The Synthesis and Applications of a Biaryl-Based Asymmetric Phosphine Ligand

by

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ABSTRACT

The asymmetric biaryl backbone of a dialkylbiphenyl phosphine ligand was developed, synthesized, and resolved. The application of the chiral phosphine ligand to the asymmetric Suzuki-Miyaura cross-coupling reaction was also investigated. This phosphine ligand has yielded promising results in the asymmetric Suzuki-coupling of hindered boronic acids with the electron-rich aryl bromide, 1-bromo-2-methoxynaphthalene, to synthesize biaryls in modest enantioselectivity.

Thesis Supervisor: Professor Stephen L. Buchwald
Title: Camille Dreyfus Professor of Chemistry

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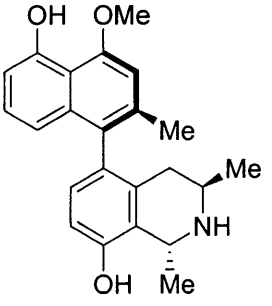
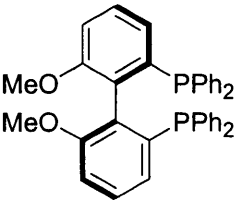
The Synthesis and Applications of a Biaryl-Based Asymmetric Phosphine Ligand

A. Introduction

The axially chiral biaryl motif is present in various natural products of pharmaceutical importance as well as in asymmetric ligands and catalysts.[1] For example, Dioncophylline C is an antimalarial naphthylisoquinoline alkaloid[2] while 2,2'-bisdiphenylphosphanyl-6,6'-dimethoxy-biphenyl (**MeO-BIPHEP**) is an asymmetric biaryl ligand used for enantioselective isomerizations and hydrogenations (Scheme **1**).[3]



Dioncophylline C



(*R*)-MeO-BIPHEP

Scheme 1: Examples of asymmetric biaryls.

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[1] (a) Bringmann, G.; Gunther, G.; Ochse, M.; Schupp, O. In *Progress in the Chemistry of Organic Natural Products*; Herz, W.; Falk, H.; Kirby, G. W.; Moore, R. E.; Tamm, C., Eds.; Springer-Verlag: New York, 2001; Vol. 82. (b) Pu, L. *Chem. Rev.* **1998**, *98*, 2405 – 2494.

[2] Bringmann, G.; Holenz, J.; Weirich, R.; Rubenacker, M.; Funke, C.; Boyd, M. R.; Gulakowski, R. J.; Fancois, G. *Tetrahedron* **1998**, *54*, 497 – 512.

[3] (a) Schmid, R.; Foricher, J.; Cereghetti, M.; Schonhoizer, P. *Helv. Chim. Acta* **1991**, *74*, 370 – 389. (b) Schmid, R.; Broger, E. A.; Cereghetti, M.; Crameri, Y.; Foricehr, J.; Lalonde, M.; Muller, R. K.; Scalone, M.; Schoettel, G.; Zutter, U. *Pure Appl. Chem.* **1996**, *68*, 131 – 138.

Enantiopure biaryls with axial chirality have been accessed via a variety of methods.[4] Most often, atropisomers are separated by classical resolution. The formation of diastereomers, synthesized from the reaction of the racemic biaryl compound with an enantiopure resolving agent, is the most common method to separate enantiomers.[5] Examples of resolving agents used include menthyl chloroformate, camphorsulfonyl chloride, and chiral sulfoxides.[6] The diastereomers can then be separated by selective re-crystallization of one diastereomer or by column chromatography. Other commonly used approaches include inclusion complex formation with a cinchona alkaloid such as (8*S*,9*R*)-(–)-N-benzylcinchonidinium chloride, which has been used to resolve the enantiomers of 2,2'-dihydoxy-1,1'-binaphthyl (BINOL),[7] and enzymatic resolution using PS-C lipase, which has the ability to desymmetrize atropisomers via enantioselective acetylation or hydrolysis.[8]

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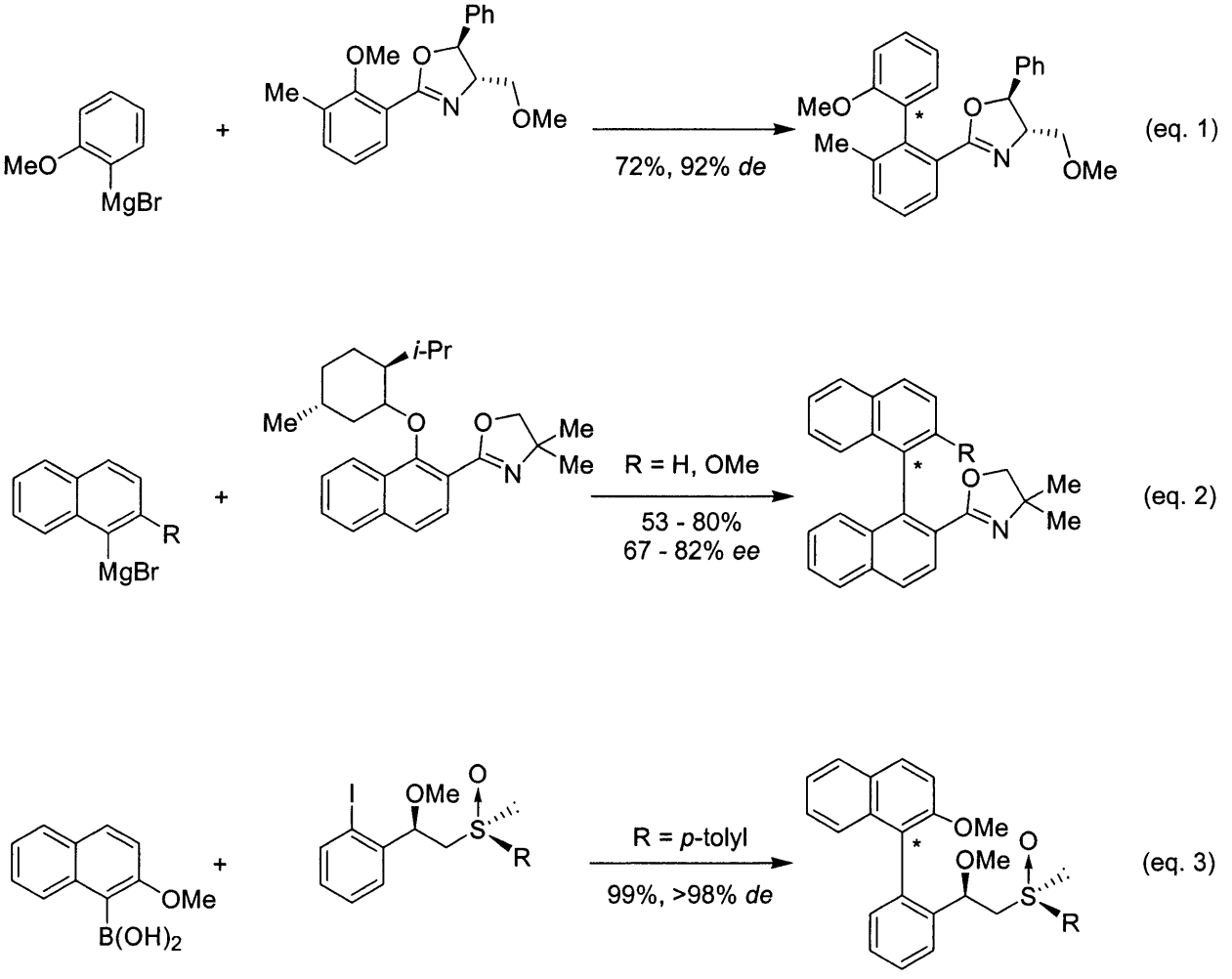
[4] Putala, M. *Enantiomer* **1999**, *4*, 243 – 262.

[5] (a) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*. Wiley & Sons: New York, 1994. (b) Cammidge, A. N.; Crepy, K. V. L. *Tetrahedron* **2004**, *60*, 4377 – 4386.

[6] (a) Nishikori, H.; Katsuki, T. *Tetrahedron Lett.* **1996**, *37*, 9245 – 9248. (b) Luo, Y.; Wang, F.; Zhu, G.; Zhang, Z. *Tetrahedron: Asymmetry* **2004**, *15*, 17 – 19. (c) Clayden, J.; Kubinski, P. M.; Sammiceli, F.; Helliwell, M.; Diorazio, L. *Tetrahedron* **2004**, *60*, 4387 – 4397.

[7] (a) Toda, F.; Tanaka, K.; Stein, Z.; Goldberg, I. *J. Org. Chem.* **1994**, *59*, 5748 – 5751. (b) Hu, Q. S.; Vitharana, D.; Pu, L. *Tetrahedron: Asymmetry* **1995**, *6*, 2123 – 2126. (c) Cai, D.; Hughes, D. L.; Verhoeven, T. R.; Reider, P. J. *Tetrahedron Lett.* **1995**, *36*, 7991. (d) Ding, K.; Wang, Y.; Yun, H.; Liu, J.; Wu, Y.; Terada, M.; Okubo, Y.; Mikami, K. *Chem. Eur. J.* **1999**, *5*, 1734 – 1737. (e) Vyskocil, S.; Meca, L.; Tislerova, I.; Cisarova, I.; Polasek, M.; Harutyunyan, S. R.; Belokon, Y. N.; Stead, R. M. J.; Farrugia, L.; Lockhart, S. C.; Mitchell, W. L.; Kocovsky, P. *Chem. Eur. J.* **2002**, *8*, 4633 – 4648.

[8] (a) Sanfilippo, C.; Nicolosi, G.; Delogu, G.; Fabbri, D.; Dettori, M. A. *Tetrahedron: Asymmetry* **2003**, *14*, 3267 – 3270. (b) Matsumoto, T.; Konegawa, T.; Nakamura, T.; Suzuki, K. *Synlett* **2002**, 122 – 124.



Scheme 2: Asymmetric synthesis of biaryls using chiral auxiliaries.

Recently, progress has been made towards the asymmetric synthesis of axially chiral biaryls using chiral auxiliaries.[9] Representative examples include work published by Meyers, Cram, and Colobert. Meyers and Cram have each developed methods for the asymmetric synthesis of biaryls in S_NAr reactions employing aryl Grignard reagents

[9] Broutin, P. E.; Colobert, F. *Org. Lett.* **2003**, *5*, 3281 – 3284 and references therein.

as the nucleophilic component.[10] Meyers has synthesized substituted biaryls using a chiral phenyloxazoline as an auxiliary (eq. **1**, Scheme **2**).[10b] Cram has utilized a chiral alkoxy leaving group, e.g. the *l*-menthoxy group, to obtain asymmetric binaphthyls in moderate to excellent enantioselectivity (eq. **2**, Scheme **2**).[10d] Colobert's work has focused on the diastereoselective Suzuki coupling with β-methoxysulfoxides as chiral auxiliaries on the aryl halide using dppf or PPh_3 as supporting ligands for the palladium catalyst (eq. **3**, Scheme **2**).[11] Although successful, the disadvantages of these novel methods include the use of an auxiliary because of the cost associated with their stoichiometric use and the extra synthetic steps needed for their attachment and removal. In the work of Meyers and Cram, the likelihood of poor functional group compatibility of the Grignard reagents is another drawback.[12]

An asymmetric variant of the Kumada-type cross-coupling reaction has also been reported in the synthesis of axially chiral biaryls.[13] Hayashi was the first to develop successful conditions for this transformation, using (*S*)-(*R*)-PFFOMe as supporting ligand for the nickel catalyst (eq. **4**, Scheme **3**).[14] The advantage of this method is the

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[10] (a) Meyers, A. I.; Lutomski, K. A. *J. Am. Chem. Soc.* **1982**, *104*, 879 – 881. (b) Meyers, A. I.; Himmelsbach, R. J. *J. Am. Chem. Soc.* **1985**, *107*, 682 – 685. (c) Wilson, J. M.; Cram, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 881 – 884. (d) Wilson, J. M.; Cram, D. J. *J. Org. Chem.* **1984**, *49*, 4930 – 4943.

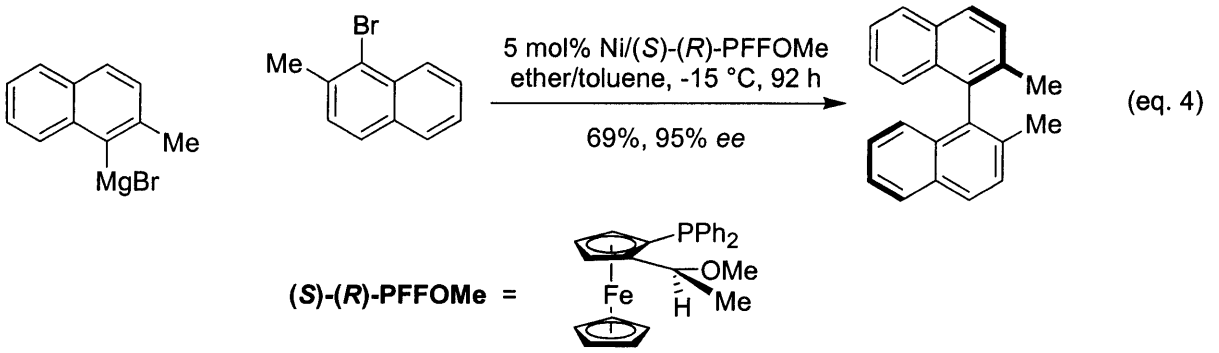
[11] Broutin, P. E.; Colobert, F. *Org. Lett.* **2003**, *5*, 3281 – 3284.

[12] Furstner has developed a method for cross-coupling reactions between alkyl Grignards and aryl chlorides containing reactive functional groups (e.g. esters, ketones) in the presence of an iron catalyst. This is due to the rapidity of the cross-coupling reaction compared to the nucleophilic addition to the ester or ketone. See Furster, A.; Leitner, A.; Mendez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856 – 13863.

[13] (a) Hayashi, T.; Tajika, M.; Tamao, K.; Kumada, M. H. *J. Am. Chem. Soc.* **1976**, *98*, 3718 – 3719. (b) Tamao, K.; Yamamoto, H.; Matsumoto, H.; Miyake, N.; Hayashi, T.; Kumada, M. *Tetrahedron Lett.* **1977**, 1389 – 1392. (c) Tamao, K.; Minato, A.; Miyake, N.; Matsuda, T.; Kiso, Y.; Kumada, M. *Chem. Lett.* **1975**, 133 – 136.

[14] (a) Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8153 – 8156. (b) Hayashi, T.; Hayashizaki, K.; Ito, Y. *Tetrahedron Lett.* **1989**, *30*, 215 – 218. (c) Hayashi, T.; Niizuma, S.; Kamikawa, T.; Suzuki, N.; Uozumi, Y. *J. Am. Chem. Soc.* **1995**, *117*, 9101 – 9102. (d) Kamikawa, T.; Hayashi, T. *Tetrahedron* **1999**, *55*, 3455 – 3466. (e) Shimada, T.; Cho, Y. H.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 13396 – 13397.

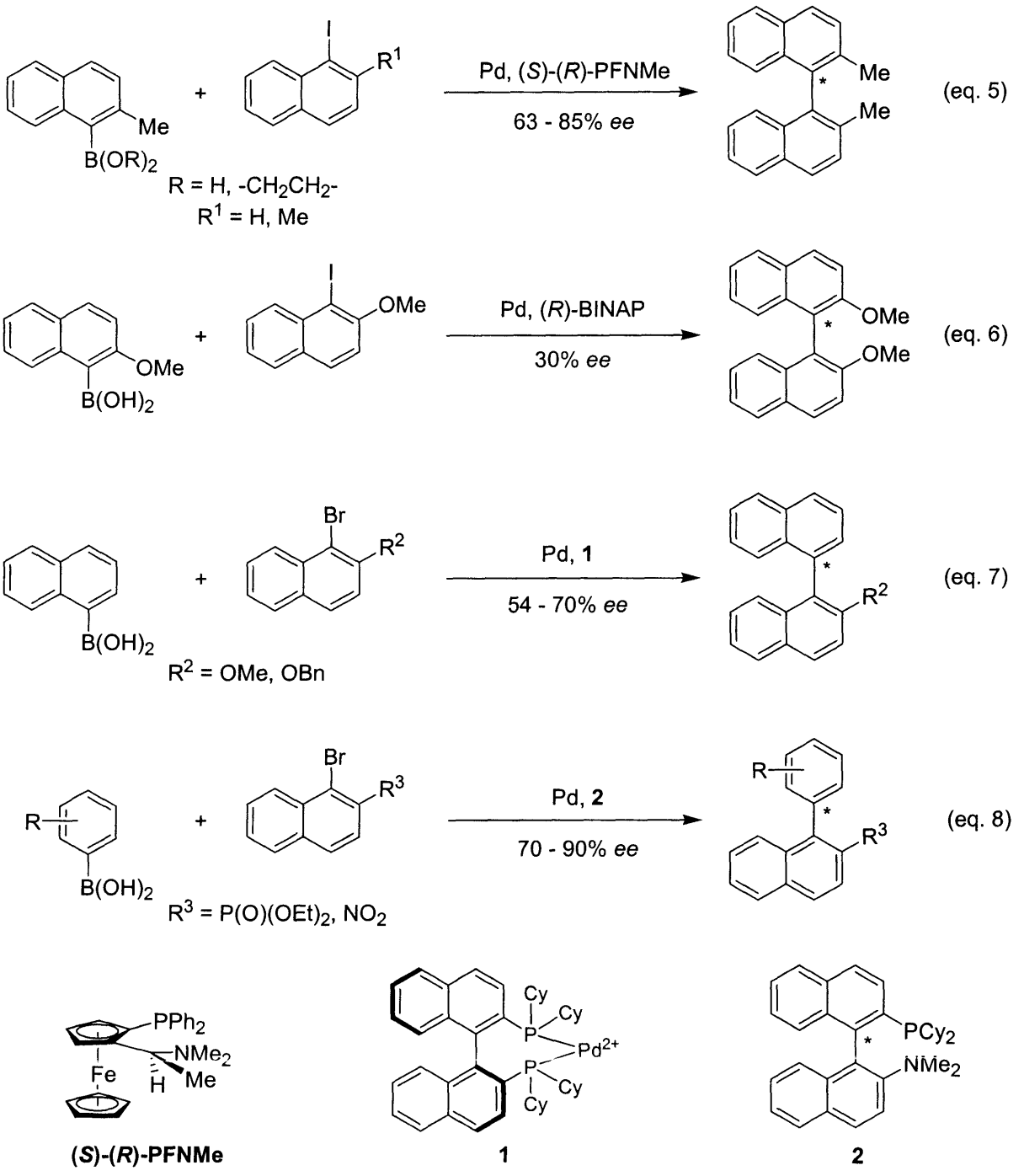
catalytic use of the chiral reagent, which in this case is the ligand. Unfortunately, as in the procedures reported by Meyers and Cram, the use of the reactive aryl magnesium halide species is a potential problem.[12]



Scheme 3: Asymmetric Kumada-type cross coupling of binaphthyls.

Due to the severity of Kumada-type conditions, there have been recent reports of efforts towards asymmetric biaryl syntheses using the Suzuki-Miyaura reaction, which employs air-stable and functional group compatible boronic acids as the nucleophilic component under milder reaction conditions.[15] Cammidge, Colobert, and Mikami have all developed methods for the synthesis of chiral binaphthalenes using ferrocene ligand (*S*)-(*R*)-PFNMe, (*R*)-BINAP, or a cationic Pd/dicyclohexyl BINAP complex **1**, respectiveiy, under varying reaction conditions in moderate to good enantioselectivities (eq. **5** – **7**, Scheme **4**).[16] Buchwald has developed a binaphthyl ligand, **2**, which has been found to be effective in the asymmetric Suzuki-Miyaura reaction between various phenyl and naphthyl boronic acids with electron-poor aryl halides containing an *ortho*

[15] Suzuki, A. In Metal-*catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Ed.; Wiley – VCH: Weinheim, 1998; p 49.
[16] (a) Cammidge, A. N.; Crepy, K. V. L. *Tetrahedron* **2004**, *60*, 4377 – 4386. (b) Cammidge, A. N.; Crepy, K. V. L. *Chem. Commun.* **2000**, *18*, 1723 – 1724. (c) Castanet, A.S.; Colobert, F.; Broutin, P.E.; Obringer, M. *Tetrahedron: Asymmetry* **2002**, *13*, 659 – 665. (d) Mikami, K.; Miyamoto, T.; Hatano, M. *Chem. Commun.* **2004**, *18*, 2082 – 2083.

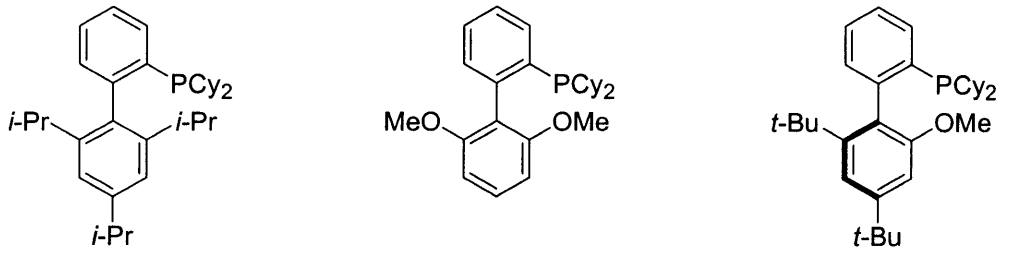


(*S*)-(*R*)-PFNMe **1** **2**

Scheme 4: Previous examples of the asymmetric Suzuki-Miyaura cross-coupling reaction

phosphonate ester or nitro functional group (eq. **8**, Scheme **4**).[17] Unfortunately, all of these systems suffer from severe limitations in substrate scope. Currently, there is no universal ligand or catalyst system effective for the asymmetric Suzuki-Miyaura cross-coupling reaction of a wide variety of substrates; thus, we began to pursue the development of an asymmetric ligand which could improve the enantioselectivity and substrate scope of this transformation.

Rational Design of Asymmetric Phosphine Ligand, **5**



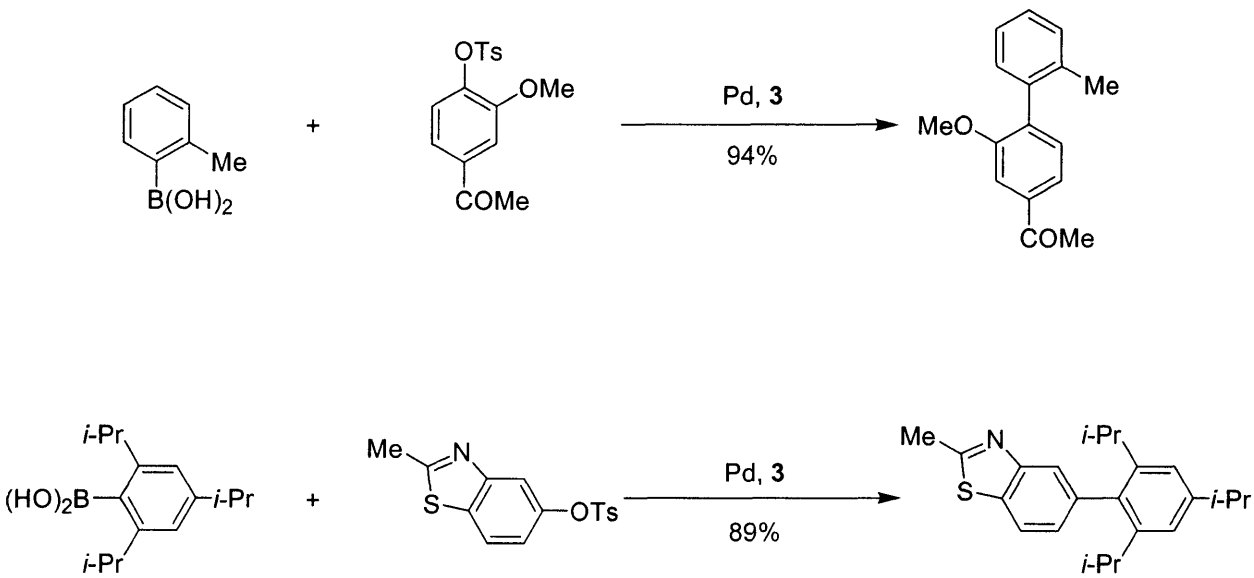
3 **4** **5**

Scheme 5: Dicyclohexylbiphenyl phosphine ligands developed in the Buchwald laboratory.

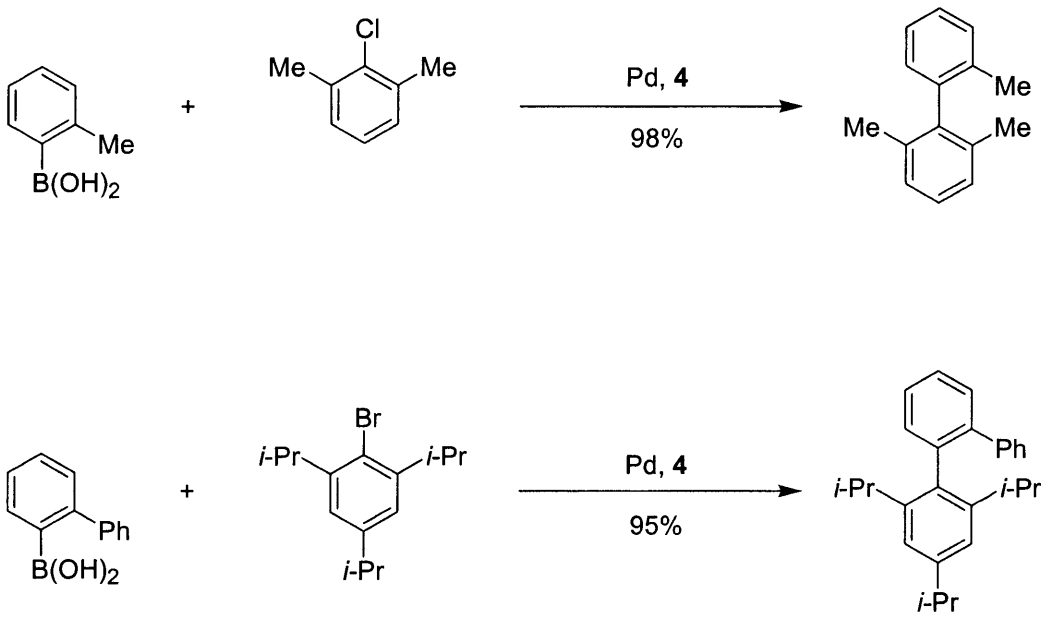
In recent years, the Buchwald group has introduced a variety of dialkylbiphenylphosphine ligands that are excellent for promoting Pd-catalyzed cross-coupling reactions.[18] In order to design a ligand suitable for the asymmetric Suzuki coupling, we surveyed those ligands shown to be effective in the non-asymmetric Suzuki-Miyaura reaction of hindered substrates (Scheme **5**). Ligand **3** is successful in the Suzuki-Miyaura cross-couplings of moderately to extremely hindered boronic acids

[17] Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12051 – 12052.
[18] (a) Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818 – 11819. (b) Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2004**, *16*, 2649 – 2652. (c) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 1871 – 1876. (d) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685 – 4696.

with moderately hindered aryl tosylates and select heteroaryl tosylates (Scheme **6**).[18a] In addition, ligand **4** has been used for the Suzuki-Miyaura cross coupling reactions of the most hindered substrates to date in excellent yields with minimal catalyst loadings (Scheme **7**).[18c, 18d]

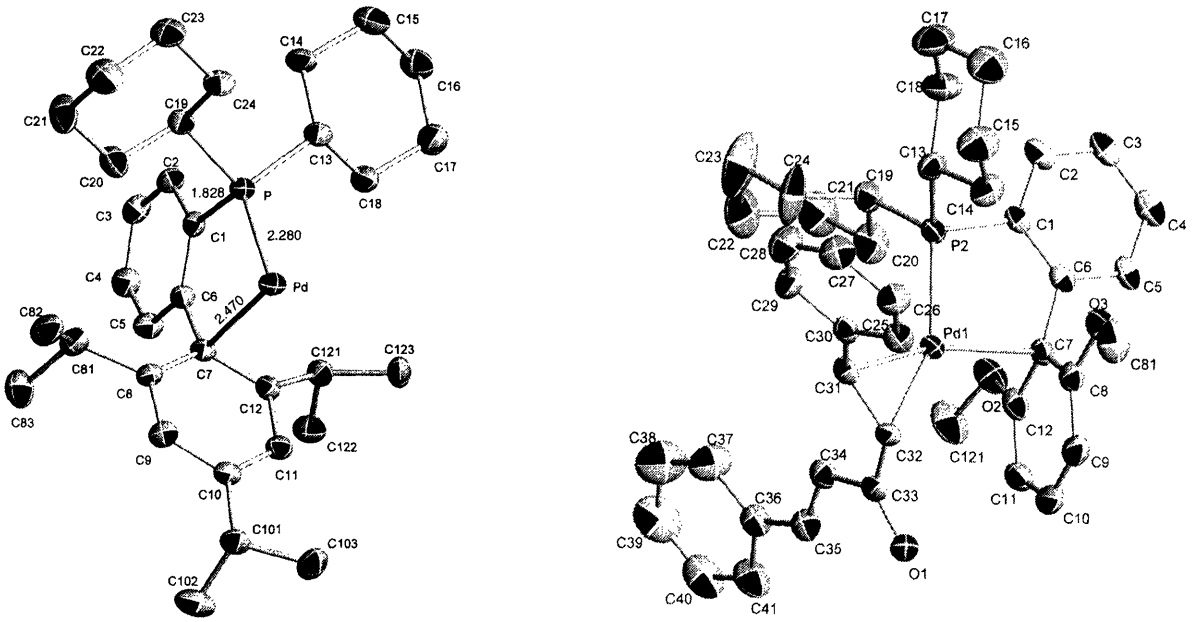


Scheme 6: Examples of reactions using ligand 3.



Scheme 7: Examples of reactions using ligand 4.

The rationale behind the successes of **3** and **4** has not yet been fully elucidated. Possible explanations focus on the bulky nature of the biaryl phosphine ligands. Due to their large size, it is believed that the equilibrium between $L_2Pd \leftrightarrows LPd$ strongly favors the mono-ligated complex. This results in a more reactive 12-electron palladium species, facilitating oxidative addition of the aryl halide component to the palladium center. In addition, there exists an η^1 interaction between the palladium and the ipso carbon of the non-phosphine containing ring for both ligands **3** and **4** (Scheme **8**). This interaction is believed to stabilize the 12-electron mono-ligated complex, as the LPd becomes a pseudo 14-electron complex with this interaction, thereby impeding catalyst decomposition.



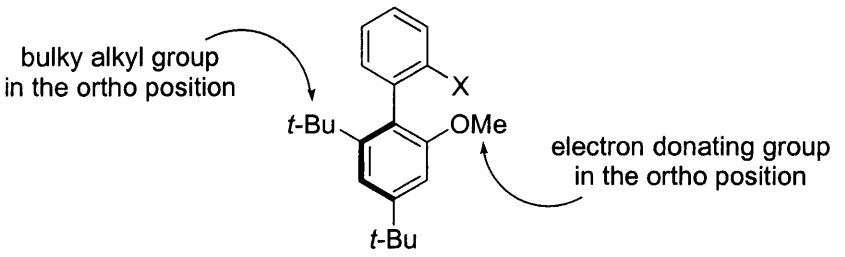
(a) (b)

Scheme 8: (a) ORTEP diagram of 3·Pd(dba) with hydrogens and dba removed for clarity. Thermal ellipsoids are at 30% probability.[19] (b) ORTEP diagram of 4·Pd(dba) with hydrogens removed for clarity. Thermal ellipsoids are at 30% probability.[20]

Thus, ligand **5** was designed with the structures of ligands **3** and **4** in mind. As evident from structure **6**, the asymmetric biaryl backbone of ligand **5** has a bulky *tert*-butyl group in the *ortho* position, similar to ligand **3**, which has the bulky isopropyl groups on the two *ortho* positions of the non-phosphine containing ring (Scheme **9**). The other *ortho* position on ligand backbone **6** has an electron donating methoxy group. This structure has obvious similarities to ligand **4**; it is also akin to ligand **2**, which has the dimethylamino group in the *ortho* position. In addition, the objective was to develop resolution conditions for the biaryl halide (X = Br, I) rather than the biaryl phosphine (X = PR_2), so that various enantiopure dialkylphosphine and non-phosphine ligands (e.g. X =

[19] Barder, T. E.; Buchwald, S. L. unpublished results.
[20] (a) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 1871 – 1876. (b) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685 – 4696.

BR_2) could be synthesized without the need to develop separate resolution conditions for each ligand system.



6

Scheme 9: The rationalization behind the design of the dialkylbiphenyl phosphine ligand.

B. Results and Discussion

I. Synthesis and resolution of the asymmetric biaryl-based phosphine ligand.

The asymmetric biaryl backbone of the phosphine ligand was synthesized starting from 3,5-di-*tert*-butylphenol, which was mono-brominated selectively at the 2-position to afford **7** (Figure **1**).[21] The brominated phenol was methylated to form the aryl methyl ether **8**. The Grignard reagent derived from **8** reacts readily with benzyne, generated by the reaction of 1-bromo-2-chlorobenzene with magnesium, to provide the biaryl magnesium halide. This was subsequently quenched with either

[21] Zhang, H. C.; Kwong, F. Y.; Tian, Y.; Chan, K. S. *J. Org. Chem.* **1998**, *63*, 6886 – 6890.

bromine or iodine to yield **6a** and **6b**.[22] Deprotection of the methyl group with boron tribromide furnished the desired biaryl alcohols **9a** and **9b**.

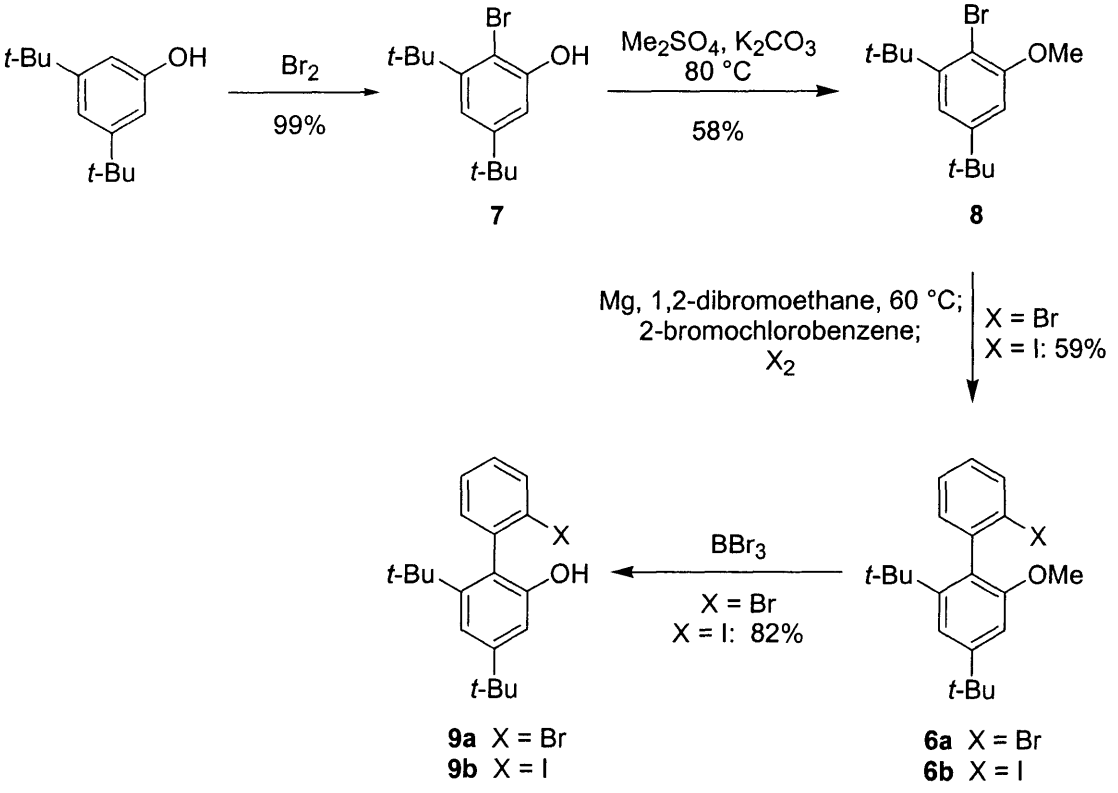


Figure 1: Synthesis of racemic biaryl backbone 9.

Next, the configurational stability of **9a** (X = Br) and **9b** (X = I) were determined. After separation of the two enantiomers of **9a** using semi-prep HPLC followed by immediate re-injection of one enantiomer into the HPLC, it was discovered that **9a** rotates freely around the aryl-aryl single bond,s thus suggesting that the enantiomers of **9a** are not configurationally stable at room temperature (Figure **2**).

[22] Tomori, H.; Fox, J. M.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 5334 – 5341.

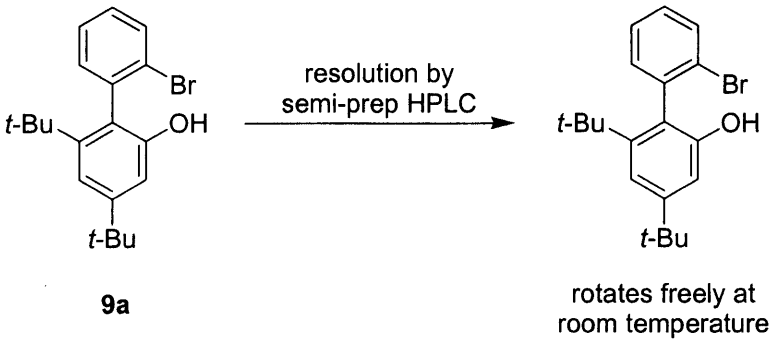


Figure 2: Configurational stability of 9a.

On the other hand, when **9b** was subjected to the same conditions, it was determined that the two enantiomers of **9b**, **(*R*)-9b** and **(*S*)-9b**, are stable atropisomers at room temperature (Figure **3**). In order to test the feasibility of using enantiopure **6b** as a precursor to other enantiopure analogues without racemization of axial chirality during lithium-halogen exchange at the iodo-position, **(*R*)-9b** was methylated to obtain **(*R*)-6b**, which was treated with *n*-butyllithium and iodine at –78 °C to re-obtain **(*R*)-6b**. We were pleased to discover that there was no racemization during this transformation. Thus, it was decided to move forward with **9b** as the biaryl halide precursor.

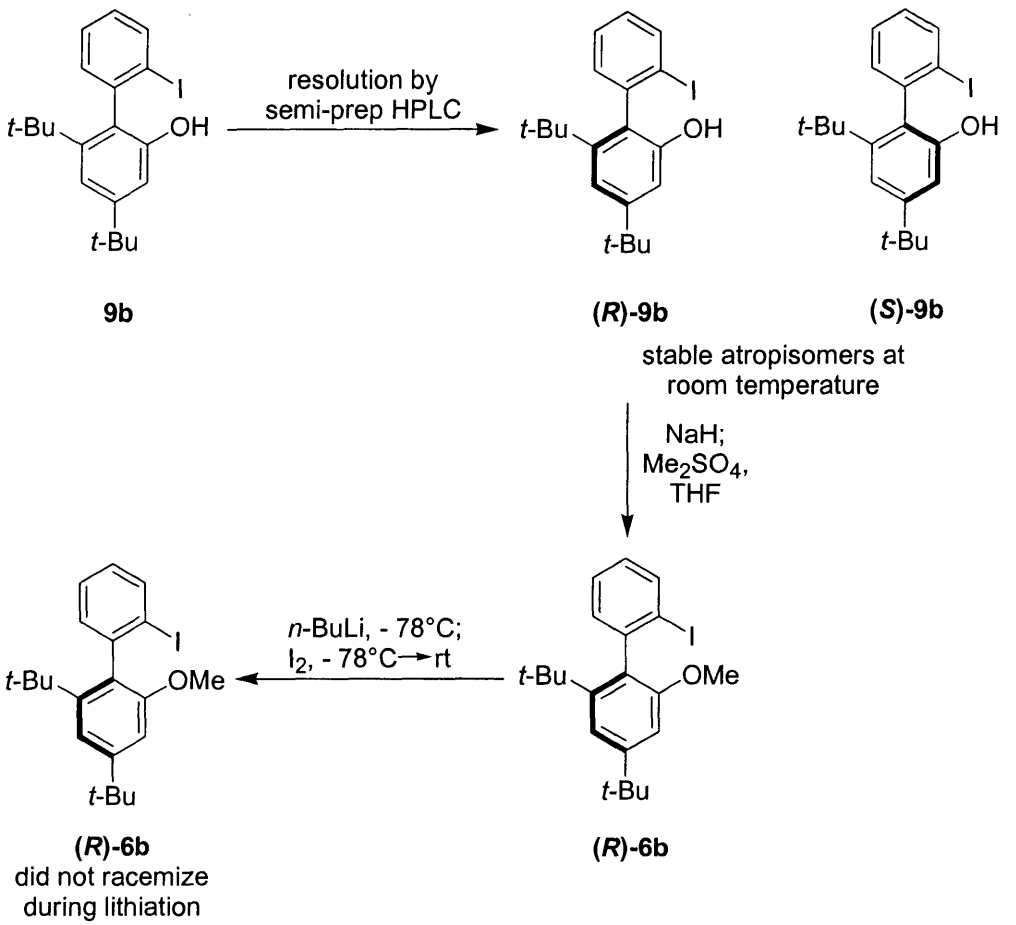
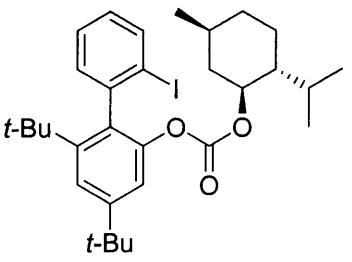
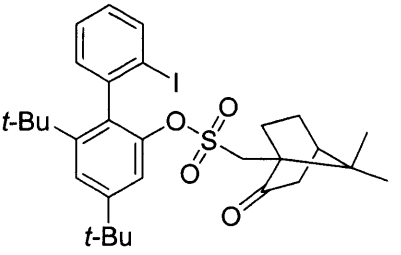


Figure 3: Configurational stability of 9b.

The development of larger-scale resolution conditions for **9b** proved to be challenging. Various resolution conditions were examined, including inclusion complex formation with (8*S*,9*R*)-(–)-N-benzylcinchonidinium chloride, enzymatic resolution using PS-C lipase, and diastereomeric ester formation using (1*S*)-(+)-menthyl chloroformate (**10**, Figure **4**). Unfortunately, these attempts at resolution were not successful.



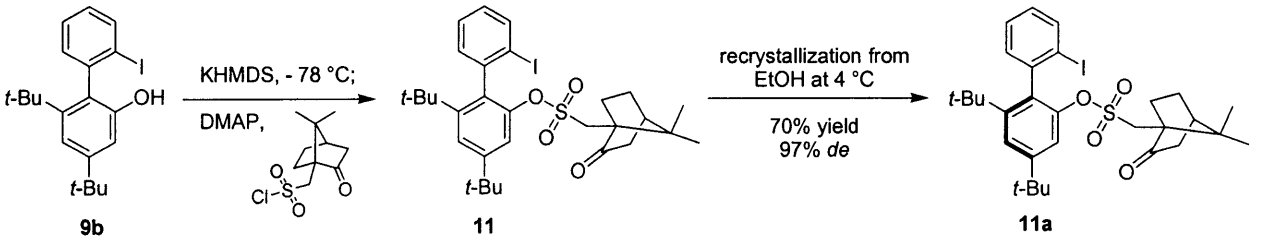
10



11

Figure 4: Diastereomeric esters.

Fortunately, the diastereomers of **11**, which were synthesized from the reaction of deprotonated **9b** with (1*S*)-(+)-10-camphorsulfonyl chloride in the presence of 4-dimethylaminopyridine as catalyst (Figure **5**), were found to be separable by crystallization. Diastereomer **11a** was selectively recrystallized from ethanol at 4 °C in 70% yield to give product with 97% diastereomeric excess.



9b **11** **11a**

Figure 5: Resolution of 9b.

With diastereomer **11a** in hand, steps were taken to complete the synthesis of the asymmetric phosphine ligand (Figure **6**). The camphorsulfonate ester group was cleaved under basic conditions using potassium hydroxide to obtain **(*R*)-9b** without loss of optical activity. The crystal structure of this compound, **(*R*)-9b**, was determined in order to establish the absolute configuration (Figure **7**). Alcohol **(*R*)-**

9b was methylated to form the biaryl methyl ether **(*R*)-6b**, then treated with *n*-butyllithium and dicyclohexylchlorophosphine to form **(*R*)-5** in 48% yield over the last two steps without loss of enantiopurity, thereby completing the synthesis of the phosphine ligand in enantiomerically pure form.

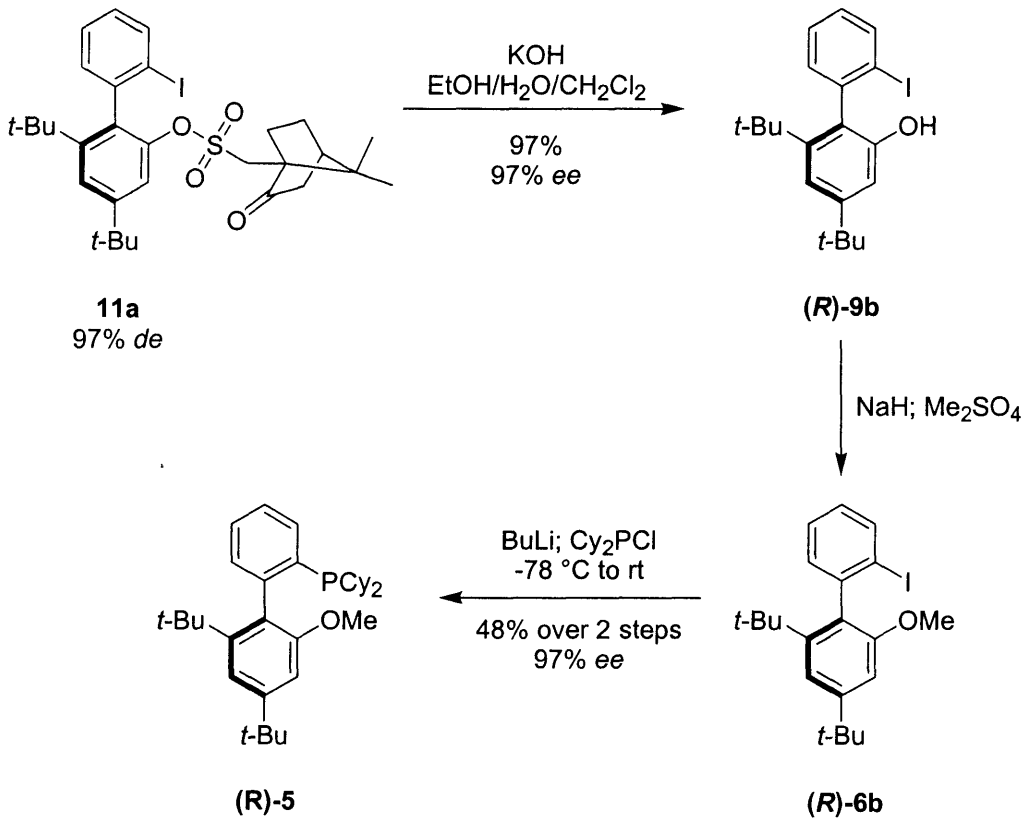


Figure 6: Synthesis of ligand (*R*)-5.

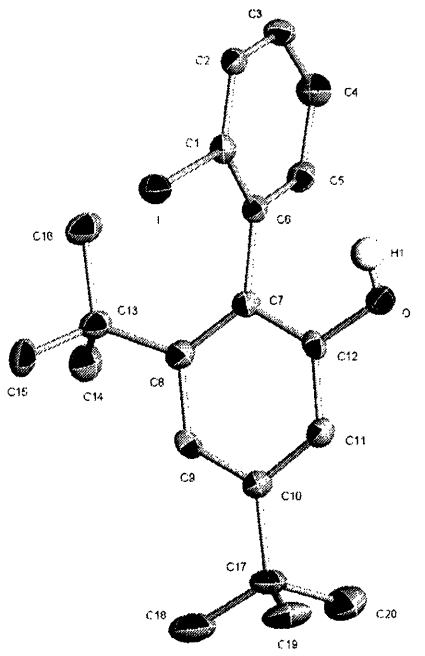


Figure 7: ORTEP diagram of (*R*)-9b. The hydrogens, with the exception of H1, have been removed for clarity. Thermal ellipsoids are at 30% probability.[23]

II. Applications of the phosphine ligand 5 to the asymmetric Suzuki-Miyaura reaction.

With the ligand in hand, the efficacy of **(*R*)-5** on the asymmetric Suzuki-Miyaura cross-coupling reaction was explored. When selecting substrates for the synthesis of axially chiral biaryls via the Suzuki-Miyaura reaction, a few factors must be taken into consideration. In order to have an axially chiral biaryl that is configurationally stable at room temperature, the biaryl must have at least three *ortho* substituents of sufficient bulk. On the other hand, substituents of extreme bulk hamper the cross-coupling itself, leading to poor product yields. Thus, the substrates 1-bromo-2-methoxynaphthalene and 2-tolylboronic acid were chosen as

[23] I thank Timothy E. Barder for solving the crystal structure of **(*R*)-9b**.

the model substrates with which to optimize conditions due to their moderately hindered nature (Figure **8**).

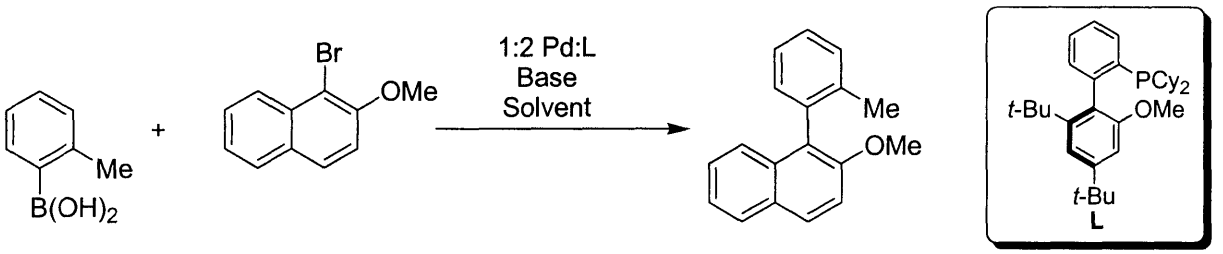


Figure 8: Model reaction for optimization.

The standard Suzuki-Miyaura conditions for ligand **3** were first attempted, using K_3PO_4 as base and toluene as solvent at varying temperatures with $Pd_2(dba)_3$ as the palladium source. It was found that lower reaction temperatures led to increased enantioselectivity. Unfortunately at a temperature range of 30 – 40 °C, the yield was very low (Entry **1**, Chart **1**). In order to increase the reaction rate, fluoride sources were used in hopes that the fluoride anion would create a more reactive –ate complex of the boronic acid for transmetallation due to fluoride's high affinity for boron, thereby increasing the rate and yield of the reaction.[24] The use of 3 equivalents of potassium fluoride increased the yield of the reaction to 99% with 27% *ee* (Entry **2**, Chart **1**).

Next, the effect of solvent on the reaction was studied. The use of solvents THF and dioxane gave similar results as toluene (Entries **3** & **4**, Chart **1**); DMF, on the other hand, gave a noticeably higher *ee* with 45%, albeit with lower yields (Entry **3**, Chart **1**). In an effort to optimize both the yield and enantioselectivity, the use of

[24] Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095 – 6097.

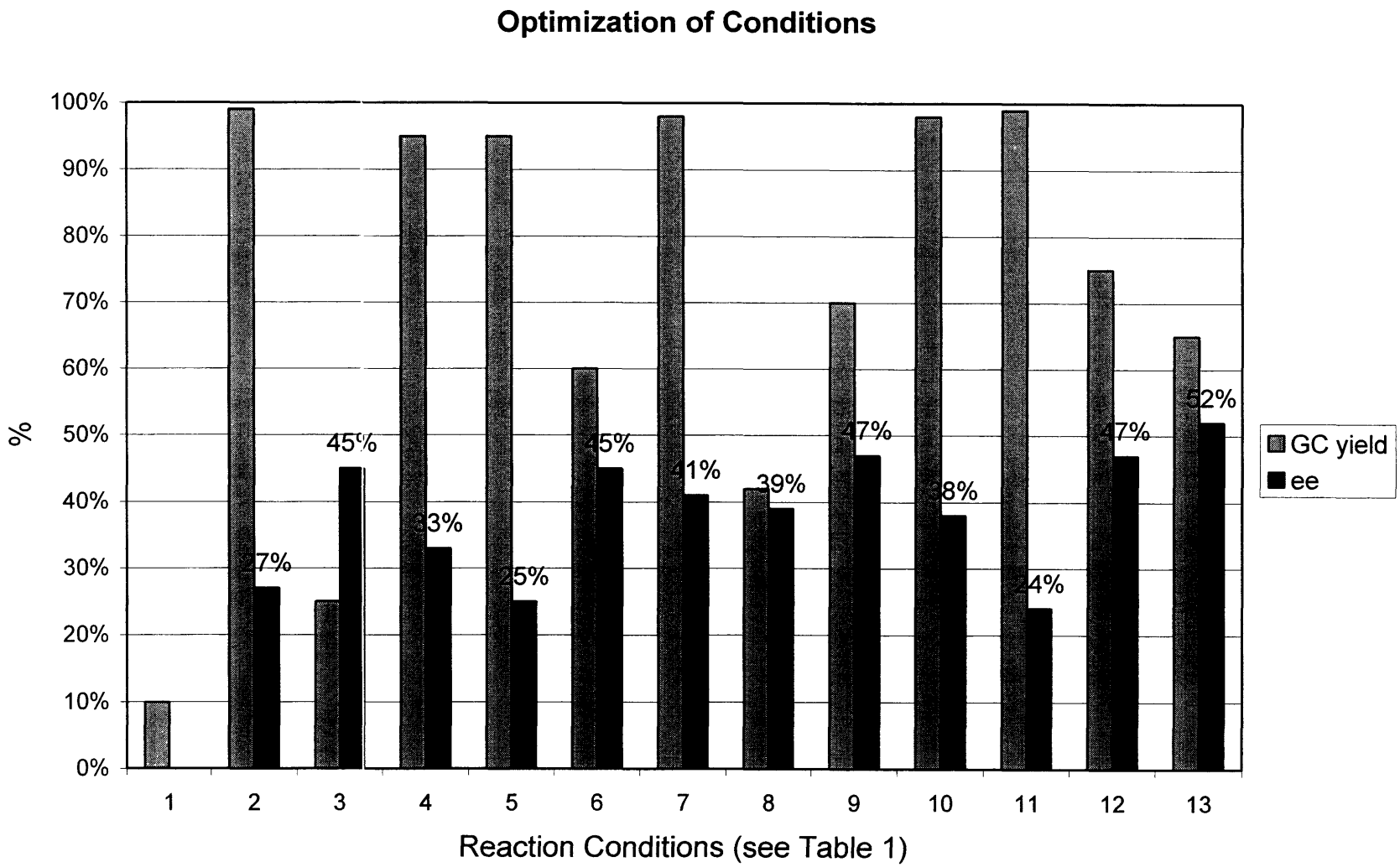


Chart 1: Optimization of Conditions

i

Table 1: Reaction conditions.[a]

Entry	Temperature	Pd Source	Base	Solvent
1	40 °C	$Pd_2(dba)_3$	K_3PO_4	toluene
2	40 °C	$Pd_2(dba)_3$	KF	toluene
3	40 °C	$Pd_2(dba)_3$	KF	DMF
4	40 °C	$Pd_2(dba)_3$	KF	THF
5	40 °C	$Pd_2(dba)_3$	KF	dioxane
6	30 °C	$Pd_2(dba)_3$	KF	DMF/THF[b]
7	30 °C	$Pd_2(dba)_3$	KF	DMF/toluene[b]
8	30 °C	$Pd_2(dba)_3$	KF	DMF/dioxane[b]
9	30 °C	$Pd(OAc)_2$	KF	DMF
10	30 °C	$Pd(OAc)_2$	KF	DMF/toluene
11	30 °C	$Pd(OAc)_2$	KF	dimethoxyethane
12	30 °C	$Pd(OAc)_2$	K_3PO_4	DMF
13	30 °C	$Pd(OAc)_2$	$K_3PO_4 \cdot H_2O$	DMF

[a] Reaction conditions: 1 equiv of 1-bromo-2-methoxynaphthalene, 1.5 equiv of 2-tolylboronic acid, 3 equiv of base, solvent (2 mL/mmol halide), 5 mol % Pd, ligand **(*R*)-5**, L:Pd = 2:1. [b] The two solvents were used in a 1:1 ratio.

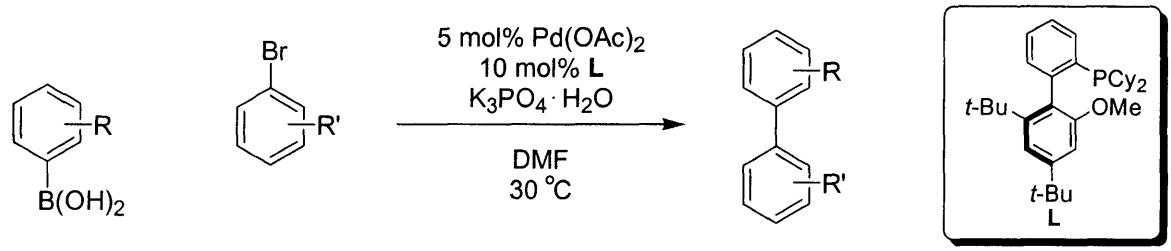
various mixtures of the aforementioned solvents were attempted (Entries **6 – 8**, Chart **1**). Using DMF in combination with other solvents did not increase the enantioselectivity compared to that obtained with pure DMF as solvent.

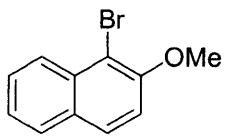
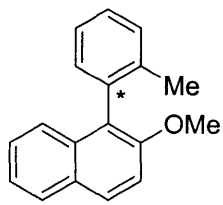
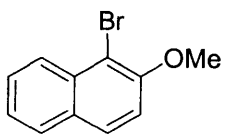
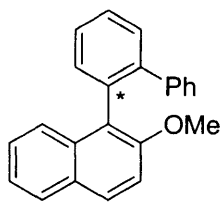
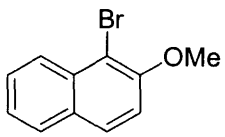
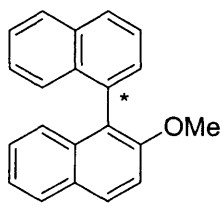
Next, the effect of $Pd(OAc)_2$ on the reaction was investigated. With $Pd(OAc)_2$ as the palladium source and DMF as solvent, the yield increased dramatically from 25% to almost 70% (Entry **9**, Chart **1**). Unfortunately, the *ee* remained unchanged with the alteration of palladium source (Entry **9**, Chart **1**) as well as with change of base to anhydrous K_3PO_4 (Entry **12**, Chart **1**).

At this time, we discovered that residual water in the DMF was necessary for the Suzuki-Miyaura reaction to take place. Thus, a hydrated base was used to provide 3 equivalents of water for reactions run with anhydrous DMF. The use of potassium phosphate monohydrate led to a slight increase in *ee*; additional Suzuki-Miyaura reactions were conducted using this method (Entry **13**, Chart **1**).

With the optimized conditions in hand, the method was extended to a few different substrates (Table **2**). Unfortunately, ligand **(*R*)-5** under these reaction conditions was not as effective in the asymmetric Suzuki reactions of the other substrates examined. The reactions of 1-bromo-2-methoxynaphthalene with either 2-biphenylboronic acid (Entry **2**, Table **2**) or 1-naphthylboronic acid (Entry **3**, Table **2**) had lower enantioselectivity than the reaction with 2-tolylboronic acid. In addition, ligand **(*R*)-5** was unsuccessful in the attempts to couple boronic acids with electron-poor aryl bromides 2-bromo-3-nitrotoluene and diethyl 1-bromo-2-naphthylphosphonate (Table **3**).

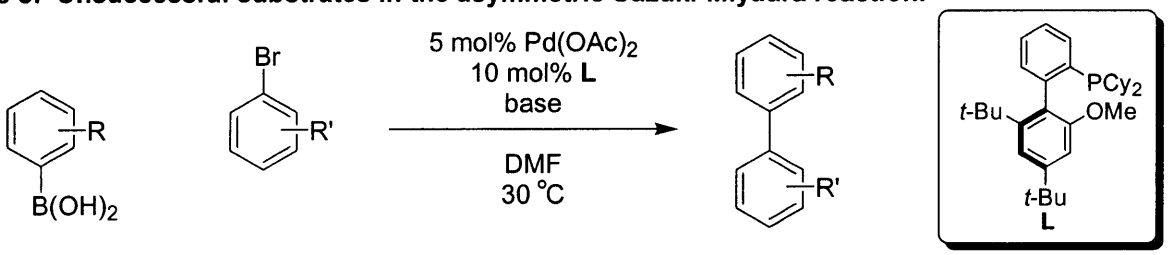
Table 2: Extension of method to different substrates.[a]

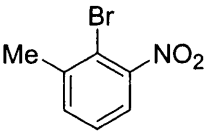
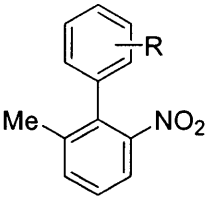
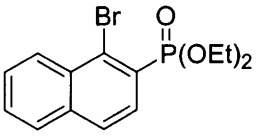
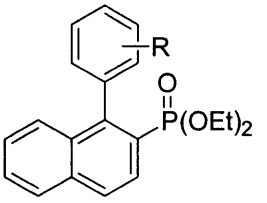


Entry	Aryl Bromide	Product	Yield (%)[b]	*ee* (%)[c]
1			61%	52%
2			33%	16%
3			79%	32%

[a] Reaction conditions: 1 equiv of 1-bromo-2-methoxynaphthalene, 1.5 equiv of boronic acid, 3 equiv of K_3PO_4 H_2O, DMF(2 mL/mmol halide), 5 mol % Pd, ligand ***(R)*-5**, L:Pd = 2:1. [b] Isolated yield. [c] Determined by HPLC analysis.

Table 3: Unsuccessful substrates in the asymmetric Suzuki-Miyaura reaction.



Entry	Aryl Bromide	Desired Product[b, c]
1		
2		

[a] Reaction conditions: 1 equiv of 1-bromo-2-methoxynaphthalene, 1.5 equiv of boronic acid, 3 equiv of base (KF or $K_3PO_4 \cdot H_2O$), DMF(2 mL/mmol halide), 5 mol % Pd, ligand **(*R*)-5**, L:Pd = 2:1. [b] R = Me, Ph. [c] The only products observed were the aryl bromide, dehalogenated aryl bromide, protodeboronated boronic acid, and homocoupled boronic acid in varying ratios.

C. Conclusions

A new asymmetric biaryl phosphine ligand with axial chirality, **(*R*)-5**, was designed, synthesized, and resolved. The efficacy of ligand **(*R*)-5** on the asymmetric Suzuki-Miyaura cross-coupling reaction for the synthesis of axially chiral biphenyls and

phenylnaphthyls was investigated. Modest enantioselectivities of the cross-coupled phenylnaphthyl products were observed; these results show promise for success in the Suzuki-Miyaura coupling of electron-neutral aryl boronic acids with electron-rich aryl halides. Future efforts will be directed at increasing the enantioselectivity and substrate scope of this transformation by fine-tuning the structure of the phosphine ligand.

D. Experimental

I. General considerations.

All reactions were carried out in oven-dried or flame-dried glassware cooled under vacuum. Flash column chromatography was performed on EMD silica gel (230 - 400 mesh). Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. IR spectra were recorded on an Perkin Elmer 2000 FT-IR instrument using KBr plates. Nuclear Magnetic Resonance spectra were recorded at ambient temperature on a 400 MHz Bruker, 300 MHz Varian, or 500 MHz Varian instruments. All ^{1}H NMR experiments are reported in δ units, parts per million (ppm) downfield from tetramethylsilane (internal standard) and were measured relative to the signals for residual chloroform (7.26 ppm) in the deuterated solvent. All ^{13}C NMR spectra are reported in ppm relative to deuterochloroform (77.23 ppm) and all were obtained with ^{1}H decoupling. All ^{31}P NMR spectra are reported in ppm relative to H_3PO_4 (0 ppm). GC analyses were performed on Hewlett Packard 6890 gas chromatography

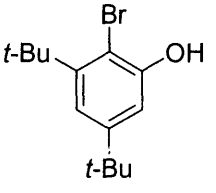
instruments with an FID detector using 25 m x 0.20 mm capillary column with cross-linked methyl siloxane as a stationary phase. Mass spectra (GC/MS) were recorded on a Hewlett Packard model G1800B. Uncorrected melting points were determined using a Mel-Temp capillary melting point apparatus. Anhydrous THF, diethyl ether, dichloromethane, and toluene were purchased from J. T. Baker in CYCLE-TAINER® solvent delivery kegs and vigorously purged with argon for two h, then further purified by passing them under argon pressure through two packed columns on neutral alumina (for THF) or through neutral alumina and copper (II) oxide (for toluene and CH_2Cl_2). All reagents were commercially available and ordered from Aldrich, Strem, Alfa Aesar, Acros, or Lancaster, and used without further purification. The PS-C lipase was a gift from Amano Enzymes. All reagents were weighed and handled in air. The yields given refer to isolated yields (unless otherwise noted) of compounds estimated to be ≥ 95% pure as determined by ^1H NMR and GC analysis and/or combustion analysis. The procedures described in this section are representative, and thus the yields may differ from those shown in Figues 1 – 6.

II. Representative procedure.

Representative procedure for the asymmetric Suzuki-Miyaura cross-coupling of hindered aryl boronic acids with hindered aryl bromides using asymmetric phosphine ligand (*R*)-5: A screw-cap test tube containing a magnetic stirbar was allowed to cool to room temperature under vacuum, then backfilled with argon. The tube was charged with the boronic acid (0.375 m mol), aryl bromide (0.25 mmol),

palladium source (5 mol%), ligand **(*R*)-5** (10 mol%), and base (0.75 mmol). The tube was capped with a rubber septum, then evacuated and backfilled with argon three times. Anhydrous DMF (0.5 mL) and *n*-dodecane as standard (if employed) were added sequentially via syringe through the septum. The septum was replaced with a Teflon-coated screwcap, and the test tube was sealed. The reaction mixture was heated in a preheated oil bath for 13 h. The reaction mixture was allowed to cool to room temperature, diluted with diethyl ether (10 mL) and washed twice with saturated sodium bicarbonate solution (10 mL x 2) and once with brine (10 mL). The organic layer was dried with anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude material obtained was purified by flash chromatography to yield the biaryl product. Spectral data (^{1}H and ^{13}C NMR, IR spectra) were obtained.

III. Individual procedures.

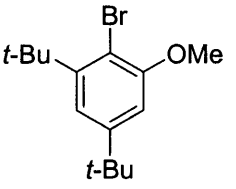


7

2-bromo-3,5-di-*tert*-butylphenol (**7**).[25] An oven-dried 100 mL round-bottomed flask equipped with a stirbar and a rubber septum was charged with 3,5-di-*tert*-butylphenol (1 equiv, 39.2 mmol, 8.08 g) and carbon disulfide (16 mL). The reaction mixture was cooled to 0 °C. Neat bromine (1 equiv, 39.2 mmol, 2 mL) was added

[25] Zhang, H. C.; Kwong, F. Y.; Tian, Y.; Chan, K. S. *J. Org. Chem.* **1998**, *63*, 6886 – 6890.

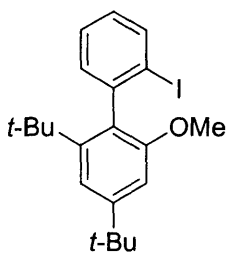
via syringe over 20 min. The mixture was warmed to room temperature, then stirred for three h. It was quenched with aqueous $Na_2S_2O_3$ (10 min) and stirred for 45 min. The layers were separated and the aqueous layer was extracted with dichloromethane (25 mL x 2). The combined organics were washed with brine (75 mL), dried with magnesium sulfate, and concentrated *in vacuo* to afford a yellow oil which solidified upon standing to yield 10.86 g, 97% of the title compound which was used without further purification. Mp: 43 – 46 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.04 (d, J = 2.5 Hz, 1 H), 6.97 (d, J = 2.5 Hz, 1 H), 5.92 (s, 1 H), 1.51 (s, 9 H), 1.29 (s, 9H) ppm. The spectra were in agreement with those described in the literature.



8

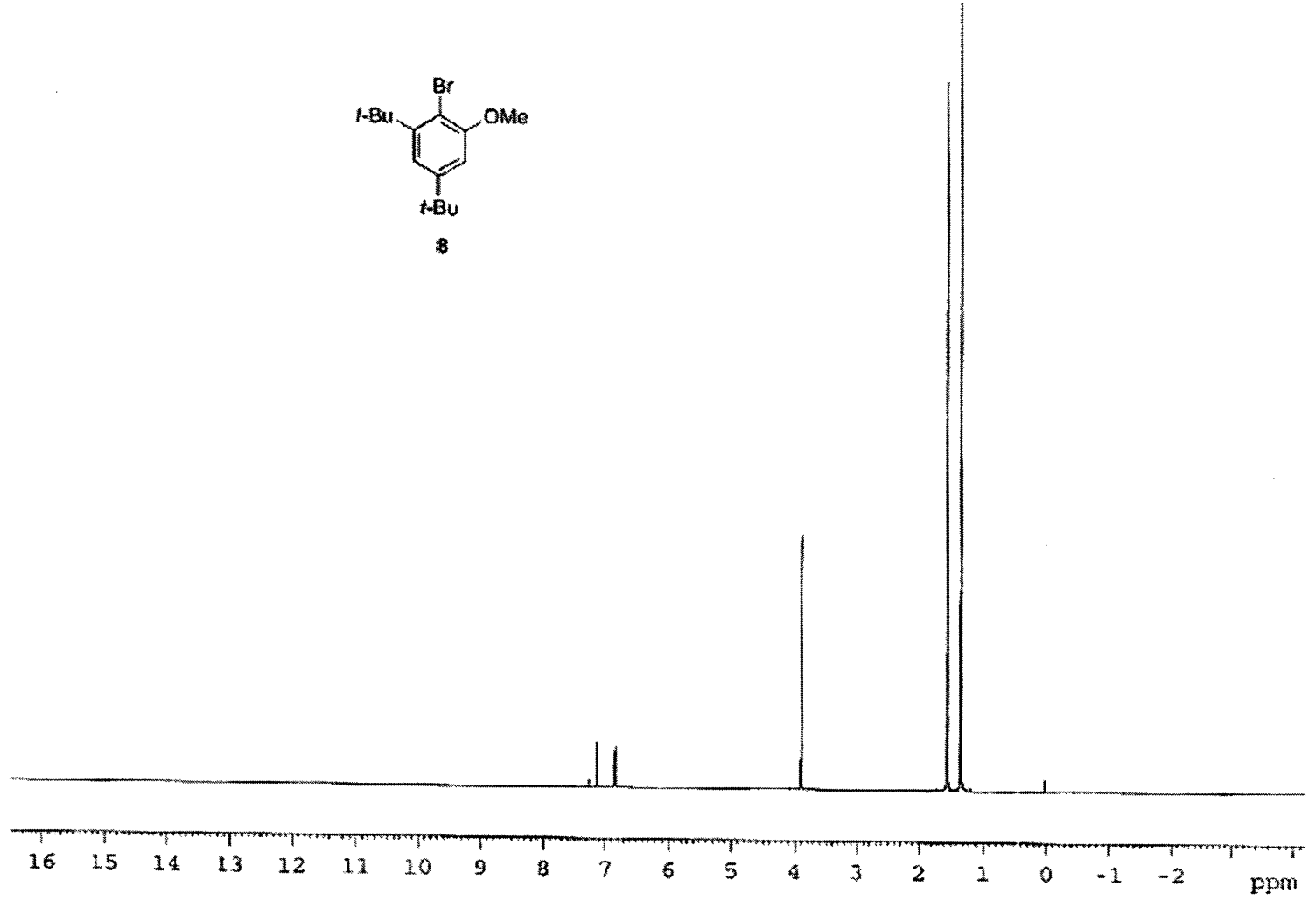
2,4-di-*tert*-butyl-6-methoxy-bromobenzene (**8**). An oven-dried 100 mL round-bottomed flask equipped with a magnetic stirbar, septum, and reflux condenser was charged with **7** (1 equiv, 16 mmol, 4.58 g), K_2CO_3 (1.3 equiv, 26 mmol, 3.59 g), dimethyl sulfate (1.2 equiv, 24 mmol, 2.24 mL), and ethyl acetate (30 mL). The mixture was heated to reflux and stirred at 80 °C for 5 h. After cooling to room temperature, the reaction mixture was poured into water and extracted with ethyl acetate (50 mL x 3). The combined organic extracts were washed with brine (150 mL), dried with magnesium sulfate, filtered, and concentrated *in vacuo* to obtain a pale yellow oil. Compound **8** was crystallized from ethanol at 4 °C to give 3.83 g, 80% of a white solid. Mp: 48 – 50 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.14 (d, J =

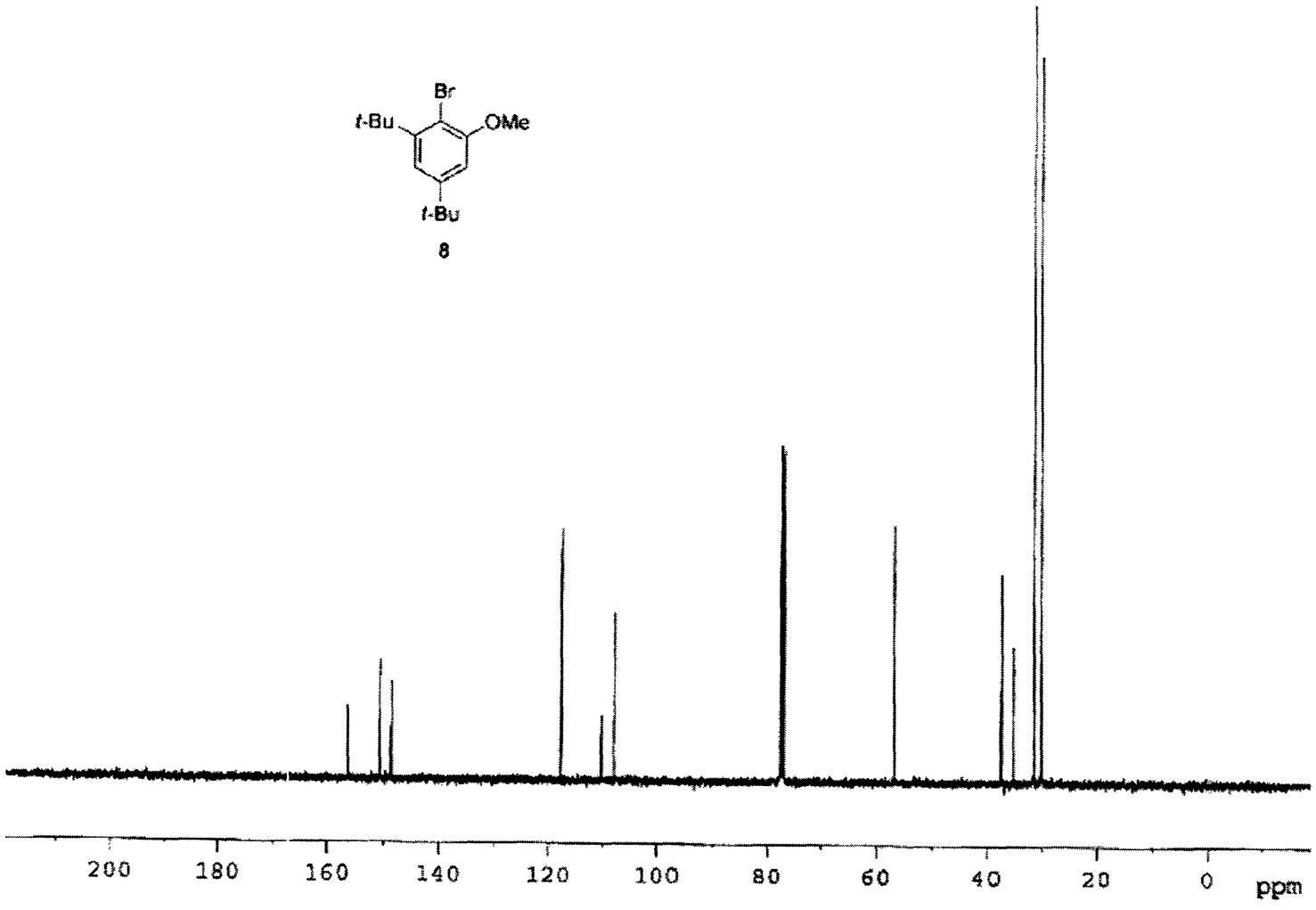
2.2 Hz, 1H), 6.85 (d, J = 2.1 Hz, 1H), 3.91 (s, 3H), 1.56 (s, 9H), 1.34 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.3, 150.8, 148.8, 117.8, 110.3, 107.9, 56.8, 37.6, 35.3, 31.5, 30.2 ppm. IR (CCl_4, cm^{-1}): 3003, 2964, 2871, 1589, 1567, 1465, 1430, 1404, 1363, 1303, 1273, 1240, 1190, 1144, 1069, 1022, 931, 866, 847, 655, 586. A satisfactory elemental analysis was not obtained for this compound. The ^1H and ^{13}C NMR spectra follow.



6b

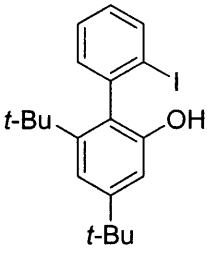
2-iodo-2'-methoxy-4',6'-di-*tert*-butylbiphenyl (**6b**). A flame-dried 250 mL three-necked flask was charged with magnesium turnings (2.3 equiv, 48.72 mmol, 1.184 g) and THF (25 mL). A solution of **8** (1.1 equiv, 23.2 mmol, 6.97 g) and THF (25 mL) was slowly added via syringe. The mixture was heated to reflux, and 1,2-dibromoethane (0.2 equiv, 4.24 mmol, 0.37 mL) was added dropwise via syringe over 5 min. The solution was refluxed at 60 °C for two h. 2-bromochlorobenzene (1 equiv, 21.2 mmol, 2.48 mL) was added dropwise over 10 min, and the resulting mixture was refluxed for two h and subsequently cooled to room temperature. A solution of iodine (1.2 equiv, 25.4 mmol, 6.45 g) and THF (30 mL) was added dropwise via syringe, and the mixture was stirred at ambient temperature for 13 h. The resulting suspension was quenched with an aqueous solution of $Na_2S_2O_3$ (70 mL). It was diluted with ether (50 mL) and the layers were separated. The organic


Br
t-Bu
OMe
t-Bu
8
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
ppm



8

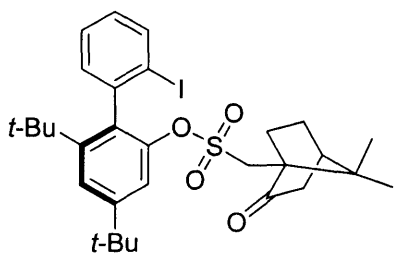
layer was washed with saturated aqueous $NaHCO_3$ (150 mL) and brine (150 mL), dried with magnesium sulfate, and concentrated *in vacuo* to afford a yellow oil. The title compound was crystallized from ethanol at 4 °C as a white solid (5.59 g, 62%). Mp: 83 – 85 °C. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.87 (dd, *J* = 7.9, 1.1 Hz, 1 H), 7.34 (td, *J* = 7.5, 1.2 Hz, 1 H), 7.25 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.19 (d, *J* = 1.7 Hz, 1H), 6.98 (td, *J* = 7.7, 1.8 Hz, 1H), 6.82 (d, *J* = 1.7 Hz, 1H), 3.67 (s, 3H), 1.38 (s, 9H), 1.16 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 157.0, 151.4, 147.6, 145.6, 138.5, 131.8, 130.2, 128.2, 127.3, 117.1, 106.3, 105.0, 56.4, 37.3, 35.4, 32.8, 31.7 ppm. IR (CCl_4, cm^{-1}): 2962, 2362, 1603, 1559, 1463, 1405, 1362, 1302, 1236, 1068, 1021, 919, 847. Anal. Calcd for $C_{21}H_{27}IO$: C, 59.72; H, 6.44 ppm. Found: C, 59.99; H, 6.45.



9b

2-iodo-2'-hydroxy-4',6'-di-*tert*-butylbiphenyl (9b). An oven-dried 250 mL flask equipped with a magnetic stirbar and septum was charged with **6b** (1 equiv, 16.8 mmol, 7.09 g) and methylene chloride (50 mL). The mixture was cooled to 0 °C. Boron tribromide as a 1.0 M solution in methylene chloride (1.5 equiv, 25.2 mmol, 25.2 mL) was dropwise via syringe, and the reaction mixture was allowed to warm up to room temperature and stirred for 13 h. An aqueous solution of $Na_2S_2O_3$ (30 mL) was slowly added to the reaction mixture and stirred for 30 min. The layers were separated and the organic layer was washed with saturated sodium

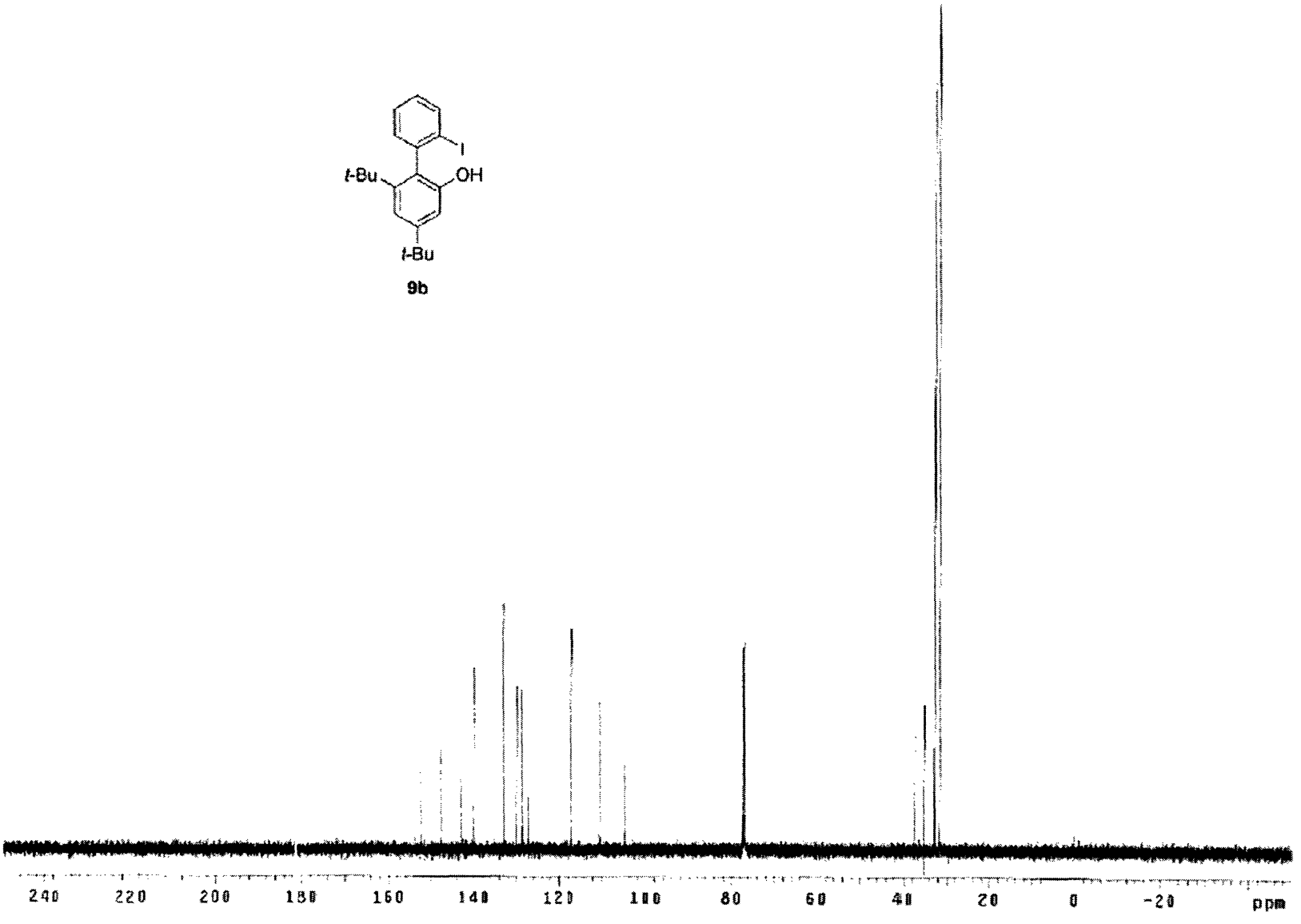
bicarbonate (70 mL x 2) and brine (70 mL), dried with magnesium sulfate, and concentrated *in vacuo* to obtain a light brown solid. The solid was re-dissolved in minimal methylene chloride. Hexanes were added and **9b** was re-crystallized at 4 °C to afford 5.58 g, 79% of **9b** as a white solid. Mp: 130 – 132 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.45 (td, *J* = 7.5, 1.2, 1H), 7.38 (dd, *J* = 7.6, 1.8 Hz), 7.16 (d, *J* = 1.9 Hz, 1H), 7.10 (td, *J* = 7.4, 2.0 Hz, 1H), 6.89 (d, *J* = 1.9 Hz, 1H), 4.20 (s, 1H), 1.35 (s, 9H), 1.17 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 152.4, 152.3, 147.6, 143.1, 140.0, 133.0, 129.9, 128.6, 127.2, 117.1, 110.4, 104.9, 37.3, 35.1, 32.7, 31.6 ppm. IR (CCl_4, cm^{-1}): 3561, 2966, 1616, 1558, 1461, 1409, 1363, 1297, 1189, 1168, 1015, 967, 863. A satisfactory elemental analysis was not obtained for this compound. The ^{1}H and ^{13}C NMR spectra follow.



11a

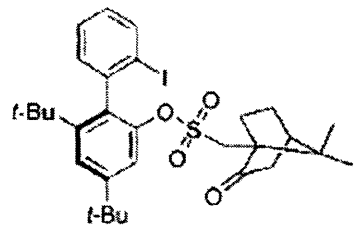
Synthesis and resolution of 11a. A n o ven-dried 2 50 m L flask e quipped w ith a stirbar and septum was charged with ***rac*-9b** (1 equiv, 12.3 mmol, 5.02 g) and THF (75 mL). It was cooled to –78 °C and KHMDS as a 0.91 M solution in THF (1.3 equiv, 16.0 mmol, 17.6 mL) was added dropwise via syringe. The mixture was stirred at –78 °C for 1 h. (1*S*)-(+)-camphorsulfonyl chloride (1.3 equiv, 16.0 mmol, 4.01 g) and DMAP (0.25 equiv, 3.1 mmol, 0.375 g) were then added; the reaction mixture was allowed to warm up to room temperature and stirred for 13 h. The

16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2
ppm
t-Bu
t-Bu
OH
I
9b

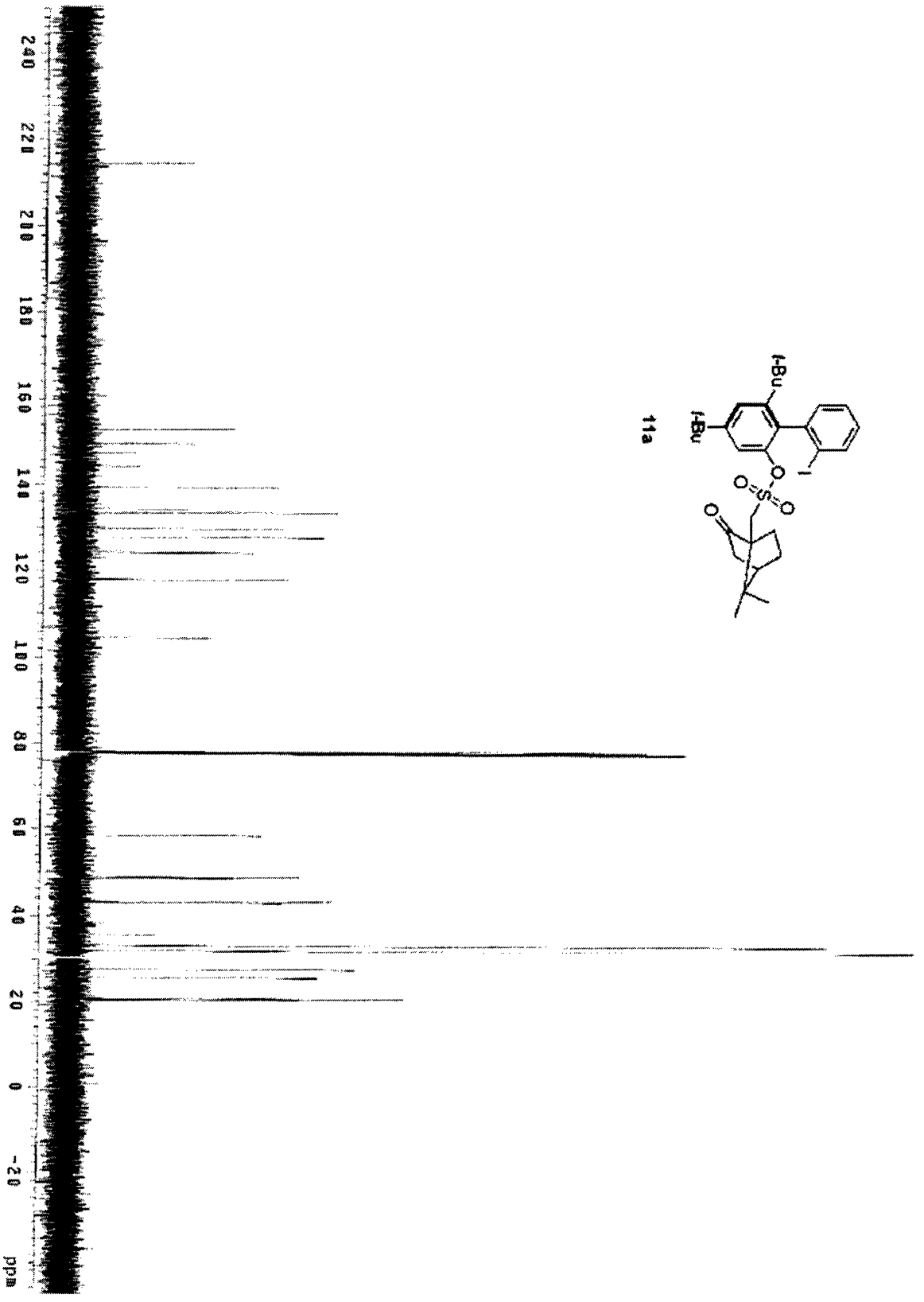


9b

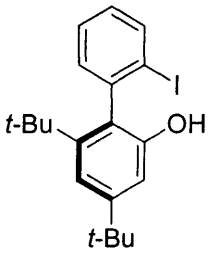
mixture was concentrated *in vacuo* to afford an orange oil, purified on a silica gel plug (5 cm diameter x 3 cm, ethyl acetate), and concentrated under reduced pressure to afford ***rac*-11**. It was diluted with ethanol (25 mL) and stored at 4 °C. Diastereomer **11a** was selectively crystallized to yield 2.57 g, 34% (out of 50%) of a white solid with 97% *de* as determined by HPLC analysis (Chiralcel OD, 1:99 isopropanol:hexane, 0.7 mL/min). Mp: 161 – 163 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.92 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.52 (d, *J* = 1.8 Hz, 1H), 7.39 – 7.34 (m, 2H), 7.29 (d, *J* = 1.8 Hz, 1H), 7.04 (ddd, *J* = 9.15, 6.71, 2.44 Hz, 1H), 3.30 (d, *J* = 14.5, 2H), 2.35 – 2.28 (m, 1H), 2.18 (d, *J* = 15.0 Hz, 1H), 2.04 (t, *J* = 4.6 Hz, 1H), 2.01 – 1.94 (m, 1H), 1.89 (d, *J* = 18.6 Hz, 1H), 1.36 (s, 9H), 1.19 (s, 9H), 1.01 (s, 3H), 0.74 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 214.0, 152.3, 148.9, 146.8, 143.8, 138.8, 133.7, 129.1, 127.0, 123.5, 117.3, 104.1, 57.9, 48.2, 47.9, 43.0, 42.6, 37.6, 35.3, 32.7, 31.5, 27.0, 25.0, 20.1, 19.8 ppm. IR (CCl_4, cm^{-1}): 2966, 1751, 1610, 1557, 1455, 1417, 1401, 1362, 1278, 1225, 1181, 1156, 1056, 1003, 956, 903, 877, 667, 643, 575, 523. A satisfactory elemental analysis was not obtained for this compound. The ^{1}H and ^{13}C NMR spectra follow.



11a

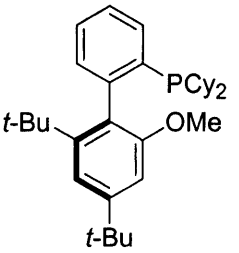

240
220
200
180
160
140
120
100
80
60
40
20
0
-20
ppm
t-Bu
t-Bu
I
O
O=S=O
O

11a



(*R*)-9b

(*R*)- 2-iodo-2'-hydroxy-4',6'-di-*tert*-butylbiphenyl ((*R*)-9b). A 100 mL flask equipped with a stir bar and septum was charged with **11a** (1 equiv, 4.1 mmol, 2.57 g), potassium hydroxide (5 equiv, 20.6 mmol, 1.16 g), ethanol (40 mL), water (5 mL) and methylene chloride (15 mL). The reaction was stirred at room temperature for 48 h until the reaction was judged complete by TLC. The solution was acidified to pH 7 with 10% aqueous citric acid, then diluted with methylene chloride (30 mL). The layers were separated and the aqueous layer was extracted with methylene chloride (40 mL x 3). The combined organic layers were dried with magnesium sulfate, filtered, and concentrated *in vacuo* to afford a white solid. This was re-dissolved in minimal hexane and re-crystallized to obtain 1.66 g, 97% of the title compound in 97% *ee* (Chiralcel OD, 5:95 isopropanol: hexane, 1.0 mL/min). Mp: 90 – 92 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.99 (dd, *J* = 7.9, 0.7 Hz, 1H), 7.45 (td, *J* = 7.54, 1.0 Hz, 1H), 7.38 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.16 (d, *J* = 1.7 Hz, 1H), 7.10 (td, *J* = 7.9, 1.7 Hz, 1H), 6.88 (d, *J* = 1.7 Hz, 1H), 4.20 (s, 1H), 1.35 (s, 9H), 1.17 (s, 9H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 152.4, 152.3, 147.5, 143.1, 132.9, 129.9, 128.6, 127.2, 117.0, 110.4, 104.9, 37.3, 35.1, 32.7, 31.6 ppm. IR (CCl_4, cm^{-1}): 3559, 2965, 2869, 2905, 1615, 1559, 1480, 1460, 1409, 1395, 1363, 1297, 1277, 1239, 1189, 1168, 1015, 1001, 967, 863, 706, 662, 644. Anal. Calcd for $C_{20}H_{25}IO$: C, 58.83; H, 6.17. Found: C, 59.01; H, 6.23.

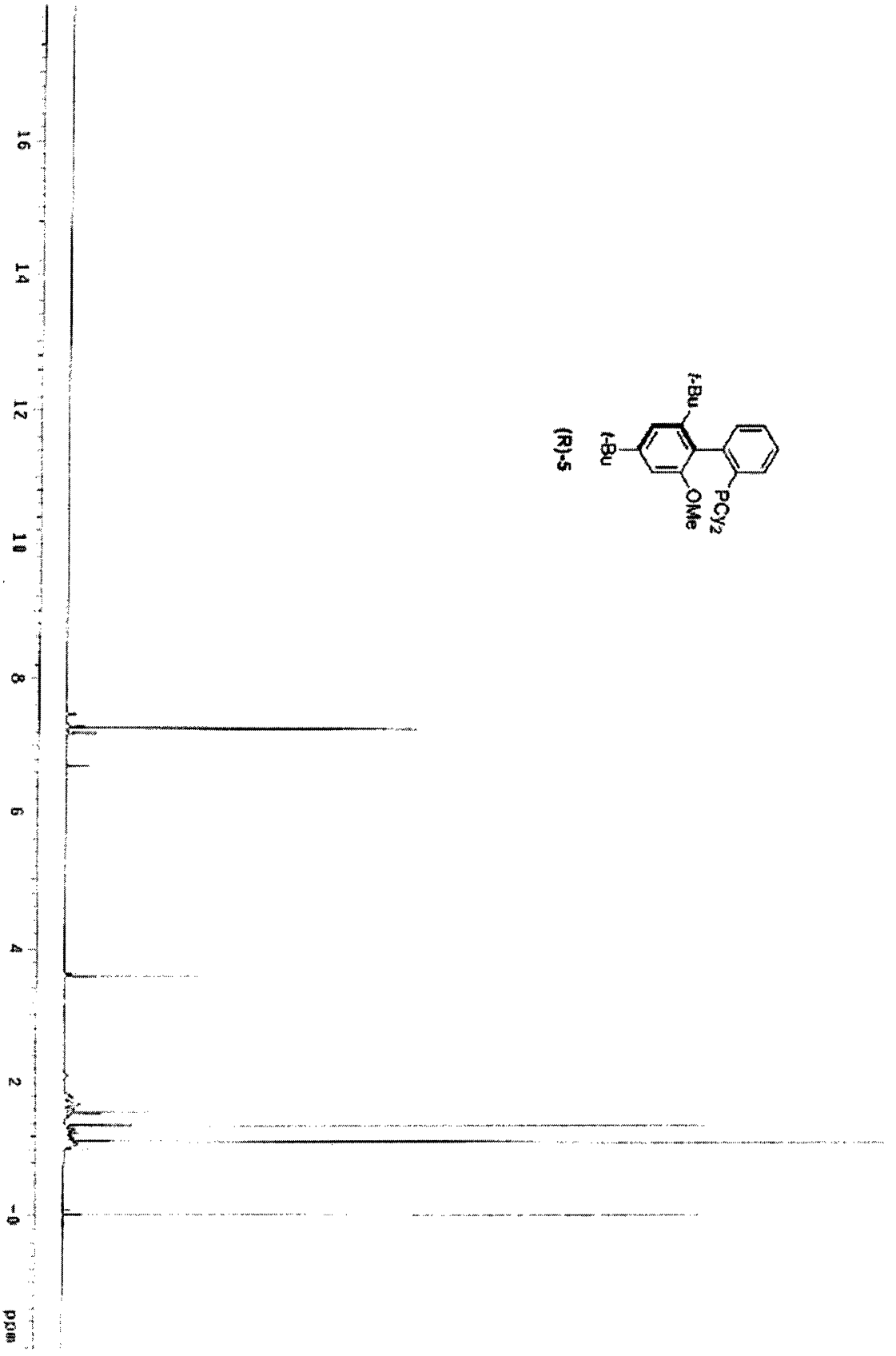


(R)-5

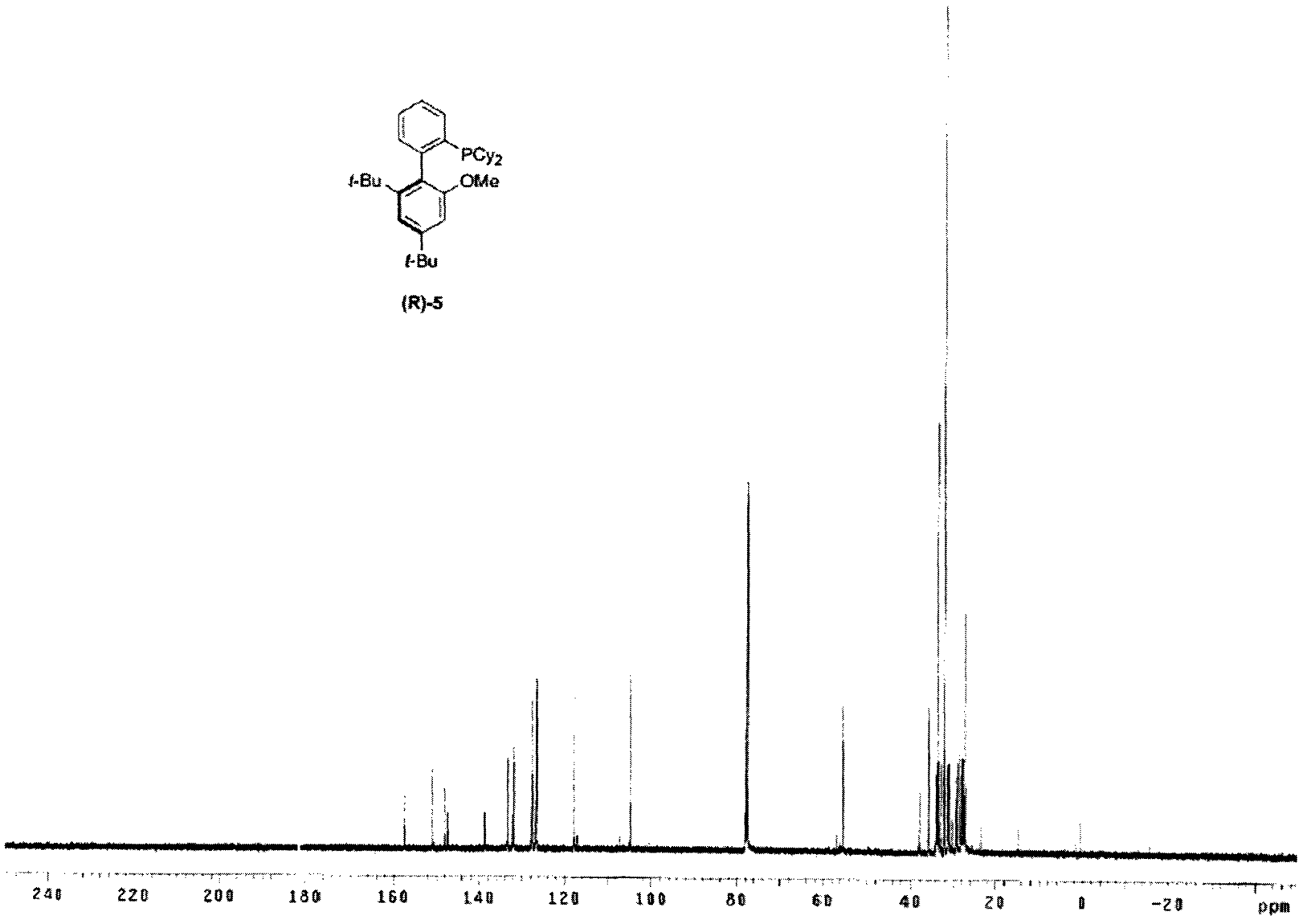
(*R*)- 2-dicyclohexylphosphino-2'-methoxy-4',6'-di-*tert*-butylbiphenyl (**(*R*)-5**). An oven-dried 50 mL flask equipped with a magnetic stirbar and septum was charged with NaH (1.5 equiv, 6.11 mmol, 0.245 g) and THF (10 mL), and subsequently cooled to 0 °C. A solution of **(*R*)-9b** (1 equiv, 4.07 mmol, 1.66 g) in THF (10 mL) was added dropwise via syringe, then stirred for 45 min. Dimethyl sulfate (1.25 equiv, 5.09 mmol, 0.48 mL) was added at room temperature and the reaction mixture was stirred for 13 h. The septum was removed and NaOH as a 1 M aqueous solution was added (20 mL) and stirred for 1 h. The layers were separated and the organic layer was washed with aqueous 1M NaOH (20 mL x 2), dried with magnesium sulfate, filtered, and concentrated *in vacuo* to afford a clear oil, **(*R*)-6**, which was used without further purification.

An oven-dried 25 mL flask equipped with a magnetic stirbar and septum was charged with **(*R*)-6** (1 equiv, 4.07 mmol, 1.72 g) and THF (20 mL), and subsequently cooled to –78 °C. *n*-butyllithium as a 2.5 M solution in hexane (1.5 equiv, 6.11 mmol, 2.5 mL) was added dropwise via syringe and the reaction was stirred for 1 h at –78 °C. Dicyclohexylphosphine chloride (1.5 equiv, 6.11 mmol, 1.4 mL) was added dropwise via syringe, and the mixture was slowly warmed up to room temperature and stirred for 5 h. The mixture was diluted with ether and washed with saturated aqueous sodium bicarbonate (20 mL x 2) and brine (20 mL), dried with

magnesium sulfate, filtered, and concentrated *in vacuo*, giving a clear oil. It was purified by flash chromatography (1:99 ethyl acetate:hexanes) to afford 0.961 g, 48% of the title compound **(*R*)-5** as a white solid. The enantiomeric purity (97% *ee*) was determined by HPLC analysis of the corresponding phosphine oxide (Chiralcel AD, 2:98 isopropanol:hexane, 1.0 mL/min). Mp: 70 – 75 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.48 – 7.47 (m, 1H), 7.32 – 7.28 (m, 2H), 7.20 – 7.19 (m, 2H), 6.70 (d, *J* = 1.2 Hz, 1H), 3.59 (s, 3H), 2.12 – 1.93 (m, 1H), 1.83 – 1.60 (m, 10H), 1.53 – 1.48 (m, 2H), 1.36 (s, 9H), 1.32 – 1.16 (m, 6H), 1.12 (s, 9H), 1.09 – 1.02 (m, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 156.9, 150.3, 147.5, 146.8, 146.6, 138.2, 138.1, 132.8, 132.7, 131.6, 131.4, 131.3, 127.3, 127.2, 127.1, 126.1, 117.3, 104.4, 55.1, 37.6, 35.4, 35.2, 33.4, 33.38, 33.36, 33.1, 33.0, 32.9, 32.5, 32.4, 31.8, 31.7, 30.8, 30.6, 30.5, 30.4, 28.7, 28.6, 28.2, 28.1, 27.6, 27.5, 27.3, 27.2, 27.0, 26.7 ppm (observed complexity due to P-C splitting; definitive assignments have not yet been made); ^{31}P NMR (121 MHz, $CDCl_3$) δ: –8.49 ppm. IR (CCl_4, cm^{-1}): 2928, 2852, 2614, 2241, 1868, 1604, 1559, 1448, 1405, 1385, 1362, 1301, 1260, 1235, 1181, 1071, 1016, 919. Anal. Calcd for $C_{33}H_{49}OP$: C, 80.44; H, 10.02. Found: C, 80.37; H, 10.08.



(R)-5


PCy2
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OMe
t-Bu
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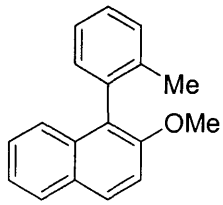
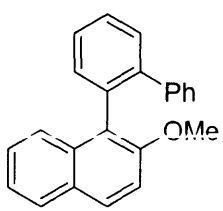
180
160
140
120
100
80
60
40
20
0
-20
ppm

(*R*)-5

(R)-5



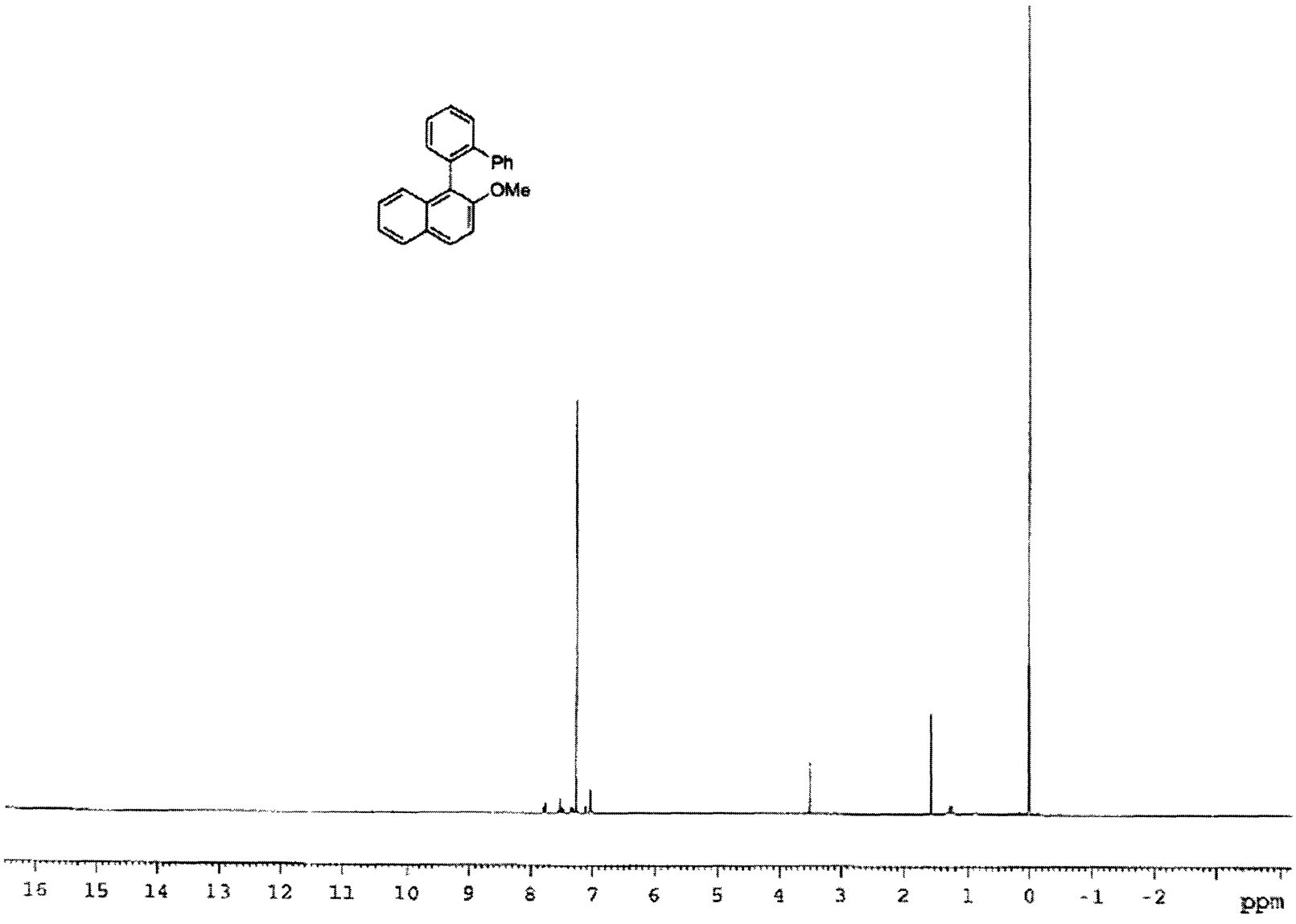
2-methoxy-1-(2-tolyl)-naphthalene (Table **2**, Entry **1**).[26] Following the representative procedure, a mixture of 1-bromo-2-methoxynaphthalene (0.059 g, 0.25 mmol), 2-tolylboronic acid (0.051 g, 0.375 mmol), $K_3PO_4 \cdot H_2O$ (0.173 g, 0.75 mmol), $Pd(OAc)_2$ (0.003 g, 0.0125 mmol), ligand **(*R*)-5** (0.013 g, 0.025 mmol) in DMF (0.5 mL) was heated at 30 °C for 13 h. The crude product was purified by flash chromatography (2:98 CH_2Cl_2:hexane to 15:85 CH_2Cl_2:hexane) to provide the title compound as a white solid (0.038 g, 61%) in 52% *ee* (Chiralcel OJ, 4:96 isopropanol:hexane, 1.0 mL/min). Mp: 94 – 97 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.90 (d, J = 9.1 Hz, 1H), 7.85 – 7.82 (m, 1H), 7.40 – 7.27 (m, 6H), 7.18 (d, J = 6.6, 1H), 3.85 (s, 3H), 1.99 (s, 3H) ppm. The spectra were in agreement with those described in the literature.



2-methoxy-1-(2-biphenyl)-naphthalene (Table **2**, Entry **2**). Following the representative procedure, a mixture of 1-bromo-2-methoxynaphthalene (0.059 g, 0.25 mmol), 2-biphenylboronic acid (0.075 g, 0.375 mmol), $K_3PO_4 \cdot H_2O$ (0.173 g, 0.75 mmol), $Pd(OAc)_2$ (0.003 g, 0.0125 mmol), ligand **(*R*)-5** (0.013 g, 0.025 mmol) in

[26] Terao, Y.; Wakui, H.; Nomoto, M.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* **2003**, *68*, 5236 – 5243.

DMF (0.5 mL) was heated at 30 °C for 15 h. The crude product was purified by flash chromatography (1:99 Et_2O:hexane) to provide the title compound as a white solid (0.030 g, 43%) in 16% *ee* (Chiralcel OJ, 4:96 isopropanol:hexane, 1.0 mL/min). Mp: 90 – 93 °C. ^1H NMR (400 MHz, $CDCl_3$) δ: 7.78 (d, J = 8.5 Hz, 1H), 7.53 – 7.48 (m, 4H), 7.36 – 7.33 (m, 3H), 7.12 (d, J = 9.1 Hz, 1H), 7.04 – 7.02 (m, 5H), 3.52 (s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ: 153.7, 143.2, 142.0, 135.0, 134.0, 132.1, 130.0, 129.3, 129.0, 128.8, 128.1, 127.9, 127.4, 127.3, 126.5, 126.4, 125.4, 124.4, 123.5, 113.3, 56.3 ppm. IR (CCl_4, cm^{-1}): 3061, 2931, 1623, 1594, 1512, 1482, 1465, 1382, 1334, 1263, 1147, 1127, 1073, 1022. A satisfactory elemental analysis was not obtained for this compound. The ^1H and ^{13}C NMR spectra follow.


Ph
OMe
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
ppm

240
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200
180
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140
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60
40
20
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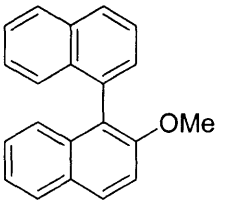
ppm

Ph
OMe



2-methoxy-1-naphthyl-naphthalene (Table **2**, Entry **3**).[27] Following the representative procedure, a mixture of 1-bromo-2-methoxynaphthalene (0.059 g, 0.25 mmol), 1-naphthylboronic acid (0.064 g, 0.375 mmol), $K_3PO_4 \cdot H_2O$ (0.173 g, 0.75 mmol), $Pd(OAc)_2$ (0.003 g, 0.0125 mmol), ligand ***(R)*-5** (0.013 g, 0.025 mmol) in DMF (0.5 mL) was heated at 30 °C for 13 h. The crude product was purified by flash chromatography (15:85 CH_2Cl_2:hexane) to provide the title compound as a white solid (0.056 g, 79%) in 32% *ee* (Chiralcel OJ, 4:96 isopropanol:hexane, 1.0 mL/min). Mp: 109 – 111 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.99 (d, *J* = 8.9 Hz, 1H), 7.95 (d, *J* = 7.9 Hz, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.62 (dd, *J* = 8.3, 7.0 Hz, 1H), 7.48 – 7.42 (m, 3H), 7.34 – 7.31 (m, 2H), 7.29 – 7.27 (m, 1H), 7.24 – 7.21 (m, 1H), 7.15 (d, *J* = 8.5 Hz, 1H), 3.77 (s, 3H) ppm. The spectra were in agreement with those described in the literature.

[27] Terao, Y.; Wakui, H.; Nomoto, M.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* **2003**, *68*, 5236 – 5243.

X-Ray Crystal Data for (*R*)-9b.

Table 1. Crystal data and structure refinement for 05062t.

Identification code	05062t	
Empirical formula	C20 H25 I K O	
Formula weight	447.40	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 10.8579(7) Å	α= 90°.
	b = 11.4427(8) Å	β= 90°.
	c = 30.359(2) Å	γ = 90°.
Volume	3772.0(4) $Å^3$	
Z	8	
Density (calculated)	1.576 Mg/m^3	
Absorption coefficient	1.921 mm^{-1}	
F(000)	1800	
Crystal size	0.36 x 0.26 x 0.19 mm^3	
Theta range for data collection	1.90 to 23.31°.	
Index ranges	-12<=h<=12, -12<=k<=12, -33<=l<=33	
Reflections collected	53148	
Independent reflections	5431 [R(int) = 0.0245]	
Completeness to theta = 23.31°	99.7 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5431 / 0 / 428	
Goodness-of-fit on F^2	1.130	
Final R indices [I>2sigma(I)]	R1 = 0.0181, wR2 = 0.0471	
R indices (all data)	R1 = 0.0182, wR2 = 0.0472	
Absolute structure parameter	-0.004(14)	
Largest diff. peak and hole	0.612 and -0.235 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 05062t. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(15)	10470(4)	5096(4)	8792(2)	40(1)
I(2)	7973(1)	6925(1)	8211(1)	27(1)
I(1)	4238(1)	6076(1)	8226(1)	25(1)
C(31)	4078(3)	8918(3)	8335(1)	20(1)
C(8)	6937(3)	3778(3)	8318(1)	19(1)
C(27)	6286(3)	9310(3)	8403(1)	19(1)
C(32)	5230(3)	9050(3)	8152(1)	18(1)
C(35)	2332(3)	10054(4)	9244(1)	32(1)
C(6)	4699(3)	3489(3)	8417(1)	19(1)
O(1)	6807(2)	3532(2)	7877(1)	25(1)
C(28)	6149(3)	9399(3)	8866(1)	20(1)
C(24)	8759(3)	10956(3)	7780(1)	31(1)
C(26)	7450(3)	9540(3)	8150(1)	20(1)
C(2)	2749(3)	3903(3)	8050(1)	20(1)
C(13)	9721(3)	4238(4)	9065(1)	30(1)
C(12)	6151(3)	4135(3)	9050(1)	22(1)
C(22)	9388(3)	8949(3)	7818(1)	25(1)
C(33)	2651(3)	8900(3)	9011(1)	24(1)
C(9)	8138(3)	3923(3)	8461(1)	23(1)
C(29)	4964(3)	9258(3)	9038(1)	21(1)
C(30)	3918(3)	9025(3)	8789(1)	20(1)
C(21)	8308(3)	8678(3)	8036(1)	19(1)
C(23)	9617(3)	10097(3)	7690(1)	28(1)
C(7)	5925(3)	3835(3)	8609(1)	20(1)
C(11)	7387(3)	4290(3)	9183(1)	22(1)
C(20)	5436(3)	3527(3)	9811(1)	33(1)
C(17)	5184(3)	4344(3)	9422(1)	27(1)
C(37)	7177(3)	9673(3)	9204(1)	24(1)
C(38)	6926(4)	10900(4)	9396(1)	41(1)
C(39)	7141(4)	8763(4)	9572(1)	42(1)
C(10)	8380(3)	4167(3)	8902(1)	22(1)

C(34)	2702(3)	7907(3)	9353(1)	33(1)
C(14)	9827(4)	4564(4)	9548(1)	49(1)
O(2)	5295(2)	8907(2)	7702(1)	24(1)
C(25)	7692(3)	10682(3)	8007(1)	25(1)
C(18)	3836(3)	4167(4)	9301(1)	39(1)
C(4)	3302(3)	1919(3)	8208(1)	28(1)
C(1)	3859(3)	4272(2)	8234(1)	19(1)
C(5)	4382(3)	2289(3)	8398(1)	24(1)
C(3)	2476(3)	2724(3)	8040(1)	24(1)
C(19)	5332(4)	5623(3)	9577(1)	34(1)
C(36)	1638(3)	8621(3)	8680(1)	34(1)
C(16)	10316(4)	3002(4)	9007(1)	42(1)
C(40)	8496(4)	9682(4)	9032(1)	46(1)

Table 3. Bond lengths [Å] and angles [°] for 05062t.

C(15)-C(13)	1.520(6)
I(2)-C(21)	2.107(3)
I(1)-C(1)	2.106(3)
C(31)-C(32)	1.377(5)
C(31)-C(30)	1.394(4)
C(8)-O(1)	1.374(4)
C(8)-C(9)	1.384(5)
C(8)-C(7)	1.413(5)
C(27)-C(32)	1.408(4)
C(27)-C(28)	1.419(5)
C(27)-C(26)	1.503(4)
C(32)-O(2)	1.377(4)
C(35)-C(33)	1.536(5)
C(6)-C(1)	1.393(4)
C(6)-C(5)	1.416(5)
C(6)-C(7)	1.507(5)
C(28)-C(29)	1.397(5)
C(28)-C(37)	1.547(5)
C(24)-C(23)	1.382(5)
C(24)-C(25)	1.382(5)
C(26)-C(21)	1.399(4)
C(26)-C(25)	1.401(5)
C(2)-C(3)	1.381(5)
C(2)-C(1)	1.394(4)
C(13)-C(14)	1.519(6)
C(13)-C(10)	1.540(5)
C(13)-C(16)	1.565(6)
C(12)-C(7)	1.404(5)
C(12)-C(11)	1.412(5)
C(12)-C(17)	1.559(5)
C(22)-C(21)	1.382(5)
C(22)-C(23)	1.392(5)
C(33)-C(36)	1.525(5)
C(33)-C(30)	1.539(4)

C(33)-C(34)	1.540(5)
C(9)-C(10)	1.395(5)
C(29)-C(30)	1.390(5)
C(11)-C(10)	1.382(5)
C(20)-C(17)	1.532(5)
C(17)-C(18)	1.523(5)
C(17)-C(19)	1.545(5)
C(37)-C(40)	1.524(5)
C(37)-C(39)	1.529(5)
C(37)-C(38)	1.545(5)
C(4)-C(5)	1.374(5)
C(4)-C(3)	1.383(5)

C(32)-C(31)-C(30)	120.2(3)
O(1)-C(8)-C(9)	115.2(3)
O(1)-C(8)-C(7)	122.6(3)
C(9)-C(8)-C(7)	122.1(3)
C(32)-C(27)-C(28)	117.8(3)
C(32)-C(27)-C(26)	116.5(3)
C(28)-C(27)-C(26)	125.6(3)
C(31)-C(32)-O(2)	115.7(3)
C(31)-C(32)-C(27)	123.0(3)
O(2)-C(32)-C(27)	121.3(3)
C(1)-C(6)-C(5)	116.6(3)
C(1)-C(6)-C(7)	124.3(3)
C(5)-C(6)-C(7)	119.0(3)
C(29)-C(28)-C(27)	117.2(3)
C(29)-C(28)-C(37)	116.2(3)
C(27)-C(28)-C(37)	126.6(3)
C(23)-C(24)-C(25)	120.1(3)
C(21)-C(26)-C(25)	117.1(3)
C(21)-C(26)-C(27)	124.2(3)
C(25)-C(26)-C(27)	118.7(3)
C(3)-C(2)-C(1)	119.4(3)
C(14)-C(13)-C(15)	109.1(3)
C(14)-C(13)-C(10)	113.2(3)

C(15)-C(13)-C(10)	111.5(3)
C(14)-C(13)-C(16)	107.4(3)
C(15)-C(13)-C(16)	107.6(3)
C(10)-C(13)-C(16)	107.9(3)
C(7)-C(12)-C(11)	118.0(3)
C(7)-C(12)-C(17)	127.6(3)
C(11)-C(12)-C(17)	114.4(3)
C(21)-C(22)-C(23)	119.8(3)
C(36)-C(33)-C(35)	108.7(3)
C(36)-C(33)-C(30)	112.0(3)
C(35)-C(33)-C(30)	108.9(3)
C(36)-C(33)-C(34)	108.4(3)
C(35)-C(33)-C(34)	109.4(3)
C(30)-C(33)-C(34)	109.4(3)
C(8)-C(9)-C(10)	120.1(3)
C(30)-C(29)-C(28)	124.9(3)
C(29)-C(30)-C(31)	116.9(3)
C(29)-C(30)-C(33)	120.6(3)
C(31)-C(30)-C(33)	122.5(3)
C(22)-C(21)-C(26)	121.7(3)
C(22)-C(21)-I(2)	118.7(2)
C(26)-C(21)-I(2)	119.6(2)
C(24)-C(23)-C(22)	119.7(3)
C(12)-C(7)-C(8)	118.2(3)
C(12)-C(7)-C(6)	126.0(3)
C(8)-C(7)-C(6)	115.6(3)
C(10)-C(11)-C(12)	123.5(3)
C(18)-C(17)-C(20)	106.1(3)
C(18)-C(17)-C(19)	107.4(3)
C(20)-C(17)-C(19)	109.0(3)
C(18)-C(17)-C(12)	116.9(3)
C(20)-C(17)-C(12)	110.2(3)
C(19)-C(17)-C(12)	107.2(3)
C(40)-C(37)-C(39)	106.2(3)
C(40)-C(37)-C(38)	106.8(3)
C(39)-C(37)-C(38)	109.7(3)

C(40)-C(37)-C(28)	116.9(3)
C(39)-C(37)-C(28)	109.2(3)
C(38)-C(37)-C(28)	107.9(3)
C(11)-C(10)-C(9)	117.9(3)
C(11)-C(10)-C(13)	122.3(3)
C(9)-C(10)-C(13)	119.7(3)
C(24)-C(25)-C(26)	121.5(3)
C(5)-C(4)-C(3)	120.2(3)
C(6)-C(1)-C(2)	122.0(3)
C(6)-C(1)-I(1)	120.5(2)
C(2)-C(1)-I(1)	117.5(2)
C(4)-C(5)-C(6)	121.5(3)
C(2)-C(3)-C(4)	120.2(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 05062t. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(15)	16(2)	57(3)	46(3)	12(2)	-7(2)	-5(2)
I(2)	25(1)	23(1)	34(1)	5(1)	4(1)	6(1)
I(1)	25(1)	19(1)	32(1)	-1(1)	-4(1)	0(1)
C(31)	19(2)	17(2)	25(2)	2(1)	-2(1)	3(1)
C(8)	25(2)	17(2)	14(2)	0(1)	-2(1)	2(1)
C(27)	18(2)	16(2)	22(2)	1(1)	0(1)	3(1)
C(32)	26(2)	15(2)	15(2)	1(1)	2(1)	5(1)
C(35)	26(2)	40(2)	30(2)	-5(2)	6(2)	4(2)
C(6)	20(2)	23(2)	15(2)	2(1)	3(1)	0(1)
O(1)	21(1)	35(1)	20(1)	-1(1)	-2(1)	5(1)
C(28)	20(2)	19(2)	22(2)	-2(1)	-1(1)	3(1)
C(24)	36(2)	26(2)	31(2)	1(2)	6(2)	-8(2)
C(26)	19(2)	19(2)	20(2)	-3(1)	-3(1)	-2(1)
C(2)	20(2)	24(2)	15(2)	1(1)	-1(1)	2(2)
C(13)	20(2)	44(2)	27(2)	2(2)	-5(2)	-2(2)
C(12)	21(2)	23(2)	23(2)	2(1)	1(1)	2(1)
C(22)	18(2)	33(2)	23(2)	-5(2)	-1(1)	-1(2)
C(33)	18(2)	29(2)	26(2)	1(2)	3(1)	4(2)
C(9)	21(2)	23(2)	24(2)	1(2)	2(1)	3(2)
C(29)	23(2)	26(2)	13(2)	0(1)	3(1)	5(1)
C(30)	19(2)	17(2)	24(2)	3(1)	-1(1)	4(1)
C(21)	21(2)	19(2)	16(2)	1(1)	-2(1)	-3(1)
C(23)	21(2)	44(2)	19(2)	-2(2)	1(1)	-12(2)
C(7)	20(2)	19(2)	20(2)	3(1)	-2(1)	1(1)
C(11)	26(2)	28(2)	11(2)	0(1)	-4(1)	0(1)
C(20)	33(2)	44(2)	21(2)	3(2)	6(2)	1(2)
C(17)	20(2)	41(2)	20(2)	2(2)	0(1)	3(2)
C(37)	20(2)	34(2)	18(2)	-3(1)	0(1)	1(2)
C(38)	38(2)	47(2)	39(2)	-11(2)	-6(2)	-2(2)
C(39)	39(2)	54(3)	34(2)	7(2)	-16(2)	-4(2)
C(10)	21(2)	22(2)	23(2)	2(1)	0(1)	0(1)

C(34)	24(2)	40(2)	35(2)	7(2)	7(2)	-1(2)
C(14)	25(2)	75(3)	46(3)	0(2)	-10(2)	-1(2)
O(2)	18(1)	36(1)	16(1)	0(1)	1(1)	-3(1)
C(25)	25(2)	24(2)	26(2)	-2(1)	4(1)	-1(1)
C(18)	22(2)	73(3)	22(2)	-2(2)	5(2)	2(2)
C(4)	30(2)	19(2)	35(2)	5(2)	-3(2)	-2(1)
C(1)	22(2)	16(1)	19(2)	1(2)	3(2)	-2(1)
C(5)	24(2)	25(2)	21(2)	4(1)	0(1)	7(1)
C(3)	20(2)	29(2)	24(2)	-2(1)	-2(1)	-4(2)
C(19)	33(2)	41(2)	27(2)	-7(2)	6(2)	7(2)
C(36)	15(2)	47(2)	41(2)	-4(2)	4(2)	0(2)
C(16)	32(2)	46(2)	47(2)	6(2)	-6(2)	9(2)
C(40)	28(2)	78(3)	33(2)	-16(2)	-10(2)	0(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 05062t.

	x	y	z	U(eq)
H(15A)	10050(40)	5940(40)	8876(15)	59(13)
H(15B)	11260(40)	5070(40)	8849(13)	45(12)
H(15C)	10490(40)	4970(40)	8457(14)	41(11)
H(31)	3391	8754	8151	24
H(35A)	2307	10687	9026	48
H(35B)	2959	10227	9466	48
H(35C)	1525	9983	9386	48
H(24)	8902	11736	7687	37
H(2)	2185	4457	7933	23
H(22)	9972	8353	7755	29
H(9)	8799	3856	8257	27
H(29)	4865	9326	9347	25
H(23)	10359	10289	7541	33
H(11)	7544	4489	9482	26
H(20A)	4883	3726	10056	49
H(20B)	6293	3617	9907	49
H(20C)	5292	2716	9721	49
H(38A)	6090	10927	9518	62
H(38B)	7006	11487	9163	62
H(38C)	7522	11066	9630	62
H(39A)	7789	8935	9788	64
H(39B)	7276	7984	9448	64
H(39C)	6336	8788	9718	64
H(34A)	3345	8076	9570	49
H(34B)	2888	7168	9204	49
H(34C)	1904	7845	9502	49
H(14B)	10695	4551	9637	73
H(14C)	9363	4002	9727	73
H(14A)	9491	5350	9594	73
H(25)	7111	11281	8066	30

H(18A)	3695	3345	9225	59
H(18B)	3629	4660	9047	59
H(18C)	3315	4383	9552	59
H(4)	3122	1108	8192	33
H(5)	4930	1727	8519	28
H(3)	1718	2466	7917	29
H(19A)	5185	6151	9328	51
H(19B)	6168	5742	9689	51
H(19C)	4735	5787	9811	51
H(36A)	852	8529	8835	51
H(36B)	1839	7893	8525	51
H(36C)	1571	9260	8467	51
H(16B)	10303	2783	8695	63
H(16C)	9849	2427	9178	63
H(16A)	11170	3021	9112	63
H(40A)	9065	9812	9277	70
H(40B)	8590	10310	8815	70
H(40C)	8680	8929	8893	70
H(99)	5970(40)	9030(40)	7639(12)	20(11)
H(98)	6180(40)	3660(40)	7803(16)	50(16)