over night. The mixture was quenched by aq. Sat. NH₄Cl (50 ml) and extracted with EtOAc (3* 75 ml). The combined extracts were sequentially washed with aq. sat. NH₄Cl (3* 50 ml), aq. sat. NaCl (50 ml), dried over MgSO₄ and concentrated to afford orange-color oil. Then the oil was dissolved in acetonitrile, washed with hexanes (3 * 50 ml) and evaporated to afford product as light orange oil (19.81 g, 43.9 mmol, 98%) without request for further purification.

**1H NMR (CDCl₃):**
7.67-7.61 (m, 4H); 7.49-7.37 (m, 6H); 4.64 (d, J=8.6, 1H);
3.80-3.63 (m, 2H); 3.61 (br, 1H); 2.87 (s, 3H); 2.55 (br, 2H);
2.08 (s, 3H); 1.92-1.82 (m, 2H); 1.08 (s, 9H)

**13C NMR (CDCl₃):**
135.5; 132.67; 132.65; 130.1; 127.95; 127.92; 65.8; 54.3; 41.5; 31.5; 30.3; 26.9; 19.2; 15.2

**IR:**
3283; 2930; 1323; 1152

**HRMS:**
calcd. for C₂₂H₃₃NO₃SiS₂ 474.1569 [M+Na]⁺
found: 474.1573 [M+Na]⁺

**[α]₀¹⁹**
-26.4° (CH₂Cl₂, c = 0.94)
Figure A.7: $^1$H NMR spectrum of 2.11

Figure A.8: $^{13}$C NMR spectrum of 2.11
Figure A.9: IR spectrum of 2.11
Preparation of 2.10

To a solution of 2.7 (4.0 g, 18.9 mmol) and imidazole (2.59 g, 38.0 mmol) in DCM (40 ml) at 0°C, TBSCl (3.72 g, 24.7 mmol) was added. The reaction mixture was warmed up to room temperature and stirred over night. Then mixture was quenched by aq. sat. NH₄Cl (10 ml) and extracted with EtOAc (3* 25 ml). The combined extracts were sequentially washed with aq. sat. NH₄Cl (3* 25 ml), aq. sat. NaCl (25 ml), dried over MgSO₄ and concentrated. Chromatography of the residue (EtOAc: hexanes = 1: 3) gave 5.56 g (17.0 mmol, 90 %) product as light yellow oil.

\[\text{S} \quad \text{NHMs} \quad \text{OTBS}\]

\(^1\)H NMR (CDCl₃): 4.65 (br, 1H); 3.78-3.54 (m, 2H); 3.61 (br, 1H); 3.00 (s, 3H); 2.62 (br, 2H); 2.10 (s, 3H); 1.87-1.76 (m, 2H); 0.89 (s, 9H); 0.079 (s, 3H); 0.072 (s, 3H)

\(^{13}\)C NMR (CDCl₃): 65.3; 54.3; 41.6; 31.4; 30.3; 25.8; 18.3; 15.2; -5.45; -5.48

IR: 3283; 2928; 1317; 1152

HRMS: calcd. for C\textsubscript{12}H\textsubscript{29}NO\textsubscript{3}SiS\textsubscript{2} 328.1436 [M+H]\textsuperscript{+} found: 328.1445 [M+H]\textsuperscript{+}

[\(\alpha\)]\textsuperscript{D}

-31.8° (CH\textsubscript{2}Cl\textsubscript{2}, c = 0.83)
Figure A.10: $^1$H NMR spectrum of 2.10

Figure A.11: $^{13}$C NMR spectrum of 2.10
Figure A.12: IR spectrum of 2.10
Preparation of 2.9

To a solution of 2.7 (0.852, 4.0 mmol) and pyridine (0.49 ml, 6.0 mmol) in DCM (8 ml) at 0°C, acetic anhydride (0.45 ml, 4.8 mmol) was added. The reaction mixture was warmed up to room temperature and stirred over night. Then mixture was quenched by aq. sat. NaHCO₃ (5 ml) and extracted with EtOAc (3* 15 ml). The combined extracts were sequentially washed with aq. sat. NaHCO₃ (3* 10 ml), aq. sat. NaCl (10 ml), dried over MgSO₄ and concentrated. Chromatography of the residue (EtOAc: hexanes = 1: 2) gave 0.918g (3.6 mmol, 95 %) product as light yellow oil.

$^1$H NMR (CDCl₃): 5.23 (d, J=9, 1H); 4.12-3.99 (m , 2H); 3.79-3.66 (m, 1H); 2.96 (s, 3H); 2.64-2.46 (m, 2H); 2.03 (s, 3H); 2.01 (s, 3H); 1.84-1.64 (m, 2H)

$^{13}$C NMR (CDCl₃): 170.8; 66.2; 51.8; 41.6; 31.4; 29.9; 20.7; 15.2

IR: 3281; 1739; 1316; 1150

HRMS: calcd. for C₈H₁₁NO₄S₂ 278.0497 [M+Na]$^+$
found: 278.0494 [M+Na]$^+$

$[\alpha]_{D}^{20}$ -33.6° (CH₂Cl₂, c = 1.63)
Figure A.13: $^1$H NMR spectrum of 2.9

Figure A.14: $^{13}$C NMR spectrum of 2.9
Figure A.15: IR spectrum of 2.9
Preparation of 2.15

Sodium periodate (0.847 g, 3.96 mmol) in de-ionized water (11 ml) in addition funnel was slowly added to a solution of compound 2.9 (0.918 g, 3.6 mmol) in MeOH (11 ml), at 0 °C with good stirring. The reaction mixture was warmed up to room temperature and stirred for 4 hours. Once the reaction was completed, the mixture was diluted in 30 ml EtOAc. The organic layer was separated and sequentially washed with aq. sat. NaHCO₃ (3* 10 ml), aq. sat. NaCl (10 ml), dried over MgSO₄ and concentrated. Then the crude product was dissolved in 1, 2 – dichlorobenzene (5 ml), and Na₂CO₃ powder (0.763 g, 7.2 mmol) was added. The reaction was heated up to 190 °C to keep refluxing and stirred overnight under the protection of Argon. Once the reaction was completed, NH₄Cl (10 ml) was added to quench the reaction. The mixture was diluted with 15 ml EtOAc, washed with aq. sat. NH₄Cl (3* 10 ml), aq. sat. NaCl (10 ml), dried over MgSO₄ and concentrated. Chromatographic purification of the residue (1: 1 = EtOAc: Hexane) was provided 2.15 (0.537 g, 72% over two steps) as light yellow oil.

¹H NMR: 5.87-5.73 (m, 1H); 5.41 (d, J=17, 1H); 5.32 (d, J=10, 1H); 4.89 (br, 1H); 4.25 (br, 1H); 4.21-4.09 (m, 1H); 2.98 (s, 3H); 2.09 (s, 3H)

¹³C NMR: 170.8; 134.0; 118.6; 65.8; 55.2; 42.1; 20.8

IR: 3280; 1741; 1319; 1147
HRMS: calcd. for C\textsubscript{7}H\textsubscript{13}NO\textsubscript{4}S: 230.0463 [M+Na]\textsuperscript{+}
found: 230.0457 [M+Na]\textsuperscript{+}

$\left[\alpha\right]_{D}^{20}$ -20.3° (CH\textsubscript{2}Cl\textsubscript{2}, c = 1.25)

Figure A.16: $^1$H NMR spectrum of 2.15
Figure A.17: $^{13}$C NMR spectrum of 2.15

Figure A.18: IR spectrum of 2.15
Preparation of 2.16

Sodium periodate (3.95 g, 18.7 mmol) in de-ionized water (40 ml) in addition funnel was slowly added to a solution of compound 2.10 (5.55 g, 17 mmol) in MeOH (50 ml), at 0 °C with good stirring. The reaction mixture was warmed up to room temperature and stirred for 4 hours. Once the reaction was completed, the mixture was concentrated on roto vap and then diluted in 100 ml EtOAc. The organic layer was separated and sequentially washed with aq. sat. NaHCO₃ (3* 25 ml), aq. sat. NaCl (25 ml), dried over MgSO₄ and concentrated. Then the crude product was dissolved in 1, 2 – dichlorobenzene (20ml), and Na₂CO₃ powder (3.64 g, 34 mmol) was added. The reaction was heated up to 190 °C to keep refluxing and stirred overnight under the protection of Argon. Once the reaction was completed, NH₄Cl (10 ml) was added to quench the reaction. The mixture was diluted with 30 ml EtOAc, washed with aq. sat. NH₄Cl (3* 25 ml), aq. sat. NaCl (25 ml), dried over MgSO₄ and concentrated. Additional extraction was performed using hexanes (30 ml) and acetonitrile (30 ml) to remove the excess 1, 2 – dichlorobenzene. Chromatographic purification of the residue (1: 4 = EtOAc: Hexane) provided 2.16 (2.77 g, 85% over two steps) as light yellow oil.

¹H NMR (CDCl₃): 5.88-5.74 (m, 1H); 5.33 (d, J=17, 1H); 5.25 (d, J= 10.3, 1H); 4.82 (br, 1H); 3.99 (br, 1H); 3.78-3.54 (m, 2H); 2.96 (s, 3H); 0.88 (s, 9H); 0.067 (s, 3H); 0.059 (s, 3H)

¹³C NMR (CDCl₃): 135.5; 117.9; 65.7; 57.8; 41.9; 25.8; 18.2; -5.5; -5.4

IR: 3284; 2857; 1325; 1154
HRMS: calcd for C_{11}H_{25}NO_{3}Si: 302.1222 [M+Na]^+
found: 302.1222 [M+Na]^+

[\alpha]_D^{20} 14.7^\circ \text{ (CH}_2\text{Cl}_2, c = 1.08)
Figure A.20: $^{13}$C NMR spectrum of 2.16

Figure A.21: IR spectrum of 2.16
Preparation of 2.22

Sodium periodate (6.33g, 29.6 mmol) dissolved in de-ionized water (80 ml) was slowly added to the solution of compound 2.11 (12.14 g, 26.9 mmol) in MeOH (80 ml), at 0 °C with good stirring. The mixture was warmed up to room temperature and stirred for 4 hours. Once the reaction was completed, the mixture was concentrated and then diluted in EtOAc (100 ml). The organic layer was separated and sequentially washed with aq. sat. NaHCO3 (3* 35 ml), aq. sat. NaCl (35 ml), dried over MgSO4 and concentrated. Then the crude product was dissolved in 1, 2 – dichlorobenzene (30 ml), and Na2CO3 powder (5.7g, 53.8 mmol) was added. The reaction was heated up to 190 °C to keep refluxing and stirred overnight under Argon protection. Then, NH4Cl (20 ml) was added to quench the reaction. The mixture was diluted with 50 ml EtOAc, washed with aq. sat. NH4Cl (3* 35 ml), aq. sat. NaCl (35 ml) dried over MgSO4 and concentrated. Additional extraction was performed using hexanes (50 ml) and acetonitrile (50 ml) to remove excess 1, 2 – dichlorobenzene. Chromatographic purification of the residue (1: 4 = EtOAc: Hexane) provided 2.22 (7.59 g, 18.8 mmol, 70% over two steps) as an orange solid.

1H NMR (CDCl3): 7.71-7.62 (m, 4H); 7.51-7.37 (m, 6H); 5.91-5.77 (m, 1H); 5.36 (d, J=17, 1H); 5.27 (d, J= 10, 1H); 4.94 (br, 1H); 4.06 (br, 1H); 3.83-3.63 (m, 2H); 2.94 (s, 3H); 1.09 (s, 3H)

13C NMR (CDCl3): 135.58; 135.55; 135.46; 132.69; 132.66; 130.03; 130.02; 127.9; 127.8; 118.1; 66.3; 57.8; 41.9; 26.9; 26.8; 19.3

IR: 3290; 2931; 1361
HRMS: calcd. for $\text{C}_{21}\text{H}_{29}\text{NO}_{3}\text{Si}$ 426.1535 $[\text{M+Na}]^+$
found 426.1525 $[\text{M+Na}]^+$

M.P.: 71.5-72.5 °C

$[\alpha]_D^{23}$ -10.12 ° (CHCl$_3$, c = 1.00)

Figure A.22: $^1$H NMR spectrum of 2.17
Figure A.23: $^{13}$C NMR spectrum of 2.17

Figure A.24: IR spectrum of 2.17
Preparation of 2.37e

\[
\begin{align*}
\text{NHMs} & \quad \text{OH} \\
\end{align*}
\]

In ice bath, 1 M TBAF solution in THF (1.2 ml, 1.2 mmol) was slowly added into a solution of 2.22 (484 mg, 1.2 mmol) in THF (3 ml). Then the reaction mixture was warmed up to room temperature and stirred over night. The reaction was quenched by 5 ml aq. sat. NH₄Cl and diluted with EtOAc (15 ml), washed with aq. Sat. NH₄Cl (3* 10 ml), aq. sat. NaCl (10 ml), dried over MgSO₄ and concentrated. Chromatography of the residue (EtOAc: Hexane = 1:1) gave 181 mg (1.1 mmol, 93 %) product as light yellow oil.

\(^1\)H NMR (CDCl₃): 5.89-5.73 (m, 1H); 5.52-5.43 (m, 1H); 5.38 (d, J=17, 1H); 5.30 (d, J=10, 1H); 4.11-4.00 (m, 1H); 3.82-3.52 (m, 2H); 3.00 (s, 3H)

\(^13\)C NMR (CDCl₃): 134.8; 118.3; 64.9; 58.1; 41.8

IR: 3280

HRMS: calcd. for C₅H₁₁NO₃S: 188.0357 [M+Na]^+ 
found: 188.0358 [M+Na]^+

[\(\alpha\)]\(_{D}^{20}\) -21.81° (CH₂Cl₂, c = 0.94)
Figure A.25: $^1$H NMR spectrum of 2.37e

Figure A.26: $^{13}$C NMR spectrum of 2.37e
Figure A.27: IR spectrum of 2.37e
General procedure for Heck coupling

Pd (OAc)$_2$ (10 mol %), ligand (20 mol %), and potassium carbonate (0.6 mmol) was added to the solution of 4-iodine phenol (0.6 mmol) and vinyl glycinol derivative (0.5 mmol) in degassed DMF (1.5 ml). The reaction mixture was heated up to 105 °C-110 °C under Argon protection. After 2-4 hours stirring (NMR was used to monitor the reaction), the mixture was cooled down to room temperature, quenched with aq. sat. NH$_4$Cl (10 mL) and then extracted with EtOAc (15 ml). The combined extracts were sequentially washed with aq. sat. NH$_4$Cl (10 mL), aq. sat. NaCl (10 ml) dried with MgSO$_4$ and concentrated. Chromatography (1:3 = EtOAc: Hexane) of the residue afforded desired coupling products.
Preparation of 2.34

![Chemical Structure](image)

Light yellow oil

$^1$H NMR (CDCl$_3$): 7.68-7.60 (m, 4H); 7.49-7.31 (m, 8H); 7.06 (d, $J=8.6$, 2H); 6.62 (d, $J=15.7$, 1H); 6.07 (dd, $J=15.7$, 7.5, 1H); 4.93 (d, $J=6.7$, 1H); 4.25-4.15 (m, 1H); 3.90-3.68 (m, 2H); 2.93 (s, 3H); 2.31 (s, 3H); 1.08 (s, 9H)

$^{13}$C NMR (CDCl$_3$): 169.4; 150.4; 135.56; 135.54; 133.7; 132.5; 132.3; 130.07; 130.04; 127.95; 127.90; 127.50; 126.5; 121.8; 66.4; 57.4; 42.2; 26.8; 21.1; 19.2

IR: 3288; 2931; 1750; 1324; 1156

HRMS: calcd. for C$_{29}$H$_{35}$NO$_5$SSi: 560.1903 [M+Na]$^+$
found: 560.1894 [M+Na]$^+$

EA: Calcd. for C$_{29}$H$_{35}$NO$_5$SSi: C, 64.77; H, 6.56; N, 2.60
Found: C, 64.50; H, 6.52; N, 2.79

$[\alpha]_D^{20}$ -16.6 ° (CH$_2$Cl$_2$, c= 1.17)
Figure A.28: $^1$H NMR spectrum of 2.34

Figure A.29: $^{13}$C NMR spectrum of 2.34
Figure A.30: IR spectrum of 2.34
Preparation 2.35


$^1$H NMR (CDCl$_3$): 7.70-7.61 (m, 4H); 7.48-7.34 (m, 6H); 7.16 (d, $J$=8.6, 2H); 6.78 (d, $J$=8.6, 2H); 6.54 (d, $J$=15.4, 1H); 5.98-5.85 (m, 2H); 5.01 (d, $J$=6.5, 1H); 4.24-4.13 (m, 1H); 3.89-3.67 (m, 2H); 2.95 (s, 3H); 1.09 (s, 9H)

$^{13}$C NMR (CDCl$_3$): 155.9; 135.58; 135.56; 132.9; 132.65; 132.63; 130.07; 130.03; 128.5; 127.97; 127.94; 127.91; 123.4; 115.6; 66.5; 57.8; 42.2; 26.9; 19.3

IR: 3295; 2931; 1362; 1152

HRMS: calcd. for C$_{27}$H$_{33}$NO$_4$SSi: 518.1797 [M+Na]$^+$ found: 518.1797 [M+Na]$^+$

E.A.: calcd. for C$_{27}$H$_{33}$NO$_4$SSi: C, 65.42; H, 6.71; N, 2.83
found: C, 65.23; H, 6.36; N, 2.69

$[\alpha]_D^{21}$ -3.76 ° (acetone, c = 1.75)
Figure A.31: $^1$H NMR spectrum of 2.35

Figure A.32: $^{13}$C NMR spectrum of 2.35
Figure A.33: IR spectrum of 2.35
Preparation 2.39b

Chromatographic solvent (EtOAc: Hexanes = 1:2), light yellow oil.

\(^1\)H NMR \( (d_6\text{-acetone}) \):
8.47 (br, 1H); 7.31 (d, \( J=8.6 \), 2H); 6.82 (d, \( J=8.6 \), 2H); 6.67 (d, \( J=15.8 \), 1H); 6.13 (d, \( J=15.8 \), 1H); 6.12-6.07 (m, 1H); 4.22-4.16 (m, 1H); 3.80 (d, \( J=5.7 \), 2H); 2.94 (s, 3H); 0.92 (s, 9H); 0.11 (s, 3H); 0.10 (s, 3H)

\(^{13}\)C NMR \( (d_6\text{-acetone}) \):
157.3; 131.8; 128.3; 127.7; 124.4; 115.4; 115.4; 66.3; 57.9; 41.0; 25.4; 18.0; -6.1

IR: 3380

HRMS:
calcd. for C\(_{17}\)H\(_{29}\)NO\(_4\)SSi: 394.1484 [M+Na]\(^+\)
found: 394.1493 [M+Na]\(^+\)

\([\alpha]_D^{20}\): +20.70 ° (acetone, c = 1.15)
Figure A.34: $^1$H NMR spectrum of 2.39b

Figure A.35: $^{13}$C NMR spectrum of 2.39b
Figure A.36: IR spectrum of 2.39b
Preparation of 2.39e

Chromatographic solvent (EtOAc: Hexanes = 3: 1), light yellow solid.

$^1$H NMR ($d_6$-acetone): 8.46 (br, 1H); 7.30 (d, $J$=8.6, 2H); 6.82 (d, $J$=8.6, 2H); 6.65 (d, $J$=16, 1H); 6.17-6.06 (m, 2H); 4.21-4.06 (m, 2H); 3.76-3.62 (m, 2H); 2.96 (s, 3H)

$^{13}$C NMR ($d_6$-acetone): 157.2; 131.7; 128.3; 127.7; 124.5; 115.4; 65.1; 58.3; 41.0

IR: 3426; 1644

HRMS: calcd. for C$_{11}$H$_{15}$NO$_4$S: 280.0619 [M+Na]$^+$
found: 280.0616 [M+Na]$^+$

EA: calcd. for C$_{11}$H$_{15}$NO$_4$S: C, 51.35; H, 5.88; N, 5.44
found: C, 51.75; H, 5.80; N, 5.49

M.P. 142-143 °C

$[\alpha]_D^{23}$ -63.6° (acetone, c = 0.79)
Figure A.37: $^1$H NMR spectrum of 2.39e

Figure A.38: $^{13}$C NMR spectrum of 2.39e
Figure A.39: IR spectrum of 2.39e
General procedure for silyl group deprotection

HF-Pyridine solution (70 % HF, 2ml) was drop-wise added into the solution of coupling product (1mmol) in THF (3ml) which was cooled in the ice bath. The reaction mixture was warmed up to room temperature and stirred overnight under Argon protection. Once the reaction was completed, the mixture was neutralized with solid NaHCO$_3$ (a tsp of base was slowly added every two minutes especially for larger scale reaction) until there was no bubble coming out any more. Then the mixture was filtrated through celite and concentrated under reduced pressure. Chromatography (EtOAc: Hexanes = 3:1) of the residue afforded the desired products.

**Preparation 2.39e**

Chromatographic solvent (EtOAc: Hexanes = 3:1), light yellow solid.

See page 99 for characterization data and spectrums.
Preparation of 2.42

Light yellow solid, 95 % yield.

$^1$H NMR (CDCl$_3$): 7.39 (d, $J$=8.6, 2H); 7.06 (d, $J$=8.6, 2H); 6.68 (d, $J$=16, 1H); 6.10 (dd, $J$=16, 7.2, 1H); 4.27-4.17 (m, 1H); 3.88-3.62 (m, 2H); 2.99 (s, 3H); 2.30 (s, 3H)

$^{13}$C NMR (CDCl$_3$): 169.4; 150.5; 133.5; 132.5; 127.6; 125.7; 121.9; 65.2; 57.7; 42.1; 21.1

IR: 3504; 3284; 1754

HRMS: calcd. for C$_{13}$H$_{17}$NO$_5$S: 322.0725 [M+Na]$^+$
found: 322.0722 [M+Na]$^+$

HRMS: calcd. for C$_{13}$H$_{17}$NO$_5$S: C, 52.16; H, 5.72; N, 4.68
found: C, 52.10; H, 5.74; N, 4.66

M. P. 125.5-126.5 °C

$[\alpha]_D^{23}$ -63.7 ° (CHCl$_3$, $c$ = 0.73)
Figure A.40: $^1$H NMR spectrum of 2.42

Figure A.41: $^{13}$C NMR spectrum of 2.42
Figure A.42: IR spectrum of 2.42
Preparation (s)-MPTA ester 2.44

Triethylamine (0.033mL, 0.24 mmol) was slowly added to a solution of 2.42 (50mg, 0.17 mmol) in DCM (1mL) with DMAP (29mg, 0.24 mmol) and (R)-MTPACl (50mg, 0.2 mmol), at 0 °C and with good stirring. Then the reaction mixture was warmed up to room temperature and stirred over night under Argon protection. Upon the completion of the reaction, the mixture was diluted with EtOAc (15mL), and then was sequentially washed with aq. sat. NH₄Cl (3*10 mL), aq. sat. NaCl (10 mL) dried over MgSO₄ and concentrated. Chromatography of the residue (EtOAc/Hex=1/2) gave 61 mg (0.12 mmol, 70%) product as light yellow oil.

¹H NMR (CDCl₃): 7.53-7.46 (m, 2H); 7.45-7.30 (m, 5H); 7.06 (d, J=8.5, 2H); 6.66 (d, J=16, 1H); 4.81-4.73 (m, 1H); 4.53-4.41 (m, 3H); 3.53 (s, 3H); 2.89 (s, 3H); 2.31 (s, 3H)

¹³C NMR (CDCl₃): 169.3; 166.4; 150.7; 133.3; 133.0; 131.7; 129.8; 128.6; 127.6; 127.2; 124.4; 121.9; 84.7; 67.7; 55.5; 54.7; 42.2; 21.1

F-NMR -71.66

HRMS: calcd. for C₂₃H₂₄NO₇F₃S: 538.1123 [M+Na]⁺
found: 538.1132 [M+Na]⁺

IR 1751

[α]D²₀ -6.09 ° (CH₂Cl₂, c = 0.92)
Figure A.43: $^1$H NMR spectrum of 2.44

Figure A.44: $^{13}$C NMR spectrum of 2.44
Figure A.45: $^{19}$F NMR spectrum of 2.44

Figure A.46: IR spectrum of 2.44
General procedure for hydrogenation

Compound 2.34 and 2.35 (1 mmol), palladium (10 wt % on activated carbon, 106 mg, and 0.1 mmol) and potassium carbonate (276mg, 2 mmol) was added to a pre-dried round-bottom flask with Argon protection on top. MeOH (5ml) was slowly added at room temperature. Hydrogen gas was bubbled into the solution for half an hour on sonicator. Then the reaction mixture was stirred at room temperature for overnight. Once upon the completion of the reaction, the mixture was quickly filtrated through 2-inch celite pad with Hexanes and concentrated. EtOAc (20 ml) and aq. sat. NH₄Cl (10 mL) were added into the crude yellow oil. The mixture was separated and extracted with EtOAc (3*10 ml). The combined organic layer was sequentially washed with aq. sat. NH₄Cl (10 mL), aq. sat. NaCl (10 ml) dried with MgSO₄ and concentrated. The products were carried over the next step without further purification.
Preparation of 2.47

![Chemical Structure]

95 % yield, light yellow oil.

$^1$H NMR (CDCl$_3$): 7.67-7.59 (m, 4H); 7.49-7.36 (m, 6H); 7.00 (d, $J$=8.6, 2H); 6.74 (d, $J$=8.6, 2H); 4.56 (d, $J$=8, 1H); 3.77-3.62 (m, 2H); 3.49-3.38 (m, 1H); 2.82 (s, 3H); 2.67-2.49 (m, 2H); 1.94-1.81 (m, 2H); 1.08 (s, 9H)

$^{13}$C NMR (CDCl$_3$): 153.8; 135.5; 133.1; 132.7; 130.0; 129.4; 127.94; 127.91; 115.3; 65.7; 55.1; 41.7; 34.4; 31.0; 26.9; 19.21

IR: 3294; 2930; 1316; 1113

HRMS: calcd. for C$_{27}$H$_{35}$NO$_4$SSi: 520.1954 [M+Na]$^+$

found: 520.1967 [M+Na]$^+$

$[\alpha]_D^{23}$ -15.8° (acetone, c = 1.51)
Figure A.47: $^1$H NMR spectrum of 2.47

Figure A.48: $^{13}$C NMR spectrum of 2.47
Figure A.49: IR spectrum of 2.47
Preparation of 2.48

95 % yield, light yellow to white solid

$^1$H NMR ($d_6$-acetone): 8.08 (br, 1H); 7.07 (d, $J$=8.5, 2H); 6.75 (d, $J$=8.5, 2H); 5.94 (d, $J$=8.5, 1H); 3.99 (br, 1H); 3.63 (d, $J$=5.5, 2H); 3.49-3.38 (m, 1H); 2.98 (s, 3H); 2.81-2.56 (m, 2H); 1.98-1.65 (m, 2H)

$^{13}$C NMR ($d_6$-acetone): 155.4; 132.7; 129.2; 115.1; 64.7; 55.8; 40.8; 34.4; 30.9

IR: 3417; 1644;

HRMS: calcd. for C$_{11}$H$_{17}$NO$_4$S: 282.0776 [M+Na]$^+$
found: 282.0778 [M+Na]$^+$

E.A.: calcd. for C$_{11}$H$_{17}$NO$_4$S: C, 50.95; H, 6.61; N, 5.40
found: C, 50.98; H, 6.59; N, 5.39

M.P.: 112.5-113.5 °C

$[^{23}]$D: -6.03° (acetone, c = 0.63)
Figure A.50: $^1$H NMR spectrum of 2.48

Figure A.51: $^{13}$C NMR spectrum of 2.48
Figure A.52: IR spectrum of 2.48
**General procedure for the synthesis of 2.51**

Pd (OAc)$_2$ (5 mol %), N-phenylurea (10 mol %), and potassium carbonate (0.6 mmol) was added to the solution of 4-iodine phenol (0.6 mmol) and vinyl 2.50 (0.5 mmol) in degassed DMF (1.5 ml). The reaction mixture was heated up to 100 °C-105 °C under Argon protection. After 2 hours’ stirring (NMR was used to monitor the reaction), the mixture was cooled down to room temperature, quenched with aq. sat. NH$_4$Cl (10 mL) and then extracted with EtOAc (15 ml). The combined extracts were sequentially washed with aq. sat. NH$_4$Cl (10 mL), aq. sat. NaCl (10 mL) dried with MgSO$_4$ and concentrated. The crude product was dissolved in MeOH with suspended K$_2$CO$_3$ (0.6 mmol) and stirred for one hour at room temperature. Upon the reaction the completion of the reaction, the mixture was filtrated through celite and concentrated under reduced pressure. Chromatography of the residue gave the corresponding desired product.

The pure coupling product, palladium (10 wt % on activated carbon, 26.5mg, and 0.025 mmol) was added to a pre-dried round-bottom flask with Argon protection on top. MeOH (5ml) was slowly added at room temperature. Hydrogen gas was bubbled into the solution for 15 minutes on sonicator. Then the reaction mixture was stirred at room temperature for overnight. Once upon the completion of the reaction, the mixture was quickly filtrated through 2-inch celite pad with Hexanes and concentrated. EtOAc (10 ml) and aq. sat. NH$_4$Cl (5 mL) were added into the crude yellow oil. The mixture was separated and extracted with EtOAc (3*5 ml). The combined organic layer was sequentially washed with aq. sat. NH$_4$Cl (5 mL), aq. sat. NaCl (5 ml) dried with MgSO$_4$ and concentrated.
Preparation of 2.51a

89 % yield over 3 steps; very light yellow foam.

$^1$H NMR ($d_6$-acetone): 7.07 (d, $J$=8.6, 2H); 6.76 (d, $J$=8.6, 2H); 3.32-3.23 (m, 1H); 2.94 (s, 3H); 2.80-2.52 (m, 2H); 2.01-1.66 (m, 3H); 0.95 (dd, $J$=9.1, 6.7, 6H)

$^{13}$C NMR ($d_6$-acetone): 154.1; 133.1; 129.3; 115.4; 59.4; 42.0; 34.3; 31.6; 31.4; 18.5; 17.6

HRMS: calcd. for C$_{13}$H$_{21}$NO$_3$S: 294.1140 [M+Na]$^+$
found: 294.1143 [M+Na]$^+$
Figure A.53: $^1$H NMR spectrum of 2.51a

Figure A.54: $^{13}$C NMR spectrum of 2.51a
Preparation of 2.51b

84% yield over three steps; light yellow oil.

$^1$H NMR ($d_6$-acetone): 8.11 (br, 1H); 7.07 (d, $J$=8.1, 2H); 6.76 (d, $J$=8.1, 2H); 5.94 (d, $J$=8.2, 1H); 3.54-3.39 (m, 1H); 2.92 (s, 3H); 2.75-2.55 (m, 2H); 1.88-1.68 (m, 2H); 1.28 (d, $J$=6.5, 3H)

$^{13}$C NMR ($d_6$-acetone): 155.4; 132.6; 129.2; 115.0; 49.5; 40.6; 39.7; 31.2; 21.7

HRMS: calcd. for C$_{11}$H$_{17}$NO$_3$S: 266.0827 [$M+Na]^+$  
found: 266.0821 [$M+Na]^+$
Figure A.55: $^1$H NMR spectrum of 2.51b

Figure A.56: $^{13}$C NMR spectrum of 2.51b
Preparation of 2.51c

66% yield over three steps; light yellow oil.

$^1$H NMR ($d_6$-acetone): 8.13 (br, 1H); 7.38-7.17 (m, 5H); 7.03 (d, $J$=8.3, 2H); 6.74 (d, $J$=8.3, 2H); 6.10 (d, $J$=8.9, 1H); 3.71-3.55 (m, 1H); 2.99-2.54 (m, 4H); 2.45 (s, 3H); 1.93-1.68 (m, 2H)

$^{13}$C NMR ($d_6$-acetone): 155.4; 139.1; 132.6; 129.7; 129.1; 128.3; 126.3; 115.1; 56.0; 41.9; 40.2; 37.9; 31.0

HRMS: calcd. for C$_{17}$H$_{21}$NO$_3$S: 342.1140 [M+Na]$^+$
found: 342.1138 [M+Na]$^+$
Figure A.57: $^1$H NMR spectrum of 2.51c

Figure A.58: $^{13}$C NMR spectrum of 2.51c
Preparation of 2.64

A 0.16 M solution of 2.63 (0.3 mmol) in TFA was added slowly, dropwise into a 0.16 M solution of DIB also in TFA (final concentration of reactants = 0.08 M), at room temperature. Upon the completion of the reaction, the crude mixture was evaporated to dryness under reduced pressure. Chromatography of the residue (1% MeOH in EtOAc) would afford a light yellow solid 2.64 in a 95% yield.

${}^1$H NMR (d$_6$-acetone): 7.26 (dd, $J=9.8$, 3.0, 1H); 7.04 (dd, $J=9.9$, 3.0, 1H); 6.16 (dd, $J=9.9$, 2.3, 1H); 6.10 (dd, $J=10.1$, 2.1, 1H); 4.15 (br, 1H); 4.12-4.04 (m, 1H); 3.82-3.72 (m, 2H); 3.00 (s, 3H); 2.61-2.33 (m, 2H); 2.24-2.13 (m, 1H); 1.99-1.89 (m, 1H)

${}^{13}$C NMR (d$_6$-acetone): 184.4; 152.7; 148.7; 127.7; 127.3; 64.2; 63.9; 63.1; 39.3; 37.7; 26.5

IR: 3417; 2929; 1667; 1328

HRMS: calcd. for C$_{11}$H$_{15}$NO$_4$S: 280.0619 [M+Na]$^+$  
found: 280.0619 [M+Na]$^+$

$[\alpha]_D^{22}$ -20.35° (acetone, c = 1.103)
Figure A.59: $^1$H NMR spectrum of 2.64

Figure A.60: $^{13}$C NMR spectrum of 2.64
X-RAY CRYSTALLOGRAPHY DATA

X-ray data of compound 2.64

Empirical Formula: $C_{11}H_{15}NO_4S$

Formula Weight: 257.30

Crystal Color, Habit: colourless, needle

Crystal Dimensions: 0.12 X 0.20 X 0.25 mm

Crystal System: orthorhombic

Lattice Type: primitive

Lattice Parameters:

- $a = 5.6476(6)$ Å
- $b = 9.7999(12)$ Å
- $c = 21.490(3)$ Å
- $\alpha = 90^\circ$
- $\beta = 90^\circ$
- $\gamma = 90^\circ$

Volume: $V = 1189.4(2)$ Å$^3$

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