Note

Theoretical Elucidation of Potential Enantioselectivity in a Pd-Catalyzed Aromatic C-H Coupling Reaction

Yoshio Nishimoto, Hiroki Kondo, Kazuya Yamaguchi, Daisuke Yokogawa, Junichiro Yamaguchi, Kenichiro Itami, and Stephan Irle

J. Org. Chem., Just Accepted Manuscript • DOI: 10.1021/acs.joc.6b02675 • Publication Date (Web): 11 Apr 2017 Downloaded from http://pubs.acs.org on April 12, 2017

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a free service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are accessible to all readers and citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.



The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

Theoretical Elucidation of Potential Enantioselectivity in a Pd-Catalyzed Aromatic C–H Coupling Reaction

Yoshio Nishimoto,^{1,†} Hiroki Kondo,¹ Kazuya Yamaguchi,¹ Daisuke Yokogawa,^{1,2} Junichiro Yamaguchi,^{1,‡} Kenichiro Itami,^{1,2,3} and Stephan Irle^{*,1,2}

¹Department of Chemistry, Graduate School of Science, Nagoya University, Nagoya 464-8602, Japan. ²Institue of Transformative Bio-Molecules (WPI-ITbM), Nagoya University, Nagoya 464-8602, Japan. ³JST ERATO, Itami Molecular Nanocarbon Project, Nagoya University, Nagoya 464-8602, Japan.

E-mail: sirle@chem.nagoya-u.ac.jp

Table of Contents/Abstract Graphic



ABSTRACT. The mechanism of an aromatic C–H coupling reaction between heteroarenes and arylboronic acids using a Pd catalyst has been theoretically and experimentally investigated. We identified the C–B transmetalation as the rate-determining step. The (*S*) catalyst-reactant complex was found to be stabilized by hyperconjugation between π -orbitals on the tolyl group and the S–O σ^* anti-bonding orbital in the catalyst ligand. Our findings suggest routes for the design of new, improved Pd catalysts with higher stereoselectivity.

C–H functionalization is a rapidly growing field in organic chemistry because of its potential applications in the synthesis of pharmaceuticals, natural products, agrochemicals, and organic materials.¹ The utility of C–H functionalization is particularly pronounced when structural isomers and/or stereoisomers can be distinguished. As one of the most fundamental reactions, the C–H coupling of heteroarenes with arylboron compounds has been extensively studied both experimentally² and computationally.^{2a,3} However, this type of reaction usually requires a stoichiometric amount of co-oxidants such as 1,4-benzoquinone, Cu(II) halides and Ag(I) salts, which results in chemical waste except in some rare cases.⁴ Moreover, these catalysts generally exhibit low reactivity when sterically demanding substrates are employed.

Recently, Itami, Yamaguchi, and coworkers discovered an aromatic C–H coupling reaction of heteroarenes and sterically hindered arylboronic acids utilizing a Pd/Fe dual catalyst that could overcome the above-mentioned drawbacks.⁵ The dual catalyst consists of Pd(II)-sulfoxide-oxazoline (sox) and iron-phthalocyanine (FePc), where FePc is considered to oxidize Pd(0) to Pd(II) with oxygen in the air as the terminal oxidant. The reaction can be applied to an enantioselective aromatic C–H coupling reaction between 2,3-dimethylthiophene (**1A**) and a

hindered arylboronic acid **2a** to afford the coupling product **3Aa** (Figure 1). Despite the aforementioned attractive features, the highest enantiomeric excess (ee) value was 61%,⁵ and understanding of the reaction mechanism, which would aid in developing a catalyst which delivers a higher ee, has been limited. Although enantioselective C–H activation of diarylmethanes and C(sp³)–H groups has been reported, atropselective C–H coupling for the synthesis of biaryl compounds is rare.⁶ Herein, we report an experimental substituent effect study of a model reaction as well as a theoretical investigation to clarify the reaction mechanism of the representative reaction shown in Figure 1.



Figure 1. Aromatic C–H coupling reaction of a thiophene derivative and a hindered arylboronic acid, assisted by a Pd/Fe dual catalyst.

All of structures were optimized using the density functional theory (DFT)⁷ as implemented in Gaussian 09.⁸ We selected B3PW91 exchange–correlation functional⁹ using the ultrafine grid with 6-31G(d) and LANL2DZ basis set for typical and Pd atoms respectively (abbreviated as BSI).¹⁰ The character of stationary points has been confirmed with normal mode

analysis. Thermodynamical correction was calculated at 343.15 K. The connections of stationary points were verified by intrinsic reaction coordinate (IRC) calculations.¹¹ Energy refinement for optimized structures was performed at the MP2/(aug-)cc-pVTZ¹² level of theory with the default spin component scaling (SCS) values¹³ as implemented in MOLPRO 2012.¹⁴ We added augmented functions^{12b,12c} for N, O, and S atoms and pseudo-potential (ECP28MDF)^{12d} for Pd (BSII), and the density fitting (DF)¹⁵ with proper auxiliary functions, except for Pd for which we used TZVPP auxiliary functions, were used.¹⁶ Solvent effect was implicitly added by performing reference Hartree–Fock calculation with COSMO¹⁷ solvation model ($\varepsilon = 37.219$; *N,N*dimethylformamide). We added non-electrostatic energies calculated with the SMD¹⁸ solvation model.

We first investigated the substituent effect of the sox ligand experimentally (Table 1). The coupling reaction of 2,3-dimethylthiophene (**1A**) and hindered arylboronic acid **2b** as model substrates were conducted in the presence of 10 mol% $Pd(OAc)_2$, 10 mol% ligand (**L1–L6**), and 5 mol% FePc in DMF at 80°C under air for 12 h. All catalyst ligands gave the corresponding product (**3Ab**), and the (*S*) stereoisomer was the dominant product in all the cases (regioselectivity (C4:C5 ratio) > 89%; see Table 1). Compared to the standard sox ligand **L1**, none of the other ligands resulted in better ee values (**L2–L6**). Racemization of the product does not take place under the experimental conditions.¹⁹ In order to further improve ee, we decided to conduct a computational study to better understand the mechanism and the origin of the enantioselectivity.

Table 1. Experimental Substituent Effects of the Sox Ligand.

Me Me S 1A	(HO) ₂ B	10 mol% Pd(OAc)2 10 mo% ligand 5 mol% FePc ► DMF, 80 °C, 12 h air	Me Me SAb	>
$Me^{A} = Me^{A} = 5 + Me^{A} $				
Ligand	Yield	C4:C5 ^a	ee (%)	
L1	92	96:4	29	_
L2	41	89:11	14	
L3	90	98:2	30	
L4	78	96:4	22	
L5	76	97:3	27	
L6	28	95:5	23	

^aThe C4:C5 ratio was determined by ¹H NMR.

As shown experimentally²⁰ and theoretically,²¹ the role of FePc is to oxidize Pd(0) to Pd(II), and therefore the reaction that involves FePc is not described here. (2-Isopropylnaphthalen-1-yl)boronic acid (**2a**) which previously⁵ showed the highest enantioselectivity of 61% ee (Figure 1) was selected as a reactant in this study to make the difference in reaction profiles more apparent. The reaction mechanism (Figure 2) indicates that the C–B bond of the arylboronic acid is first transmetalated by the Pd-sox (**L1**) catalyst. The reaction profile (Figure 3) showed that the (*S*)-product should be dominant since the highest activation energy of the transition state (TS) leading to the (*S*)-product (**TS**_{4.5}^S) is 3.0 kcal/mol lower than the TS leading to the (*R*)-product (**TS**_{4.5}^R). This finding is consistent with the experimental conditions at 70°C. Other important TSs are the C–C bond formation step (**TS**_{8.9}^S and **TS**_{8.9}^R) and the abstraction of proton to form a double bond on the thiophene ring (**TS**_{1.12}^S

and TS_{11-12}^{R}). Activation energies of these steps are lower than that of the C-B bond transmetalation. The HOAc species generated in the catalytic cycle may be converted to OAc⁻ and water in the oxidation step. The water may then hydrolyze AcO-B(OH)₂, resulting in regeneration of **20ac**.



Figure 2. Proposed catalytic cycle. The oxidation mechanism^{20,21} marked by the gray box is not considered in this study.

ACS Paragon Plus Environment



Figure 3. Proposed reaction profile at the COSMO-DF-SCS-MP2/BSII//B3PW91/BSI level of theory. Blue and red lines represent free energies of reaction coordinates leading to (S)- and (R)-stereoisomers, respectively.

The concerted metalation-deprotonation (CMD) mechanism²² is well known in palladiumcatalyzed C–H arylation. However, the corresponding TS_{CMD} (Figure 4 (A)) requires a higher energy than any TS in Figure 3. We found that CH₃COO⁻ prefers to abstract the proton at the C5 position. This observation disagrees with the experimental product mainly consisting of a C4 product, which requires at least 35.9 kcal/mol in CMD mechanism. These results are consistent with the relative acidity at the C4 and C5 positions of thiophene.²³ Therefore, we conclude CH₃COO⁻ does not abstract protons on the thiophene ring at the early stage of the reaction. A structural isomer of C–B transmetalation $TS_{4.5}^{iso}$ (Figure 4 (B)) is also higher in energy, because of the steric repulsion between the sox ligand and the arylboronic acid. The oxidative addition of

 $Ar-B(OH)_2$ is prohibited, because we could not find an $Ar-(Pd-sox)-B(OH)_2$ -type intermediate. $Ar-B(OH)_3^-$ may be formed, but a reaction with the Pd catalyst is spontaneous, so the species cannot influence on the enantioselectivity. We could locate a TS which involves $2OAc^-$ (**TS**_{20ac}), but it required an activation barrier of 56.4 kcal/mol. These three observations are discussed in the Supporting Information (Figures S1–S3).



Figure 4. Structures and free energies of TSs of (A) CMD pathway and (B) a structural isomer.

As we have shown in Figures 3 and 4, (2-isopropylnaphthalen-1-yl)boronic acid approaches from one side. There is still a possibility of isomerization between two intermediates that would lead to (*S*)- and (*R*)-products: the rotation and flip of the aryl group. However, TSs of such motion given in the Supporting Information (Figure S4) respectively require free energies of 32.7 ($TS_{rotation}$) and 34.0 (TS_{nip}) kcal/mol, which suggests that such isomerization does not take place under the experimental condition. From Figures 3, 4, and S4, we conclude that the stereoselectivity of the catalytic reaction is kinetically controlled at the C–B transmetalation step $TS_{4.5}^{S}$ and $TS_{4.5}^{R}$.

The main question is why the energy difference of 3.0 kcal/mol emerges at this enantioselective step. To address this, we calculated the interaction energy between the aryl

group on the Pd center and the tolyl group of the sox ligand. To extract the interaction energy specifically, we created a truncated model containing mainly these groups and saturated the dangling bond by a hydrogen atom, using the optimized geometries of $TS_{4.5}^{S}$ and $TS_{4.5}^{R}$. The basis set superposition error was removed using standard Boys–Bernardi counterpoise correction. The interaction energies at the DF-SCS-MP2/BSII level of theory are 1.9 and 1.8 kcal/mol for $TS_{4.5}^{S}$ and $TS_{4.5}^{R}$, respectively, so the difference of 0.2 kcal/mol only represents ~5% of the total energy difference of 3.0 kcal/mol, implying that steric repulsion alone cannot reasonably explain the enantioselectivity of the catalytic reaction. In fact, the different orientation of the 'Pr group induces the rotation of the tolyl group by 44.2° in the dihedral angle between the O–S–C–C atoms (ψ , see Figure 5A) to minimize the steric repulsion between 'Pr and tolyl groups, resulting in the small difference of the interaction energies.



Figure 5. (A) Definition of dihedral angle ψ , (B) dihedral angles of $\mathbf{TS}_{4.5}^{s}$ and hypothetical $\mathbf{TS}_{4.5}^{s}$, and (C) schematic hyperconjugation between C–C π -orbital and S–O σ^{*} -orbital.

We next focused on the electronic structure effect of the rotation of the tolyl group. To minimize non-relevant effects, we compared those of $\mathbf{TS}_{4.5}^{s}$ ($\psi = 84.2^{\circ}$) and a hypothetical TS

structure whose dihedral angle is equivalent to that of $TS_{4.5}^{R}$ ($\psi = 128.4^{\circ}$) based on the $TS_{4.5}^{S}$ structure as shown in Figure 5B, viewed through the S-C (atom 2-3 in Figure 5 (A)) bond perpendicularly. We adopted the natural bond orbital (NBO) analysis²⁴ at the B3PW91/BSI level of theory. Our analysis revealed that $TS_{4.5}^{s}$ and hypothetical $TS_{4.5}^{s}$ are stabilized by 5.9 and 3.3 kcal/mol, respectively, by the interaction between the donor (occupied C–C π -orbital on the tolyl group) and the acceptor (unoccupied S–O σ^* -orbital on the sox ligand) NBOs. The interaction is schematically depicted in Figure 5C, corresponding to the hyperconjugation²⁵ between these orbitals. In $TS_{4.5}^{s}$, the molecular plane of the tolyl group is almost perpendicular to the S–O bond; therefore the overlap between the C–C π - and the S–O σ *-orbitals is at its maximum. On the other hand, the tilted tolyl group in the hypothetical TS structure representing $TS_{4.5}^{R}$ decreases the overlap between two orbitals, resulting in a smaller stabilization by the hyperconjugation. The difference of the interaction energies is 2.6 kcal/mol, which is close to the difference of the activation energies at $TS_{4.5}^{S}$ and $TS_{4.5}^{R}$, namely 3.0 kcal/mol. The analysis above has been conducted for 2a with the 'Pr group, while 2b used in our experiment has the methyl group. 2b induces a smaller degree of rotation of the tolyl group (ψ) in the structure of $TS_{4.5}^{S}$ and $TS_{4.5}^{R}$. As a consequence, the destabilization in $TS_{4.5}^{R}$ is smaller than the case with 2a; hence the difference of TS energies is also smaller, leading to lower ee value. There are a few studies which theoretically revealed that hyperconjugation may affect regioselectivity,^{25c} conformation,^{25d} and enantioselecvitity.^{25e}

As discussed above, the key for stereoselectivity is the enhancement of the hyperconjugation between the C–C π -orbitals and the S–O σ^* -orbital. In order to correlate experimental and theoretical results, we computationally investigated the substituent effect of ligands (as introduced in Table 1) at the B3PW91/BSI level of theory. To save computational

The Journal of Organic Chemistry

effort, we simply took the **20ac** structure, and the dihedral angle ψ is fixed at 84.2° and 128.4°. The computed differences of the energy are 1.7, 0.6, 1.7, 1.6, 1.7, and 1.3 kcal/mol for **L1–L6**, respectively, and the results are qualitatively consistent with the experimental tendency; smaller differences do not give higher ee. We note that the substitution with hydroxyl groups at the 4 and 6 positions or with methoxy groups at the 3 and 5 positions on tolyl group gives a difference of 2.6 or 2.3 kcal/mol, respectively, which is expected to result in higher ee than the original sox ligand, **L1** (1.7 kcal/mol). Unfortunately, these substitutions are difficult to realize in experimental chemistry.

We theoretically and experimentally investigated the mechanism of a Pd-catalyzed C–H coupling reaction of a thiophene derivative and an arylboronic acid (Figure 1). Our study indicates that the rate-determining and stereoselective step of the reaction is the C–B transmetalation of the arylboronic acid. NBO analysis reveals that the difference between the activation energy of two TSs leading to (*S*)- and (*R*)-products ($\mathbf{TS}_{4.5}^{S}$ and $\mathbf{TS}_{4.5}^{R}$) is attributed to the hyperconjugation between π -orbitals on the tolyl and the S–O σ^* -bonding orbitals on the sox ligand. Our investigations of the substituent effect of the sox ligand imply that the design of a highly selective catalyst is challenging.

Experimental Section

General Methods. Unless otherwise noted, all materials including dry solvents were obtained from commercial suppliers and used as received. 2-Methylnaphthalen-1-ylboronic acid (**2a**),²⁶ (*S*)-4-isopropyl-2-(2-((*S*)-*p*-tolylsulfinyl)phenyl)-4,5-dihydrooxazole (**L1**),²⁷ and (*S*)-2-(2bromophenyl)-4-isopropyl-4,5-dihydrooxazole (**S1**)²⁸ were synthesized according to procedures reported in the literature. Unless otherwise noted, all reactions were performed with dry solvents under an atmosphere of argon in flame-dried glassware using standard vacuum-line techniques. All C–H coupling reactions were performed in screw-cap 20 mL glass vessel tubes and heated in an 8-well reaction block (heater + magnetic stirrer). All work-up and purification procedures were carried out with reagent-grade solvents in air.

Analytical thin-layer chromatography (TLC) was performed using silica gel (60 F_{254}) precoated plates (0.25 mm). The developed chromatogram was analyzed by UV lamp (254 nm). Flash column chromatography was performed with silica gel 60 (230–400 mesh). Preparative thin-layer chromatography (PTLC) was performed using B5-F silica coated plates (0.75 mm) prepared in our laboratory. Gas chromatography (GC) analysis was conducted with a 30 m × 0.25 mm column. GCMS analysis was conducted with a 30 m × 0.25 mm column. Chiral HPLC analysis was conducted with a 4.6 mm x 250 mm column. Nuclear magnetic resonance (NMR) spectra were recorded using ¹H 400 MHz, ¹³C 100 MHz, ¹H 500 MHz, ¹³C 125 MHz, ¹H 600 MHz, and ¹³C 150 MHz spectrometers. Chemical shifts for ¹H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.00 ppm). Chemical shifts for ¹³C NMR are expressed in ppm relative to CDCl₃ (δ 77.0 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, sep = septet, m = multiplet, br = broad signal), coupling constant (Hz), and integration.

General Procedure for the Synthesis of Ligand precursors S2–S6. To a round-bottom flask, a solution of carboxylic acid (3.0 mmol), (*S*)-2-amino-3-methylbutan-1-ol (340 mg, 3.3 mmol, 1.1 equiv), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC: 378 mg, 3.6 mmol, 1.2 equiv) and 1-hydroxybenzotriazole (HOBt: 203 mg, 1.5 mmol, 0.5 equiv) in DMF (10 mL) were added. After stirring for 2 h at room temperature, saturated aqueous NaHCO₃ was added to the

The Journal of Organic Chemistry

mixture and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 . The solvent was removed *in vacuo* to give the corresponding amide. This crude product was used in next step without purification.

Amide (1.0 equiv), *p*-TsCl (743 mg, 3.9 mmol, 1.3 equiv), NEt₃ (2.1 mL, 15 mmol, 5 equiv) were dissolved in CH_2Cl_2 (30 mL) in a round-bottom flask equipped with a reflux condenser. The reaction mixture was stirred at 70 °C for overnight. After cooling to room temperature, saturated aqueous NH_4Cl was added and extracted with CH_2Cl_2 . The organic layer was washed with brine, and dried over anhydrous Na_2SO_4 . The solvent was removed *in vacuo*. The residue was purified by silica-gel column chromatography to give the corresponding phenyloxazoline.

(*S*)-2-(2-Bromo-3-methylphenyl)-4-isopropyl-4,5-dihydrooxazole (*S*2): The crude product was purified by silica-gel column chromatography (hexane/ethyl acetate = 10:1 to 4:1) to give *S*2 (459 mg, 54%) as a colorless oil. ¹H NMR (600 MHz, CDCl₃) δ 7.40 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.23 (dd, *J* = 7.8, 7.2 Hz, 1H), 4.48–4.40 (m, 1H), 4.20–4.12 (m, 2H), 2.45 (s, 3H), 1.96–1.87 (m, 1H), 1.06 (d, *J* = 7.2 Hz, 3H), 0.99 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 163.7, 139.3, 132.3, 131.3, 128.5, 126.8, 124.0, 72.9, 70.4, 32.7, 23.7, 18.8, 18.3; HRMS (DART Orbitrap) *m/z* calcd for C₁₃H₁₇BrNO [M+H]⁺: 282.0494, found: 282.0489.

(*S*)-2-(2-Bromo-4-fluorophenyl)-4-isopropyl-4,5-dihydrooxazole (S3): The crude product was purified by silica-gel column chromatography (hexane/ethyl acetate = 10:1 to 5:1) to give S3 (535 mg, 62%) as a colorless oil. ¹H NMR (600 MHz, CDCl₃) δ 7.70 (dd, *J* = 8.9, 6.2 Hz, 1H), 7.38 (dd, *J* = 8.2, 2.7 Hz, 1H), 7.08–7.03 (m, 1H), 4.45–4.40 (m, 1H), 4.19–4.12 (m, 2H), 1.94–1.85 (m, 1H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.98 (d, *J* = 6.7 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 163.1 (d, *J*_{FC} = 254 Hz), 162.0, 132.7 (d, *J*_{FC} = 7.5 Hz), 126.3 (d, *J*_{FC} = 3.0 Hz), 122.5 (d, *J*_{FC} =

10.5 Hz), 121.1 (d, $J_{FC} = 25.5$ Hz), 114.4 (d, $J_{FC} = 22.5$ Hz), 72.9, 70.3, 32.7, 18.7, 18.2; HRMS (DART) m/z calcd for C₁₂H₁₄BrFNO [M+H]⁺: 286.0243, found: 286.0238.

(*S*)-2-(2-Bromo-5-methoxyphenyl)-4-isopropyl-4,5-dihydrooxazole (S4):²⁹ The crude product was purified by silica-gel column chromatography (hexane/ethyl acetate = 4:1) to give S4 (541 mg, 60%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.48 (d, *J* = 8.8 Hz, 1H), 7.20 (d, *J* = 3.2 Hz, 1H), 6.83 (dd, *J* = 8.8, 3.2 Hz, 1H), 4.47–4.38 (m, 1H), 4.21–4.11 (m, 2H), 3.79 (s, 3H), 1.98–1.83 (m, 1H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 162.6, 158.4, 134.3, 130.6, 117.9, 116.0, 112.0, 72.8, 70.2, 55.5, 32.5, 18.7, 18.1; HRMS (DART) *m*/*z* calcd for C₁₃H₁₇BrNO₂ [M+H]⁺: 298.0443, found: 298.0445.

(*S*)-2-(2-Bromo-5-fluorophenyl)-4-isopropyl-4,5-dihydrooxazole (S5):³⁰ The crude product was purified by silica-gel column chromatography (hexane/ethyl acetate = 10:1 to 5:1) to give S5 (492 mg, 57%) as a colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.42 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.05–6.97 (m, 1H), 4.49–4.40 (m, 1H), 4.21–4.13 (m, 2H), 1.97–1.83 (m, 1H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 161.3 (d, *J*_{FC} = 246 Hz), 161.7, 135.2 (d, *J*_{FC} = 6.0 Hz), 131.5 (d, *J*_{FC} = 9.0 Hz), 118.8 (d, *J*_{FC} = 23 Hz), 118.5 (d, *J*_{FC} = 24 Hz), 116.1 (d, *J*_{FC} = 2.9 Hz), 73.0, 70.5, 32.7, 18.7, 18.2; HRMS (DART) *m*/*z* calcd for C₁₂H₁₄BrFNO [M+H]⁺: 286.0243, found: 286.0243.

(*S*)-2-Ferrocenyl-4-(1-methylethyl)oxazoline (S6):⁵ Following the general procedure with ferrocenecarboxylic acid (690 mg, 3.0 mmol), the crude amide was obtained (659 mg) as a brown solid. In the cyclization, the crude amide (580 mg), *p*-TsCl (456 mg, 2.4 mmol), and NEt₃ (1.3 mL, 9.2 mmol) were used. The crude product was purified by silica-gel column chromatography (hexane/ethyl acetate = 4:1 to 3:1) to give S6 (377 mg, 69%) as a brown solid. ¹H NMR (400 MHz, CDCl₃) δ 4.74 (dd, *J* = 13.8, 1.4 Hz, 2H), 4.34–4.25 (m, 3H), 4.19 (s, 5H),

The Journal of Organic Chemistry

4.07 (t, J = 7.8 Hz, 1H), 4.02–3.95 (m, 1H), 1.93–1.80 (m, 1H), 1.01 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 72.3, 70.13, 70.09, 69.5, 69.3, 69.0, 68.9, 32.3, 18.9, 17.8; HRMS (DART) m/z calcd for C₁₆H₂₀FeNO [M+H]⁺: 298.0894, found: 298.0890.

General Procedure for the Synthesis of L1–L6. To a solution of (*S*)-2-(2-bromophenyl)-4isopropyl-4,5-dihydrooxazole²⁹ (S1: 678 mg, 3.0 mmol) in THF (15 mL) was slowly added *n*-BuLi (1.6 M in hexane, 2.1 mL, 3.3 mmol) at -78 °C under nitrogen atmosphere. After stirring at -78 °C for 1 h, a solution of (1*R*,2*S*,5*R*)-(-)-menthyl (*S*)-*p*-toluenesulfinate (971 mg, 3.3 mmol) in THF (15 mL) was added dropwise, stirred at -78 °C for 30 min, then room temperature for 30 min. To the mixture was added saturated aqueous NH₄Cl and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous Na₂SO₄. The solvent was removed *in vacuo*. The residue was purified by silica-gel column chromatography (hexane/ethyl acetate = 3:1) to give L1 (697 mg, 71%) as a white solid.

(*S*)-4-Isopropyl-2-(2-((*S*)-*p*-tolylsulfinyl)phenyl)-4,5-dihydrooxazole (L1):¹⁹¹H NMR (400 MHz, CDCl₃) δ 8.34 (dd, J = 8.2, 1.4 Hz, 1H), 7.91 (dd, J = 7.8, 1.4 Hz, 1H), 7.75–7.68 (m, 1H), 7.58–7.48 (m, 3H), 7.16 (d, J = 8.2 Hz, 2H), 4.34 (dd, J = 9.2, 7.3 Hz, 1H), 4.15–4.01 (m, 2H), 2.32 (s, 3H), 1.82–1.70 (m, 1H), 0.90 (d, J = 6.8 Hz, 3H), 0.72 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 160.65, 146.19, 143.62, 140.85, 131.79, 130.19, 129.68, 129.47, 126.45, 125.56, 125.28, 73.29, 69.84, 32.44, 21.28, 18.93, 17.85; HRMS (DART) *m*/*z* calcd for C₁₉H₂₂NO₂S [M+H]⁺: 328.1371, found: 328.1373.

(S)-4-Isopropyl-2-(3-methyl-2-((S)-*p*-tolylsulfinyl)phenyl)-4,5-dihydrooxazole (L2): Following the general procedure with (S)-2-(2-bromo-3-methylphenyl)-4-isopropyl-4,5dihydrooxazole (S2: 330 mg, 1.2 mmol), *n*-BuLi (1.6 M in hexane, 0.8 mL, 1.3 mmol), and

(1R,2S,5R)-(-)-menthyl (*S*)-*p*-toluenesulfinate (448 mg, 1.5 mmol), the crude product was purified by silica-gel column chromatography (hexane/ethyl acetate = 5:1) to give **L2** (148 mg, 37%) as a yellow oil. ¹H NMR (600 MHz, CDCl₃) δ 7.63 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 7.2 Hz, 1H), 7.39 (dd, *J* = 7.8, 7.2 Hz, 1H), 7.26–7.20 (m, 3H), 4.46 (t, *J* = 7.8 Hz, 1H), 4.16–4.08 (m, 2H), 2.38 (s, 3H), 2.33 (s, 3H), 1.91–1.81 (m, 1H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 162.2, 141.7, 140.9, 140.5, 139.8, 135.4, 131.0, 130.6, 129.2, 127.1, 125.4, 73.4, 71.1, 32.9, 21.2, 19.0, 18.6, 18.3; HRMS (DART) *m/z* calcd for C₂₀H₂₄NO₂S [M+H]⁺: 342.1528, found: 342.1530.

(*S*)-2-(4-Fluoro-2-((*S*)-*p*-tolylsulfinyl)phenyl)-4-isopropyl-4,5-dihydrooxazole (L3): Following the general procedure with (*S*)-2-(2-bromo-4-fluorophenyl)-4-isopropyl-4,5dihydrooxazole (S3: 400 mg, 1.4 mmol), *n*-BuLi (1.6 M in hexane, 1.0 mL, 1.5 mmol), and (1*R*,2*S*,5*R*)-(-)-menthyl (*S*)-*p*-toluenesulfinate (532 mg, 1.8 mmol), the crude product was purified by silica-gel column chromatography (hexane/ethyl acetate = 2:1) to give L3 (276 mg, 58%) as a white solid. ¹H NMR (600 MHz, CDCl₃) δ 8.08 (dd, *J* = 8.9, 2.8 Hz, 1H), 7.93 (dd, *J* = 8.9, 5.5 Hz, 1H), 7.55 (d, *J* = 8.2 Hz, 2H), 7.20–7.15 (m, 3H), 4.33 (dd, *J* = 9.6, 8.3 Hz, 1H), 4.13–4.07 (m, 1H), 4.04 (t, *J* = 8.2 Hz, 1H), 2.33 (s, 3H), 1.81–1.72 (m, 1H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.71 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 164.9 (d, *J_{FC}* = 256 Hz), 159.9, 149.9 (d, *J_{FC}* = 5.9 Hz), 143.1, 141.2, 132.1 (d, *J_{FC}* = 8.6 Hz), 129.6, 126.5, 121.5 (d, *J_{FC}* = 4.4 Hz), 117.4 (d, *J_{FC}* = 22 Hz), 112.9 (d, *J_{FC}* = 26 Hz), 73.3, 69.8, 32.4, 21.3, 19.0, 17.8; HRMS (DART) *m*/*z* calcd for C₁₉H₂₁FNO₂S [M+H]⁺: 346.1277, found: 346.1279.

(S)-4-Isopropyl-2-(5-methoxy-2-((S)-*p*-tolylsulfinyl)phenyl)-4,5-dihydrooxazole (L4): Following the general procedure with (S)-2-(2-bromo-5-methoxyphenyl)-4-isopropyl-4,5dihydrooxazole (S4: 400 mg, 1.3 mmol), *n*-BuLi (1.6 M in hexane, 0.9 mL, 1.5 mmol), and

 (1R,2S,5R)-(-)-menthyl (*S*)-*p*-toluenesulfinate (513 mg, 1.7 mmol), the crude product was purified by silica-gel column chromatography (hexane/ethyl acetate = 5:1 to 1:1) to give **L4** (210 mg, 44%) as a white solid. ¹H NMR (600 MHz, CDCl₃) δ 8.19 (d, *J* = 9.0 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 2.8 Hz, 1H), 7.20 (dd, *J* = 9.0, 2.8 Hz, 1H), 7.16 (d, *J* = 8.3 Hz, 2H), 4.34 (dd, *J* = 9.7, 7.6 Hz, 1H), 4.13–4.08 (m, 1H), 4.05 (t, *J* = 8.3 Hz, 1H), 3.88 (s, 3H), 2.33 (s, 3H), 1.79–1.71 (m, 1H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.73 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 161.0, 160.5, 144.0, 140.7, 137.1, 129.4, 127.3, 127.0, 126.2, 117.5, 114.7, 73.3, 69.9, 55.7, 32.5, 21.3, 18.9, 17.9; HRMS (DART) *m/z* calcd for C₂₀H₂₄NO₃S [M+H]⁺: 358.1477, found: 358.1481.

(S)-2-(5-Fluoro-2-((S)-p-tolylsulfinyl)phenyl)-4-isopropyl-4,5-dihydrooxazole (L5):

Following the general procedure with (*S*)-2-(2-bromo-5-fluorophenyl)-4-isopropyl-4,5dihydrooxazole (**S5**: 400 mg, 1.4 mmol), *n*-BuLi (1.6 M in hexane, 1.0 mL, 1.5 mmol), and (1R,2S,5R)-(-)-menthyl (*S*)-*p*-toluenesulfinate (532 mg, 1.8 mmol), the crude product was purified by silica-gel column chromatography (hexane/ethyl acetate = 10:1 to 3:1) to give **L5** (93 mg, 19%) as a white solid. ¹H NMR (600 MHz, CDCl₃) δ 8.32 (dd, *J* = 9.0, 6.0 Hz, 1H), 7.61 (dd, *J* = 9.0, 3.0 Hz, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.41–7.37 (m, 1H), 7.17 (d, *J* = 8.4 Hz, 2H), 4.35 (dd, *J* = 9.6, 8.3 Hz, 1H), 4.15–4.10 (m, 1H), 4.06 (t, *J* = 8.3 Hz, 1H), 2.33 (s, 3H), 1.81– 1.72 (m, 1H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.72 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 163.5 (d, *J*_{*FC*} = 253 Hz), 159.7, 143.5, 141.7 (d, *J*_{*FC*} = 2.8 Hz), 141.1, 129.5, 128.0 (d, *J*_{*FC*} = 8.6 Hz), 127.6 (d, *J*_{*FC*} = 8.6 Hz), 126.3, 118.8 (d, *J*_{*FC*} = 22 Hz), 116.8 (d, *J*_{*FC*} = 25 Hz), 73.5, 70.0, 32.4, 21.3, 18.9, 17.8; HRMS (DART) *m*/*z* calcd for C₁₉H₂₁FNO₂S [M+H]⁺: 346.1277, found: 346.1275.

(L6): Following the general procedure with (*S*)-2-ferrocenyl-4-(1-methylethyl)oxazoline (S6: 297 mg, 1.0 mmol), *n*-BuLi (1.6 M in hexane, 0.7 mL, 1.1 mmol), and (1R,2S,5R)-(-)-menthyl (*S*)-*p*-toluenesulfinate (353 mg, 1.2 mmol), the crude product was purified by silica-gel column chromatography (hexane/ethyl acetate = 4:1 to 1:1) to give L6 (158 mg, 36%) as a brown solid. ¹H NMR (600 MHz, CDCl₃) δ 7.83 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 4.95 (s, 1H), 4.42–4.33 (m, 2H), 4.20–4.08 (m, 7H), 3.94 (s, 1H), 2.47 (s, 3H), 1.95–1.87 (m, 1H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (150 MHz, CDCl₃) δ 163.2, 141.5, 140.6, 129.3, 126.0, 94.7, 72.55, 72.52, 72.1, 71.2, 70.7, 70.5, 69.8, 32.4, 21.5, 19.0, 18.0; HRMS (DART) *m*/*z* calcd for C₂₃H₂₆FeNO₂S [M+H]⁺: 436.1034, found: 436.1037.

General Procedure for C–H Coupling of 2,3-dimethyl thiophene (1A) with Hindered Arylboronic Acid (2b). To a screw-cap 20 mL glass vessel containing a magnetic stirring bar were added 2,3-dimethylthiophene (1A: 28 mg, 0.25 mmol), (2-methylnaphthalene-1-yl)boronic acid (2b: 186 mg, 1.0 mmol), Pd(OAc)₂ (5.6 mg, 0.025 mmol), L1 (8.2 mg, 0.025 mmol), FePc (7.1 mg, 0.0125 mmol) and DMF (0.2 mL). The mixture was stirred at 80 °C for 12 h under air, cooled to room temperature, passed through a short pad of silica gel (ethyl acetate) and the filtrate was evaporated under reduced pressure. The residue was purified by preparative thin-layer chromatography (hexane) to give (*S*)-**3Ab** (58 mg, 92%, C4/C5 = 96:4, 29% ee) as a colorless oil. C4/C5 ratio was determined by ¹H NMR. The enantiomeric excess was determined by HPLC with a Chiracel OD-H column, UV detected at 254 nm, flow rate 1.0 mL/min (hexane). Retention times (t_r): major enantiomer $t_r = 11.7$ min, minor enantiomer $t_r = 10.0$ min. According to the literature,¹⁹ the absolute configuration was determined to be of *S*-configuration.

2,3-Dimethyl-4-(2-methylnaphthalen-1-yl)thiophene (**3Ab**):¹⁹ ¹H NMR (400 MHz, CDCl₃) δ7.86–7.73 (m, 2H), 7.44–7.31 (m, 4H), 6.84 (s, 1H), 2.47 (s, 3H), 2.22 (s, 3H), 1.71 (s, 3H).

ASSOCIATED CONTENT

Supporting Information.

Free energies of reaction profiles at the COSMO-DF-SCS-MP2/(aug-)cc-pVTZ(-PP) level of theory, Cartesian coordinates of optimized structures,¹H, ¹³C NMR and HPLC spectra of all compounds described in the experimental section.

AUTHOR INFORMATION

Corresponding Author

*E-mail: <u>sirle@chem.nagoya-u.ac.jp</u>. Phone: +81 (0)52 747-6397.

Present Addresses

[†]Fukui Institute for Fundamental Chemistry, Kyoto University, 34-4 Takano Nishihiraki-cho,

Sakyo-ku, 606-8103, Japan

‡Faculty of Science and Engineering, Waseda University, 3-4-1 Okubo, Shinjuku, Tokyo, 169-8555, Japan

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank Prof. Odile Eisenstein for helpful discussions and the Research Center for Computational Science, Okazaki, Japan, for providing computational resources. Y.N. was supported by a Research Fellowship of the Japan Society for Promotion of Science for Young Scientists (DC1). Y.N. and H.K. thank IGER Program in Green Natural Sciences, Nagoya University for fellowship. S.I. acknowledges partial support by a CREST grant from JST.

REFERENCES

(1) (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* 2010, *110*, 1147-1169. (b) Arockiam, P.;
Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* 2012, *112*, 5879-5918. (c) Yamaguchi, J.; Yamaguchi,
A. D.; Itami, K. *Angew. Chem., Int. Ed.* 2012, *51*, 8960-9009. (d) Jin, T.; Zhao, J.; Asao, N.
Yamamoto, Y. *Chem. Eur. J.* 2014, *20*, 3554-3576. (e) Colby, D. A.; Tsai, A. S.; Bergman, R.
G.; Ellman, J. A. *Acc. Chem. Res.* 2012, *45*, 814-825. (f) Segawa, Y.; Maekawa, T.; Itami, K. *Angew. Chem., Int. Ed.* 2015, *54*, 66-81.

(2) (a) Adamo, C.; Amatore, C.; Ciofini, I;. Jutand, A.; Lakmini. H J. Am. Chem. Soc.
2006, 128, 6829-6836. (b) Sun, C.-L.; Li, B.-J.; Shi Z.-J. Chem. Commun. 2010, 46, 677-685. (c) Liu, C.; Zhang, H.; Shi, W.; Lei, A. Chem. Rev. 2011, 111, 1780-1824. (d) Kirchberg, S.; Tani, S.; Ueda, K.; Yamaguchi, J.; Studer, A.; Itami, K. Angew. Chem., Int. Ed. 2011, 50, 2387-2391.

(3) (a) Sköld, C.; Kleimark, J.; Trejos, A.; Odell, L. R.; Nilsson Lill, S. O.; Norrby, P.-O.;
Larhed, M. *Chem. Eur. J.* 2012, *18*, 4714-4722. (b) Steinmetz, M.; Ueda, K.; Grimme, S.;
Yamaguchi, J.; Kirchberg, S.; Itami, K.; Studer, A. *Chem. Asian J.* 2012, *7*, 1256-1260.

(4) (a) Yang, S.-D.; Sun, C.-L.; Fang, Z.; Li, B.-J.; Shi, Z.-J. Angew. Chem., Int. Ed.
2008, 47, 1473-1476. (b) Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. J. Am. Chem. Soc. 2008, 130, 17676-17677. (c) Wen, J.; Qin, S.; Ma, L.-F.; Dong, L.; Zhang, J.; Liu, S.-S.; Duan, Y.-S.; Chen, S.-Y.; Hu, C.-W.; Yu, X.-Q. Org. Lett. 2010, 12, 2694-2697. (d) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. ChemCatChem 2010, 2, 1403-1406. (e) Ranjit, S.; Liu, X. Chem. Eur. J. 2011, 17, 1105-1108.

(5) Yamaguchi, K.; Kondo, H.; Yamaguchi, J.; Itami, K. Chem. Sci. 2013, 4, 3753-3757.

(6) For recent examples, see: (a) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* 2009, *38*, 3242–3272. (b) Wasa, M.; Engle, K. M.; Lin, D. W.; Yoo, E. J.; Yu, J.-Q. *J. Am. Chem. Soc.* 2011, *133*, 19598–19601. (c) Xiao, K.-J.; Lin, D. W.; Miura, M.; Zhu, R.-Y.; Gong, W.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* 2014, *136*, 8138–8142. (d) Chan, K. S. L.; Fu, H.-Y.; Yu, J.-Q. *J. Am. Chem. Soc.* 2015, *137*, 2042–2046. (e) Laforteza, B. N.; Chan, K. S. L.; Yu, J.-Q. *Angew. Chem. Int. Ed.* 2015, *54*, 11143–11146. (f) Chen, G.; Gong, W.; Zhuang, Z.; Andrä, M. S.; Chen, Y.-Q.; Hong, X.; Yang, Y.-F.; Liu, T.; Houk, K. N.; Yu, J.-Q. *Science* 2016, *353*, 1023–1027.

(7) (a) Hohenberg, P.; Kohn, W. *Phys. Rev.* **1964**, *136*, B864-B871. (b) Hohenberg, P.; Kohn, W. *Phys. Rev.* **1965**, *140*, A1133-A1138.

(8) Gaussian 09, Revision C.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. Gaussian, Inc., Wallingford CT, 2009.

(9) (a) Becke, A. D. J. Chem. Phys. 1993, 98, 5648-5652. (b) Becke, A. D. Phys. Rev. A
1988, 38, 3098-3100. (c) Perdew, J. P.; Chevary, A.; Vosko. S. H.; Jackson, K. A.; Pederson, M. R.; Singh, D. J.; Fiolhais, C. Phys. Rev. B 1992, 46, 6671-6687. (d) Perdew, J. P.; Wang, Y. Phys. Rev. B 1992, 45, 13244-13249.

(10) (a) Hehre, W. J.; Ditchfield, R.; Pople, J. A. 1972, *56*, 2257-2261. (b) Hariharan, P.
C.; Pople, J. A. *Theoret. Chim. Acta.* 1973, *18*, 213-222. (c) Gordon, M. S.; Binkley, J. S.; Pople,
J. A.; Pietro, W. J.; Hehre, W. J. *J. Am. Chem. Soc.* 1982, *104*, 2797-2803. (d) Francl, M. M.;

Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; Defrees, D. J.; Pople, J. A. *J. Chem. Phys.* **1982**, *77*, 3654-3665. (e) Hay, P. J.; Wadt, W. R. *J. Chem. Phys.* **1985**, *82*, 299-310.

(11) (a) Fukui, K. Acc. Chem. Res. 1981, 14, 363-368. (b) Hratchian, H. P.; Schlegel, H.
B. Finding Minima, Transition States, and Following Reaction Pathways on Ab Initio Potential Energy Surfaces. In *Theory and Applications of Computational Chemistry: The First 40 Years*; Dykstra, C. E., Frenking, G., Kim, K. S., Scuseria, G. E., Eds.; Elsevier. Amsterdam, 2005; pp 195-249. (c) Page, M.; McIver Jr., J. W. J. Chem. Phys. 1988, 88, 922-935. (d) Page, M.; Doubleday Jr., C.; McIver Jr., J. W. J. Chem. Phys. 1990, 93, 5634-5642.

(12) (a) Dunning Jr. T. H. J. Chem. Phys. 1989, 90, 1007-1023. (b) Kendall, R. A.;
Dunning Jr. T. H.; Harrison, R. J. J. Chem. Phys. 1992, 96, 6796-6806. (c) Woon, D. E.;
Dunning Jr. T. H. J. Chem. Phys. 1993, 93, 1358-1371. (d) Peterson, K. A.; Figgen, D.; Dolg,
M.; Stoll, H. J. Chem. Phys. 2007, 126, 124101.

(13) (a) Grimme, S. J. Chem. Phys. 2003, 118, 9095-9102. (b) Gerenkamp, M.; Grimme,
S. Chem. Phys. Lett. 2004, 391, 229-235.

(14) (a) Werner, H.-J.; Knowles, P. J.; Knizia, G.; Manby, F. R.; Schütz, M. *WIREs Comput. Mol. Sci.* 2012, *2*, 242-253. (b) MOLPRO, version 2012. 1, a package of ab initio
programs, Werner, H.-J.; Knowles, P. J.; Knizia, G.; Manby, F. R.; Schütz, M.; Celani, P.;
Korona, T.; Lindh, R.; Mitrushenkov, A.; Rauhut, G.; Shamasundar, K. R.; Adler, T. B.; Amos,
R. D.; Bernhardsson, A.; Berning, A.; Cooper, D. L.; Deegan, M. J. O.; Dobbyn, A. J.; Eckert,
F.; Goll, E.; Hampel, C.; Hesselmann, A.; Hetzer, G.; Hrenar, T.; Jansen, G.; Köppl, C.; Liu, Y.;
Lloyd, A. W.; Mata, R. A.; May, A. J.; McNicholas, S. J.; Meyer, W.; Mura, M. E.; Nicklass, A.;
O'Neill, D. P.; Palmieri, P.; Peng, D.; Pflüger, K.; Pitzer, R.; Reiher, M.; Shiozaki, T.; Stoll, H.;

(15) Werner, H. J.; Manby, F. R.; Knowles, P. J. J. Chem. Phys. 2003, 118, 8149-8160.

(16) (a) Weigend, F.; Köhn, A.; Hättig, C. J. Chem. Phys. **2002**, *116*, 3175-3183. (b) Weigend, F.; Häser, M.; Patzelt, H.; Ahlrichs, R. Chem. Phys. Lett. **1998**, 294, 143-152.

(17) Klamt, A.; Schüürmann, G. J. Chem. Soc., Perkin Trans. 2 1993, 5, 799-805.

The Journal of Organic Chemistry

2 3 4 5 6 7 8	(18) Maren 6396. (19) Yamag
9 10 11 12 13	(20) Bäckv Am. Chem. Soc. 19
14 15 16 17 18	(21) (a) Tsı Jiang, N.; Xia, D. J
19 20 21 22 23	(22) (a) Go 10849. (b) Balcells
24 25 26	(23) Feldma
20 27 28 29 30	(24) Glende 42.
31 32 33 34 35 36 37 38 39 40 41 42 43 44 546 47 48 49 50 51 52 53 54 55 56 57 58 59	(25) (a) Ala <i>I</i> , 109-141. (b) Arc Denehy, E.; White Basso, E. A.; Contr Stewart, P. S.; Che (26) Camm (27) Bower (28) Hu, Z. (29) Armstr K.; Nelson, N. C.; T
59 60	

(18) Marenich, A.V.; Cramer, C. J.; Truhlar, D. G. J. Phys. Chem. B 2009, 113, 6378-3396.

(19) Yamaguchi, K.; Yamaguchi, J.; Studer, A.; Itami, K. Chem. Sci. 2012, 3, 2165-2169.

(20) Bäckvall, J.-E.; Hopkins, R. B.; Grennberg, H.; Mader, M. M.; Awasthi, A. K. J. *Am. Chem. Soc.* **1990**, *112*, 5160-5166.

(21) (a) Tsuda, M.; Dy, E. S.; Kasai, H. J. Chem. Phys. **2005**, 122, 244719. (b) Sun, S.; Jiang, N.; Xia, D. J. Phys. Chem. C **2011**, 115, 9511-9517.

(22) (a) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. J. Am. Chem. Soc. 2008, 130, 1084810849. (b) Balcells, D.; Clot, E.; Eisenstein, O. Chem. Rev. 2010, 110, 749-823.

(23) Feldman, D.; Rabinovitz, M. J. Org. Chem. 1988, 53, 3779-3784.

(24) Glendening, E. D.; Landis, C. R.; Weinhold, F. WIREs Comput. Mol. Sci. 2012, 2, 1-42.

(25) (a) Alabugin, I. V.; Gilmore, K. M.; Peterson, P. W. WIREs Comput. Mol. Sci. 2011,

1, 109-141. (b) Ardura, D.; López, R.; Sordo, T. L. J. Org. Chem. 2006, 71, 7315-7321. (c)

Denehy, E.; White, J. M.; Williams, S. J. Inorg. Chem. 2007, 46, 8871-8886. (d) Gauze, G. F.;

Basso, E. A.; Contreras, R. H.; Tormena, C. F. J. Phys. Chem. A 2009, 113, 3647-2651. (e)

Stewart, P. S.; Chen, M.; Roush, W. R.; Ess, D. H. Org. Lett. 2011, 13, 1478-1481.

(26) Cammidge, A. N.; Crépy, K. V. L. Tetrahedron 2004, 60, 4377-4386.

(27) Bower, J. F.; Williams, J. M. J. Tetrahedron Lett. 1994, 35, 7111-7114.

(28) Hu, Z.; Li, Y.; Liu, K.; Shen, Q. J. Org. Chem. 2012, 77, 7957-7967.

(29) Armstrong, P. B.; Dembicer, E. A.; DesBois, A. J.; Fitzgerald, J. T.; Gehrmann, J.

K.; Nelson, N. C.; Noble, A. L.; Bunt, R. C. Organometallics 2012, 31, 6933-6946.

(30) Picktett, T. E.; Roca, F. X.; Richards, C. J. J. Org. Chem. 2003, 68, 2592-2599.