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Rhodium(I)-Catalyzed Addition of Arylboronic Acids to (Benzyl-/Arylsulfonyl)acetonitriles: Efficient Synthesis of (*Z*)-*β*-Sulfonylvinylamines and *β*-Keto Sulfones

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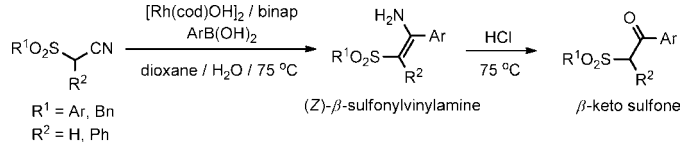
ABSTRACT



An efficient rhodium(I)-catalyzed addition of arylboronic acids to (benzyl-/arylsulfonyl)acetonitrile is described. Novel *β*-sulfonylvinylamine products are formed in a stereoselective fashion (*Z*-alkene). Upon hydrolysis, useful *β*-keto sulfones are obtained with a broad scope of aryl and sulfonyl substituents.

The insertion of carbon−heteroatom multiple bonds into carbon−transition metal bonds is an important carbon−carbon bond forming process.[1] Compared to main group organometallics such as organolithium and organomagnesium, organometallic compounds of late transition metals are generally less nucleophilic toward polar multiple bonds such as a nitrile group. Palladium and nickel complexes have been successfully employed to catalyze intra- and intermolecular addition reactions of nitriles in the synthesis of useful carbocycle, aryl ketone, and ketimine products.[2,3]

In recent years, rhodium(I)-catalyzed carbon−carbon bond forming reactions using organoboron reagents have emerged as powerful synthetic methods.[4] As part of an ongoing effort in developing novel rhodium-catalyzed addition reactions, we set out to explore the potential of rhodium-catalyzed addition of arylboronic acids to a nitrile group, which is usually more challenging than an aldehydic carbonyl group.[5] Literature examples of insertion of nitriles to carbon−rhodium bonds are mostly limited to intramolecular processes.[6] A few examples of rhodium(I)-catalyzed intermolecular additions of organoboron reagents to nitriles are known; however, the

(1) For reviews, see: (a) Tsuji, J. *Transition Metal Reagents and Catalysts*; Wiley: New York, 2004. (b) Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, Germany, 1998. (c) de Meijere, A.; Diederich, F. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; John Wiley & Sons: Weinheim, Germany, 2004.

(2) Palladium-catalyzed reactions: (a) Larock, R. C.; Tian, Q.; Pletnev, A. A. *J. Am. Chem. Soc.* **1999**, *121*, 3238. (b) Pletnev, A. A.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 2133. (c) Pletnev, A. A.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9276. (d) Zhou, C.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 2302. (e) Zhou, C.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3551. (f) Zhao, L.; Lu, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4343. (g) Zhao, B.; Lu, X. *Tetrahedron Lett.* **2006**, *47*, 6765. (h) Zhao, B.; Lu, X. *Org. Lett.* **2006**, *8*, 5987.

(3) Nickel-catalyzed reaction: Wong, Y.-C.; Parthasarathy, K.; Cheng, C.-H. *Org. Lett.* **2010**, *12*, 1736.

(4) For reviews on Rh-catalyzed C−C bond formations, see: (a) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (b) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829. (c) *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH: Weinheim, Germany, 2005. (d) Miura, T.; Murakami, M. *Chem. Commun.* **2007**, 217. (e) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013. (f) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624.

(5) Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 3279. In this Rh-catalyzed addition of phenylboronic acid to 4-cyanobenzaldehyde, the cyano group remains intact while the secondary alcohol product is formed via addition to the aldehyde group in high yield.

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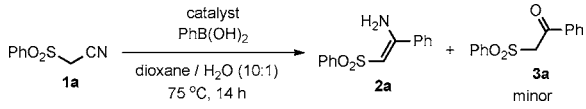
substrate scope is usually limited to aromatic nitriles and cyanoformate.[7]

We identified (phenylsulfonyl)acetonitrile **1a**, a commercially available material, as a suitable substrate. Successful addition of alkyl nitrile would extend the substrate scope in rhodium-catalyzed addition reactions. The potential product from the reaction, β-keto sulfones, has shown widespread synthetic applications such as in the synthesis of acetylenes,[8a] olefins,[8b] allenes,[8c] vinyl sulfones,[8d] and optically active β-hydroxy sulfones.[8e] Besides the versatility demonstrated by sulfones in organic synthesis,[9] we envision that the sulfone group may also play a role in activating the nitrile moiety toward the addition process.[10]

We began our investigation by screening various rhodium catalysts in the addition reactions of phenylboronic acid with **1a** using dioxane/water as solvent (Table 1). Using commercially available $[Rh(cod)OH]_2$ without added ligand gave very low yield (entry 3). Monodentate phosphine ligand PPh_3 gave no desired product (entry 2), but bidentate ligands afforded better yields (entries 5−8). To our surprise, the expected β-keto sulfone product **3a** was found to be a minor product under the reaction conditions. The major product was identified as a rather unusual β-sulfonylvinylamine **2a** (an enamine), which was formed via tautomerization of the initially formed ketimine product (not observed). The best yield was obtained with BINAP ligand (entry 9), and products **2a** and **3a** (inseparable mixture) can be isolated in 90% yield in 7:1 ratio. Using $[Rh(cod)Cl]_2$ as the precatalyst (entry 4) and catalyst-free conditions (entry 1) proved to be ineffective. A solvent screen showed dioxane as most effective (see the Supporting Information). A small amount of added water was important to obtain good yields. An excess of boronic acid was necessary to compensate for the competing hydrolytic deboronation process.[4a]

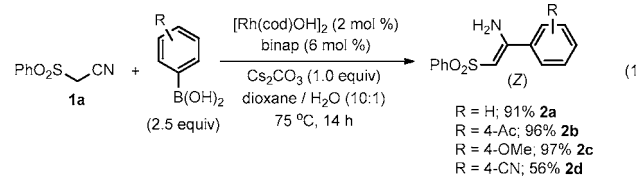
Table 1. Catalyst Screening for the Addition of Phenylboronic Acid to (Phenylsulfonyl)acetonitrile **1a**[a]



entry	catalyst	yield of **2a** + **3a** (%)[b]
1		0
2	$[Rh(PPh_3)OH]_2$	0
3	$[Rh(cod)OH]_2$	5
4	$[Rh(binap)Cl]_2$	6
5	$[Rh(dppp)OH]_2$	31
6	$[Rh(dppb)OH]_2$	38
7	$[Rh(dppf)OH]_2$	50
8	$[Rh(biphep)OH]_2$	72
9	$[Rh(binap)OH]_2$	90[c]

[a] All reactions were carried out with nitrile **1a** (0.2 mmol), boronic acid (0.5 mmol), catalyst (4 mol % Rh), dioxane (2 mL), and H_2O (0.2 mL) at 75 °C for 14 h under argon. [b] Unless specified otherwise, the yield was measured by ^1H NMR (400 MHz) of the crude material, using mesitylene as an internal standard. [c] Isolated yield of **2a** + **3a** (7:1) by flash column chromatography on silica gel with hexanes/ethyl acetate/1% Et_3N as eluent solvents.

Adding 1 equiv of Cs_2CO_3 to the reaction led to a drastic change in the product distribution (eq 1):



only the β-sulfonylvinylamine products **2** were observed. It is conceivable that adding a base will enhance the enamine formation by facilitating deprotonation of the initially formed imine. Electron-poor and -rich arylboronic acids both afforded the products **2b**,**c** in excellent yields (96−97%). 4-Cyanophenylboronic acid gave product **2d** in a lower yield (56%) due to incomplete conversion (30% starting material recovery); however, a second addition to the nitrile group in the product was not observed. This chemoselectivity is quite unusual considering most of the literature examples involve the addition to aromatic nitriles.[7] Products **2a**−**d** can be conveniently isolated by flash column chromatography on silica gel using hexanes/ethyl acetate/1% Et_3N as eluent solvents.[11] X-ray crystallographic analysis of **2b** unambiguously confirmed the identity of the β-sulfonylvinylamine product (Figure 1a). Intriguingly, the enamine has a *Z*-alkene geometry, presumably due to a stabilizing intramolecular hydrogen bonding between the amine and sulfone groups (Figure 1b).

Although several *N*-substituted β-sulfonylenamines and β-iminosulfones have been reported,[12] the synthesis of the parent β-sulfonylvinylamines has only been described by reduction of (*p*-tolylsulfonyl)acetonitrile with $LiAlH_4$ (*E*-alkene).[13] To the best of our knowledge, this is the first description of transition metal-catalyzed stereoselective (*Z*-selective) synthesis of β-sulfonylvinylamines.

(6) (a) Miura, T.; Nakazawa, H.; Murakami, M. *Chem. Commun.* **2005**, 2855. (b) Miura, T.; Murakami, M. *Org. Lett.* **2005**, *7*, 3339. (c) Miura, T.; Harumashi, T.; Murakami, M. *Org. Lett.* **2007**, *9*, 741.

(7) (a) Ueura, K.; Miyamura, S.; Satoh, T.; Miura, M. *J. Organomet. Chem.* **2006**, *691*, 2821. (b) Ueura, K.; Satoh, T.; Miura, M. *Org. Lett.* **2005**, *7*, 2229. (c) Shimizu, H.; Murakami, M. *Chem. Commun.* **2007**, 2855.

(8) Applications of β-keto sulfones: (a) Bartlett, P. A.; Green, F. R., III; Rose, E. H. *J. Am. Chem. Soc.* **1978**, *100*, 4852. (b) Ihara, M.; Suzuki, S.; Taniguchi, T.; Tokunaga, Y.; Fukumoto, K. *Tetrahedron* **1995**, *51*, 9873. (c) Baldwin, J. E.; Adlington, R. M.; Crouch, N. P.; Hill, R. L.; Laffey, T. G. *Tetrahedron Lett.* **1995**, *36*, 7925. (d) Sengupta, S.; Sarma, D. S.; Mondal, S. *Tetrahedron: Asymmetry* **1998**, *9*, 2311. (e) Svatos, A.; Hunkova, Z.; Kren, V.; Hoskovec, M.; Saman, D.; Valterova, I.; Vrkoc, J.; Koutek, B. *Tetrahedron: Asymmetry* **1996**, *7*, 1285.

(9) For descriptions of sulfone chemistry, see: (a) El-Awa, A.; Noshi, M. N.; Mollat du Jourdin, X.; Fuchs, P. L. *Chem. Rev.* **2009**, *109*, 2315. (b) Trost, B. M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 107. (c) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press, Oxford, UK, 1993; (d) Patai, S.; Rappoport, Z.; Stirling, C., Eds. *The Chemistry of Sulphones and Sulphoxides*; Wiley: Chichester, UK, 1988.

(10) We have observed activating/directing effects of the sulfone group in Rh(I)-catalyzed addition of arylboronic acids to allyl sulfones: Tsui, G. C.; Lautens, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8938.

(11) Without 1% Et_3N, product **2a** slightly hydrolyzed on column to form a small amount of **3a** (**2a**:**3a** = 20:1).

(12) (a) Stirling, C. J. M. *J. Chem. Soc.* **1964**, 5863. (b) Truce, W. E.; Brady, D. G. *J. Org. Chem.* **1966**, *31*, 3543. (c) Muraoka, M.; Yamamoto, T.; Ebisawa, T.; Kobayashi, W.; Takeshima, T. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1017.

(13) Feringa, B. L. *J. Chem. Soc., Chem. Commun.* **1985**, 466.

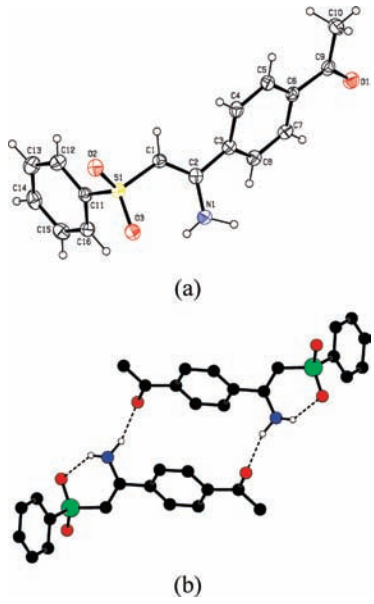
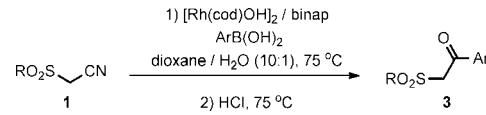


Figure 1. (a) The molecular structure of **2b** showing 30% displacement ellipsoids. (b) A pair of molecules of **2b** showing hydrogen bonds as dashed lines. Only H atoms involved in hydrogen bonds are shown.

The scope of the reaction was studied in a one-pot, two-step sequence (catalytic reaction followed by hydrolysis), by which the β-sulfonylvinylamine products **2** underwent facile hydrolysis to form useful β-keto sulfone products **3** (Table 2). Good to excellent yields were obtained when (phenylsulfonyl)acetonitrile **1a** was reacted with various arylboronic acids (entries 1−11). Electron-poor/-rich and sterically hindered groups all gave good yields, though *o*-carbonyl arylboronic acids were unreactive (see footnote d, Table 2). Sensitive groups such as chloride and sulfide were tolerated (entries 4 and 5). Furthermore, a heteroaromatic 3-thienyl group also afforded the product in good yield (entry 11). Most of the reactions were run for 14 h; however, some only required 2.5 h (entries 4−9). The scope of the substituent (R) in the sulfonyl moiety was also studied (entries 12−18). Substrates **1b**−**h** were synthesized from the corresponding thiols (see the Supporting Information). The aromatic substituents (electron-poor/-rich and sterically hindered) all led to excellent yields of products **3k**−**p**. However, *o*-halo-substituted aromatic groups severely hindered the reactions (see footnote f, Table 2). The reaction was not limited to aromatic substituents, a benzyl group also gave the product in an excellent yield (entry 18). Unfortunately, the synthetically useful benzothiazolyl group[14] did not lead to product formation, only unreacted starting material was observed.[15]

(14) For applications of heteroaromatic sulfones, see: (a) Baudin, J. B.; Hareau, G.; Julia, S. A.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 336. (b) Baudin, J. B.; Hareau, G.; Julia, S. A.; Lorne, R.; Ruel, O. *Bull. Soc. Chim. Fr.* **1993**, *130*, 856. (c) Kocienski, P. J.; Bell, A.; Blakemore, P. R. *Synlett* **2000**, 365.

Table 2. Scope of Arylboronic Acid and the Sulfonyl Substituent Group of Nitrile **1** in the Synthesis of β-Aryl Keto Sulfones **3**[a]



entry	R	Ar	yield (%)[b]	product
1	C_6H_5 **1a**	C_6H_5	97	**3a**
2	C_6H_5 **1a**	4-AcC_6H_4	97	**3b**
3	C_6H_5 **1a**	4-$OMeC_6H_4$	95	**3c**
4[c]	C_6H_5 **1a**	4-ClC_6H_4	92	**3d**
5[c]	C_6H_5 **1a**	4-$SMeC_6H_4$	86	**3e**
6[c]	C_6H_5 **1a**	3-AcC_6H_4	92	**3f**
7[c]	C_6H_5 **1a**	3-$OMeC_6H_4$	98	**3g**
8[c,d]	C_6H_5 **1a**	2-MeC_6H_4	89	**3h**
9[c]	C_6H_5 **1a**	1-naphthyl	94	**3i**
11[e]	C_6H_5 **1a**	3-thienyl	83	**3j**
12	4-$CF_3C_6H_4$ **1b**	C_6H_5	91	**3k**
13	4-$OMeC_6H_4$ **1c**	C_6H_5	99	***3l***
14	4-FC_6H_4 **1d**	C_6H_5	96	**3m**
15	3-$OMeC_6H_4$ **1e**	C_6H_5	93	**3n**
16[f]	2-MeC_6H_4 **1f**	C_6H_5	97	**3o**
17	1-naphthyl **1g**	C_6H_5	98	**3p**
18	Bn **1h**	C_6H_5	98	**3q**

[a] Unless specified otherwise, the catalytic reactions were carried out with nitrile **1** (0.32 mmol), boronic acid (0.8 mmol), $[Rh(cod)OH]_2$ (2 mol %), binap (6 mol %), dioxane (2.5 mL), and H_2O (0.25 mL) at 75 °C for 14 h under argon. The subsequent hydrolysis was carried out with 1 M aqueous HCl at 75 °C for 3 h. [b] Isolated yield. [c] The catalytic reactions were run for 2.5 h. [d] 2-Formyl and 2-acetylphenylboronic acids were unreactive. [e] The product was inseparable from a small amount of unreacted starting material **1a** (6.7:1 ratio); product = 83%, starting material recovery = 12%. [f] No desired products were obtained with R = 2-BrC_6H_4 and 2-ClC_6H_4.

A variety of methods to prepare β-keto sulfones have been reported,[16] but our protocol offers a new, efficient, and mild route to access a large array of aryl-substituted β-keto sulfones. β-Keto sulfone derivatives have exhibited fungicidal activities,[17] and some have recently shown therapeutic potential for metabolic syndrome and type 2 diabetes.[18]

An α-phenyl-substituted substrate **4** was prepared from a literature procedure,[19] and subjected to the catalytic reaction conditions (eq 2). Fortunately, the α-substituent did not impede the reaction, affording the 1,2-diaryl alkene products

(15) Similar results were observed in our studies of additions to allyl sulfones (ref 10) using the same catalyst. The benzothiazolyl sulfone gave poor conversion, possibly due to poisoning of the rhodium catalyst. The phenyltetrazolyl sulfone led to decomposition under the reaction conditions.

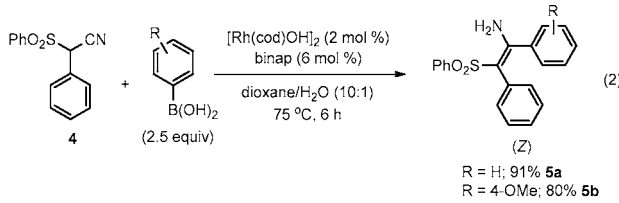
(16) For selected recent reports, see: (a) Qian, H.; Huang, X. *Synthesis* **2006**, 1934. (b) Suryakiran, N.; Reddy, T. S.; Ashalatha, K.; Lakshman, M.; Venkateswarlu, Y. *Tetrahedron Lett.* **2006**, *47*, 3853. (c) Kumar, D.; Sundaree, S.; Rao, V. S.; Varma, R. S. *Tetrahedron Lett.* **2006**, *47*, 4197. (d) Lai, C.; Xi, C.; Jiang, Y.; Hua, R. *Tetrahedron Lett.* **2005**, *46*, 513.

(17) Wolf, W. M. *J. Mol. Struct.* **1999**, *474*, 113.

(18) Xiang, J.; Ipek, M.; Suri, V.; Tam, M.; Xing, Y.; Huang, N.; Zhang, Y.; Tobin, J.; Mansour, T. S.; McKew, J. *Bioorg. Med. Chem.* **2007**, *15*, 4396.

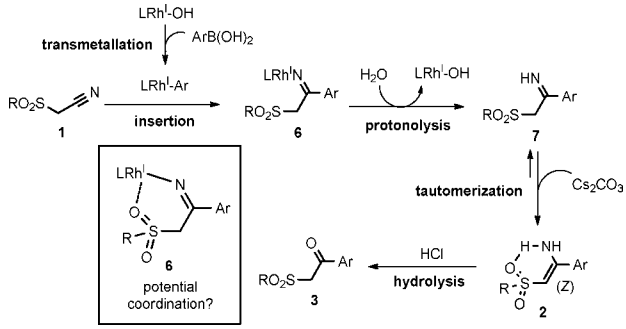
(19) Sakamoto, T.; Katoh, E.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1990**, *38*, 1513.

5a,**b** in high yields with (*Z*)-selectivity.[20] Conversions were complete in only 6 h without added base. On the other hand, α,α-dimethylated and α,α-diarylated (Ar = 4-AcC_6H_4) analogues failed to react.



The proposed mechanism is shown in Scheme 1. A rhodium-aryl species is generated from transmetalation

Scheme 1. Proposed Mechanism of Rh(I)-Catalyzed Addition of Arylboronic Acids to Nitrile **1**



between rhodium hydroxide and arylboronic acid. The insertion of the nitrile group into rhodium−aryl bond leads to imino-rhodium species **6**. The sulfone oxygen may coordinate to the rhodium to form a stabilized six-membered rhodacycle. Protonolysis regenerates the rhodium catalyst and forms imine product **7**. In the presence of a base, the imine product quickly tautomerizes to form the more favored enamine product **2**. The driving force and (*Z*)-alkene selectivity are likely due to a stabilizing intramolecular hydrogen bonding between the amine and sulfone groups. Sterics between the sulfonyl and aryl groups may also play a role in the (*Z*)-selectivity. However, the fact that the 1,2-diaryl alkene products **5a**,**b** were also formed in a (*Z*)-selective fashion (eq 2) implied that the steric effects of the substituents alone do not explain the stereoselectivity. The presence of an α-proton in **7** is necessary for the enamine formation, but an α,α-disubstituted substrate should at least lead to the imine formation, which would give the ketone product upon hydrolysis. Instead, we observed no reactions with these substrates. Significantly increased steric demands of the α,α-disubstituted substrates may have hindered the insertion process. Finally, product **2** can be isolated or hydrolyzed as desired to afford β-keto sulfone product **3**.

To gain more insight on the role of the sulfone group, several other substrates were tested (Figure 2). No reactivity

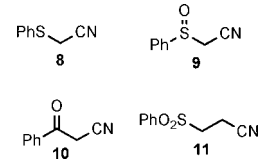


Figure 2. Unreactive substrates.

was observed with sulfide **8** and sulfoxide **9**. Benzoylacetonitrile **10** gave no conversion, despite having an electron-withdrawing and potentially coordinating group. Furthermore, substrate **11** (a homologue of **1a**) also gave no desired product. These observations seem to support the hypothesis of the unique stabilizing/coordinating ability of the sulfone group at the α-position to the nitrile moiety.

In conclusion, we have developed an efficient rhodium(I)-catalyzed addition of arylboronic acids to (benzyl-/arylsulfonyl)acetonitriles **1**. Novel β-sulfonylvinylamine products **2** were synthesized in a stereoselective fashion (*Z*-alkene). Upon hydrolysis, useful β-keo sulfone products **3** were formed with a broad scope of aryl and sulfonyl substituent groups. The synthetic utility of the enamine products **2** and **5** is currently being explored.

Acknowledgment. We thank NSERC, Merck Frosst Canada, and the University of Toronto for support of our program. We also thank Dr. Alan Lough (University of Toronto) for X-ray analysis.

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

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(20) X-ray crystal structure of **5b** confirmed the *Z*-alkene geometry (see the Supporting Information).