

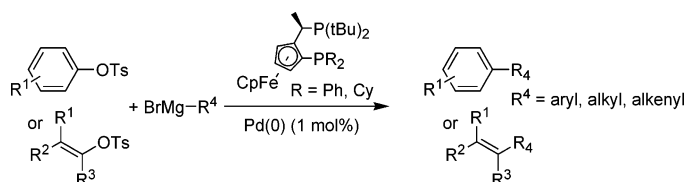
Kumada Coupling of Aryl and Vinyl Tosylates under Mild Conditions

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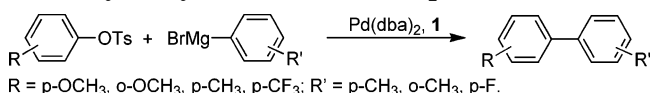


Aryl and alkenyl tosylates are easily prepared, inexpensive and, thus, attractive for transition-metal-catalyzed couplings, but their reactivity is low. We report examples of mild, palladium-catalyzed coupling of aryl, alkenyl, and alkyl Grignard reagents with aryl and alkenyl tosylates. The resulting biaryls, vinylarenes, and alkylarenes were isolated in good to excellent yield. These couplings were conducted with a nearly equimolar ratio of the two reactants, and many examples were conducted at room temperature.

Introduction

Transition-metal-catalyzed cross-coupling reactions have become a common synthetic procedure for the synthesis of organic compounds with sp^2 - sp^2 linkages.¹⁻³ Aryl bromides, chlorides, and triflates are used most commonly for the synthesis of substituted arenes, including biphenyls and vinylarenes.⁴⁻¹² Aryl and vinyl tosylates would be useful as electrophiles for cross-coupling chemistry because they can be prepared easily from phenols or ketones with reagents that are less expensive than those used to prepare aryl and vinyl triflates. Further, aryl and vinyl tosylates are more convenient to use because they are more stable to water than triflates and are highly crystalline. However, this greater stability of the tosylates makes them less reactive in palladium-catalyzed processes. Couplings of aryl tosylates with nickel,¹³⁻¹⁷ copper,¹⁸ and palladium¹⁹⁻²³ are

SCHEME 1. Coupling of Aryl Grignard Reagents with Aryl Tosylates at Room Temperature



now known. The mildest C-C coupling reported with an aryl tosylate occurred with boronic acids at room temperature with the combination of $Ni(COD)_2$ and PCy_3 .¹⁶

Because boronic acids are usually derived from Grignard reagents, Kumada couplings offer a more direct approach to the synthesis of biaryls when the substrates tolerate the background reactivity of a Grignard reagent. For this reason, interest in the coupling of organomagnesium reagents has been renewed in recent years.²⁴⁻³⁰

(1) Diederich, F.; P, S. *Metal-catalyzed cross coupling reactions*; Wiley-VCH: Weinheim, 1998.

(2) Miyaura, N. *Cross-Coupling Reactions: a Practical Guide*; Topics in Current Chemistry; Springer-Verlag: New York, 2002; Vol. 219.

(3) de Meijere, A.; Diederich, F. *Metal-catalyzed Cross-Coupling Reactions*, 2nd ed.; Wiley-VCH: Weinheim, 2004.

(4) Heck, R. F.; Nolley, J. P. *J. Org. Chem.* **1972**, *37*, 2320.

(5) Biffis, A.; Zecca, M.; Basato, M. *J. Mol. Catal. A* **2001**, *173*, 249.

(6) Beletskaya, I., P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009.

(7) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(8) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11.

(9) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.

(10) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

(11) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

(12) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374.

(13) Kobayashi, Y.; Mizojiri, R. *Tetrahedron Lett.* **1996**, *37*, 8531.

(14) Bolm, C.; Hildebrand, J. P.; Rudolph, J. *Synthesis* **2000**, 911.

(15) Zim, D.; Lando, V. R.; Dupont, J.; Monteiro, A. L. *Org. Lett.* **2001**, *3*, 3049.

(16) Tang, Z. Y.; Hu, Q. S. *J. Am. Chem. Soc.* **2004**, *126*, 3058.

(17) Percec, V.; Golding, G. M.; Smidrcal, J.; Weichold, O. *J. Org. Chem.* **2004**, *69*, 3447.

(18) Erdik, E.; Eroglu, F. *Synth. React. Inorg. Met.-Org. Chem.* **2000**, *30*, 955.

(19) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369.

(20) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473.

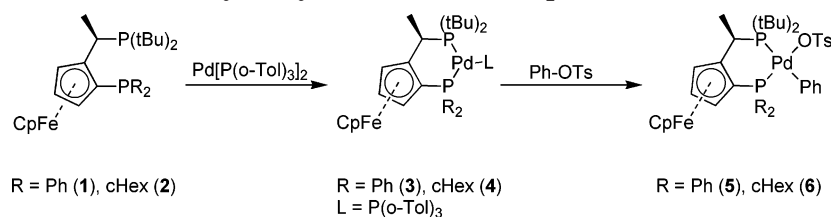
(21) Kubota, Y.; Nakada, S.; Sugi, Y. *Synlett* **1998**, 183.

(22) Huang, X. H.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.

(23) Nguyen, H. N.; Huang, X. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818.

(24) Korn, T. J.; Cahiez, G.; Knochel, P. *Synlett* **2003**, 1892.

SCHEME 2. Oxidative Addition of Aryl Tosylates at Room Temperature



Despite this renewed interest, the palladium-catalyzed coupling of organomagnesium reagents with unactivated aryl tosylates has not been reported outside of our previously communicated work.³¹

Progress has been made during the last several years on the coupling of aryl and alkyl halides with sp^3 carbon nucleophiles.^{26,27,32–35} Fürstner et al. developed an iron-catalyzed Kumada coupling of aryl chlorides and activated aryl and heteroaryl tosylates with alkylmagnesium chlorides.^{32,36} A similar process based on cobalt and an iron-catalyzed coupling of aryl Grignard reagents with vinyl halides were published by Knochel and co-workers.^{24,37} Yet, few couplings of aryl tosylates with alkyl Grignard reagents have been reported,³² and no coupling of unactivated aryl tosylates²³ with alkyl Grignard reagents has been reported.

Several years ago, we reported that palladium complexes of a bulky, electron-rich Josiphos ligand³⁸ catalyze the coupling of aryl tosylates with amines¹⁹ and with ketone enolates.²⁰ More recently, we communicated that palladium complexes of a bis-dialkylphosphino analogue of the Josiphos ligand used in the original work catalyzed the coupling of aryl tosylates with amines and aryl Grignard reagents (Scheme 1) at room temperature.³¹ Moreover, we showed that oxidative addition of aryl tosylates to complexes **3** and **4** in Scheme 2 occurred at room temperature to generate isolable arylpalladium tosylate complexes.

We now report a full set of studies on the coupling of Grignard reagents with aryl and vinyl tosylates.³⁹ We report several improvements in the reaction procedures and an increase in the reaction scope. We developed conditions to conduct the couplings without an excess of Grignard reagent, conditions to conduct reactions of alkyl and benzylic Grignard reagents with unactivated aryl

tosylates, and conditions for the coupling of a series of Grignard reagents with unactivated vinyl tosylates.

Results and Discussion

We first sought conditions to decrease the amount of Grignard reagent and to reduce the amount of biaryl produced from homocoupling of the Grignard reagent. To probe the effect of varying several reaction parameters, we studied the coupling of *p*-tolyl tosylate with *p*-fluorophenylmagnesium bromide at room temperature in toluene catalyzed by the combination of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ and **1**. This reaction occurred under our original conditions in 70% yield. After testing various palladium precursors and solvents, we found that reducing the reagent concentrations from 0.50 to 0.25 M led to a decrease in the amount of biaryl from homocoupling of the Grignard reagent to between 5% and 10%. As a result, the cross-coupling process occurred in high yield with a nearly equimolar ratio of arylmagnesium bromide and aryl tosylate (1.1–1 equiv). Under these conditions, the scope of the coupling of aryl and vinyl tosylates was investigated with aromatic, benzylic, and aliphatic Grignard reagents.

Coupling of Aryl Tosylates with Arylmagnesium Halides. The coupling of aryl tosylates with arylmagnesium halides is summarized in Table 1. In most cases, reactions conducted under the less concentrated conditions formed the coupled product in yields that are higher than those communicated earlier.³¹ The coupling of electron-rich, electron-neutral, and electron-deficient, as well as ortho-substituted, aryl tosylates occurred in good yields. The influence of substituents in the para position was not large and was the opposite of that usually observed for the coupling of aryl halides. Reactions of aryl tosylates with electron-donating substituents (OMe) occurred in yields that were higher than those of reactions of electron-neutral aryl tosylates (Me, H), and reactions of aryl tosylates with electron-withdrawing groups (F, CF_3) occurred in yields (Table 1, entries 7 and 11) that were lower than those of reactions of the electron-neutral aryl halides.

The selectivity for reaction at an aryl chloride and aryl tosylate linkage was probed. Reactions of PhMgBr with an aryl tosylate with a 4-chloro substituent occurred to cleave the aryl tosylate and to form the 4-chlorobiphenyl in good yield (Table 1, entry 12). This selectivity contrasts with that of the coupling of arylboronic acids with palladium complexes of X-phos. These reactions of palladium complexes of X-phos occurred preferentially at the aryl chloride over the aryl tosylate.²³ Reactions of bis-tosylates with 2 equiv of phenyl Grignard generated triaryl compounds in good yields. However, reactions of bis-tosylates with 1 equiv of aryl Grignard reagent were

(25) Holzer, B.; Hoffmann, R. W. *J. Chem. Soc., Chem. Commun.* **2003**, 732.

(26) Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, B. *J. Am. Chem. Soc.* **2004**, *126*, 3686.

(27) Nagano, T.; Hayashi, T. *Org. Lett.* **2004**, *6*, 1297.

(28) Huang, J. K.; Nolan, S. P. *J. Am. Chem. Soc.* **1999**, *121*, 9889.

(29) Yang, L. M.; Huang, L. F.; Luh, T. Y. *Org. Lett.* **2004**, *6*, 1461.

(30) Kamikawa, T.; Hayashi, T. *J. Org. Chem.* **1998**, *63*, 8922.

(31) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 8704.

(32) Fürstner, A.; Leitner, A.; Mendez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856.

(33) Zhou, J. R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 14726.

(34) Zhou, J. R.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 12527.

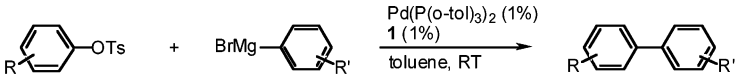
(35) Frisch, A. C.; Shaikh, N.; Zapf, A.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4056.

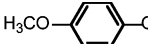
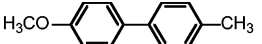

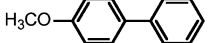
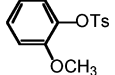
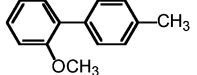

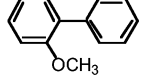
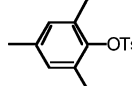
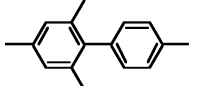
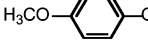


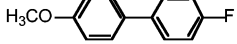
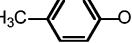
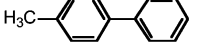
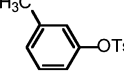
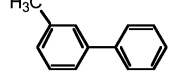
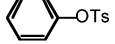
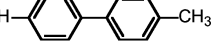
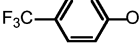
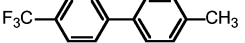
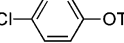
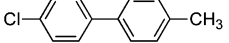
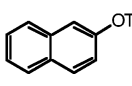
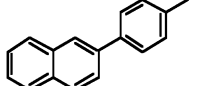

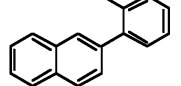
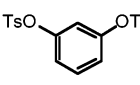
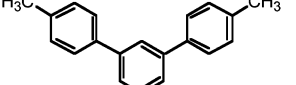
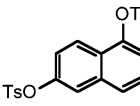
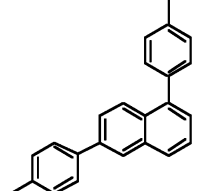
(36) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 609.

(37) Dohle, W.; Kopp, F.; Cahiez, G.; Knochel, P. *Synlett* **2001**, 1901.

(38) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc.* **1994**, *116*, 4062.

(39) For precedent in a nickel-catalyzed coupling of Grignard reagents with an aryl mesylate to form biaryl in 53% yield, along with two homocoupling products and reduction products, see: Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 6895.

TABLE 1. Coupling of Aryl Tosylates with Arylmagnesium Halides^a


| Entry | Tosylate | Product | Time (h) | Temp (°C) | Yield (%) |
|-------|---|---|----------|-----------|-----------------|
| 1 |  |  | 4 | RT | 83 |
| 2 |  |  | 12 | RT | 72 ^b |
| 3 |  |  | 3 | 80 | 65 ^b |
| 4 |  |  | 15 | 80 | 65 ^b |
| 5 |  |  | 10 | 80 | 40 ^b |
| 6 |  |  | 4 | RT | 85 |
| 7 |  |  | 4 | RT | 80 |
| 8 |  |  | 4 | RT | 87 ^c |
| 9 |  |  | 4 | RT | 86 ^c |
| 10 |  |  | 4 | RT | 87 ^c |
| 11 |  |  | 4 | RT | 75 ^c |
| 12 |  |  | 4 | RT | 78 |
| 13 |  |  | 2 | RT | 86 |
| 14 |  |  | 16 | RT | 93 |
| 15 |  |  | 4 | RT | 43 |
| 16 |  |  | 4 | RT | 69 |

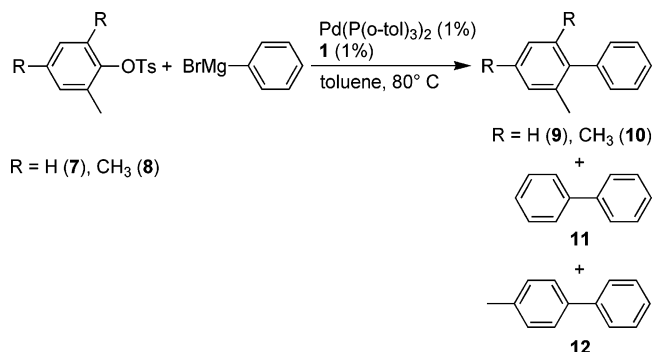
^a Reaction conditions: ArOTs (1 equiv), Ar'MgBr (1.1 equiv), 1 mol % of Pd(P(*o*-tol)₃)₂ or Pd(dba)₂, 1 mol % of **1**; isolated yield is an average of two runs. ^b Pd(dba)₂ and 2 equiv of Ar'MgBr were used. ^c Gas chromatography yield.

not selective, and a mixture of products containing predominantly the disubstitution product was obtained.

In most couplings of aryl Grignard reagents with aryl tosylates in which one of the two reagents contained an ortho substituent, 2 equiv of the magnesium reagent and elevated temperatures were required for full conversion,

but reasonable yields were obtained (Table 1, entries 2–4). An excess of Grignard reagent was needed, regardless of whether the catalyst was generated from Pd₂dba₃ or Pd(P(*o*-tol)₃)₂. However, the reaction of 2-naphthyl-tosylate with *o*-tolylmagnesium bromide occurred in excellent yield with only 1 equiv of the magnesium

SCHEME 3



reagent (Table 1, entry 14). Aryl tosylates that are substituted in both the 2- and 6-position reacted in lower yields. In addition to the products from cross-coupling and homocoupling of the Grignard reagent, a biaryl containing the *p*-tolyl group of the tosylate was observed, as shown in Scheme 3, perhaps from coupling of a sulfone^{18,40,41} generated by cleavage of the tosylate. Coupling of aryl halides containing ester and nitrile groups did not occur, and coupling of functionalized Grignard reagents⁴² could not be accomplished because the couplings did not occur below room temperature. Unfortunately, reactions of nitrogen-containing heterocycles such as quinolines also did not occur.

Biaryl couplings catalyzed by complexes generated from this hindered Josiphos ligand are, thus far, limited to reactions of organomagnesium compounds. Phenylzinc bromide reacted with phenyl tosylate to give only traces of biphenyl, and arylboronic acids did not react to give any biaryl products. Because oxidative addition of aryl tosylates to the Pd(0) species containing the Josiphos ligand is facile, transmetalation of these complexes with arylboronic acids and arylzinc halides is apparently slow.

Coupling of Aryl Tosylates with Alkenyl- and Alkylmagnesium Halides. The coupling of aryl tosylates with alkenyl, benzylic, and aliphatic magnesium halides was also investigated in the presence of the catalyst generated from a Pd(0) precursor and the Josiphos ligands **1** and **2**. Reactions of aryl tosylates with these Grignard reagents are summarized in Table 2. In general, reactions catalyzed by complexes of the bulkier and more electron-rich phosphine **2** occurred faster and in higher yield than reactions catalyzed by complexes of ligand **1**. However, the optimal reaction conditions were not identical with each class of Grignard reagent. For example, the coupling with 2-methylpropenylmagnesium chloride (Table 2, entry 1) required heating, while the coupling of isobutyl- and cyclohexylmagnesium bromide occurred at room temperature.

Nevertheless, alkenyl, *n*-alkyl, β -branched alkyl, cycloalkyl, and benzyl Grignard reagents all coupled with the electron-rich anisyl tosylate in good to excellent yields. Reactions of this aryl tosylate generally occurred in higher yield with a catalyst generated from the more electron-rich ligand **2** than with a catalyst generated from the less electron-rich ligand **1**. Reactions conducted with

a catalyst generated from ligand **2** formed larger amounts of arene from hydrodesulfonation than did reactions conducted with a catalyst generated from ligand **1**. However, the coupling of the cyclohexylmagnesium bromide occurred in higher yield with ligand **1** than with ligand **2**. This reaction also occurred in lower yields at elevated temperatures than at room temperature.

Less electron-rich aryl tosylates, such as 4-trifluoromethylphenyl tosylate and 2-naphthyltosylate, also underwent coupling with alkyl Grignard reagents. The yields from coupling of the modestly activated naphthyl tosylate were higher than those of the more activated trifluoromethylphenyl tosylate, and the naphthyl electrophile reacted in excellent yield with linear or β -branched Grignard reagents and with benzylic Grignard reagents at room temperature in the presence of a palladium catalyst generated from **1**. However, the reaction of the trifluoromethylphenyl tosylate did not occur to completion with 1 mol % of palladium, even after 8 h. The coupling of ortho-substituted aryl tosylates is also challenging. Two equivalents of Grignard reagent, elevated temperatures, and long reaction times were required. The yield of the coupling of the *o*-anisyl tosylate with isobutylmagnesium chloride was estimated as 65% by GC methods.

Coupling of secondary alkylmagnesium halides with a methyl group adjacent to the nucleophilic carbon, such as *sec*-butylmagnesium chloride or phenethylmagnesium bromide occurred in low yield. The major product from reaction of *sec*-butyl Grignard was arene. This product, presumably, forms by β -hydride elimination of the alkyl group and C–H bond-forming reductive elimination. Some product from rearrangement of the branched to the linear alkyl prior to reductive elimination was also observed (Scheme 4).

Kumada and Hayashi proposed⁴³ a relationship between the P–Pd–P bite angle of bis-phosphines and the amount of product from rearrangement of the branched alkyl group. This isomerization was suppressed by conducting the reactions of branched alkyl Grignard reagents with catalysts derived from 1,1'-bis(diphenylphosphino)ferrocene (DPPF). DPPF generates complexes with a P–Pd–P angle of about 99°. Although the 98° bite angle of the coordinated Josiphos ligand could similarly lead to a suppression of the isomerization, the difference in steric and electronic properties of this ligand and DPPF apparently allow β -hydrogen elimination and isomerization of the branched to linear alkyl group to compete with C–C bond-forming reductive elimination.

Coupling of Alkenyl Tosylates with Arylmagnesium Halides. Previous procedures for the synthesis of vinyl tosylates from ketones were conducted with lithium diisopropylamide (LDA) as base and 2 equiv of *p*-toluenesulfonic anhydride. This procedure yielded substantial amounts of sulfonamide byproduct, and this sulfonamide can be difficult to separate from the vinyl tosylate. Thus, we prepared the vinyl tosylates by deprotonation of the ketone with lithium hexamethyldisilazide (LiHMDS)⁴⁴ at –78 °C and addition of tosic anhydride

(40) Clayden, J.; Julia, M. *Chem. Commun.* **1993**, 1682.

(41) Clayden, J.; Cooney, J. J. A.; Julia, M. *Chem. Commun.* **1995**, 7.

(42) Bonnet, V.; Mongin, F.; Trecourt, F.; Queguiner, G.; Knochel, P. *Tetrahedron* **2002**, *58*, 4429.

(43) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.

(44) Cox, R. A.; McAllister, M.; Roberts, K. A.; Stang, P. J.; Tidwell, T. T. *J. Org. Chem.* **1989**, *54*, 4899.

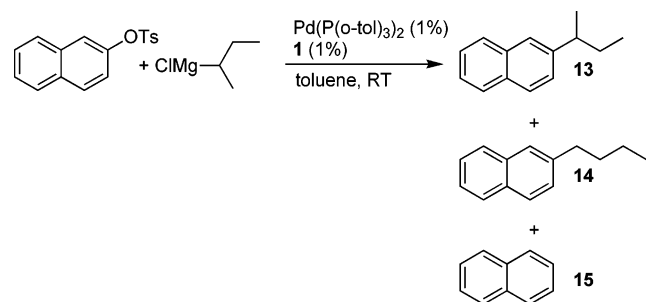
TABLE 2. Coupling of Aryl Tosylates with Alkylmagnesium Halides^a

| Entry | Tosylate | Product | L | Time (h) | Temp (°C) | Yield (%) |
|-------|----------|---------|---|----------|-----------|-----------|
| 1 | | | 2 | 4 | 80 | 87 |
| 2 | | | 2 | 4 | 80 | 91 |
| 3 | | | 2 | 4 | RT | 92 |
| 4 | | | 1 | 8 | RT | 67 |
| 5 | | | 2 | 4 | 80 | 55 |
| 6 | | | 2 | 4 | RT | 97 |
| 7 | | | 2 | 8 | RT | 66 |
| 8 | | | 1 | 2 | RT | 92 |
| 9 | | | 1 | 2 | RT | 93 |
| 10 | | | 1 | 2 | RT | 97 |

RT = room temperature.

^a Reaction conditions: ArOTs (1 equiv), RMgX (1.1 equiv, R = alkenyl, alkyl; X = Br, Cl), 1 mol % of Pd(P(o-tol)₃)₂, 1 mol % of **1** or **2**; isolated yields are an average of two runs.

SCHEME 4. Coupling of 2-Naphthyltosylate with *sec*-Butylmagnesium Bromide



to the resulting enolate.^{45,46} This procedure provided several benefits. First, the remaining disilazide or any silyl-substituted sulfonamide hydrolyzed and did not elute during chromatography. Second, the alkenyl tosylates formed after deprotonation of the ketone with

LiHMDS consisted predominantly of the *E* configuration instead of a mixture of *E* and *Z* isomers, as was obtained from reactions with LDA as base. The tosylate obtained from 2-methylcyclohexanone (Table 3, entry 2) contained about 5–10% of the more substituted vinyl tosylate.

Reactions of the vinyl tosylates with Grignard reagents are summarized in Table 3. We studied reactions of tosylates with different steric properties (Table 3, entries 1–4) and different electronic properties (Table 3, entries 5–7). Sterically hindered and unhindered cyclic alkenyl tosylates (Table 3, entries 1 and 2) reacted readily with *p*-tolylmagnesium bromide at elevated temperatures and in good yields.

The reaction of 2-methyl-3-tosyloxy-3-propene (Table 3, entry 3) with *p*-tolyl Grignard, however, generated a coupled product resulting from isomerization. The mechanism of this isomerization is not clear. Although isomerization that leads to migration of a metal center between contiguous carbons in an alkyl group is common, migration of a metal from one vinyl carbon to another is less common. β -Hydrogen elimination from an alkyl group to form an olefin hydride complex and reinsertion to generate a new alkyl species accounts for migration of a metal

(45) The following recent reference on coupling of amides with vinyl tosylates reported the preparation of vinyl tosylates by a similar procedure.

(46) Klapars, A.; Campos, K. R.; Chen, C. Y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185.

TABLE 3. Coupling of Alkenyl Tosylates with Aryl- and Alkylmagnesium Halides^a

| Entry | Tosylate | Product | L | Time (h) | Temp (°C) | Yield (%) |
|-------|----------|---------|---|----------|-----------|-----------------|
| 1 | | | 2 | 4 | 80 | 81 |
| 2 | | | 1 | 4 | 80 | 71 ^b |
| 3 | | | 2 | 16 | 80 | 43 |
| 4 | | | 1 | 1 | RT | 82 |
| 5 | | | 1 | 1 | RT | 30 |
| 6 | | | 1 | 16 | RT | 82 |
| 7 | | | 1 | 16 | 80 | 87 |

^a Reaction conditions: ROTs (1 equiv), 4-MeC₆H₄MgBr/^tBuMgCl (1.1 equiv), 1 mol % of Pd₂(dba)₃·CHCl₃, 1 mol % of **1** or **2**; isolated yield is an average of two runs. ^b The parent tosylate already consists of two isomers; hence, the product is obtained as a mixture with about 6% of the higher substituted alkene.

along an alkyl chain, but β -hydrogen elimination from a vinyl group to form an alkyne hydride complex has less precedent. Isomerization induced by the reaction of a strong base, like the elimination of vinyl triflates to give alkynes,⁴⁷ may also account for the isomerization. In any case, the mechanism of the formation of the rearranged product is speculative at this time.

α -Styryl tosylates (Table 3, entries 5–7) also coupled with alkyl and aryl Grignard reagents. The products from coupling of alkenyl Grignard reagents were isolated in 30–87% yields (Table 3, entries 5–7). In contrast to the reaction of the vinyl tosylate in entry 3, the electronically distinct but sterically similar 1-phenylpropenyl tosylate (Table 3, entry 6) did not undergo isomerization during the coupling process. Although the products from coupling with aryl Grignard reagents were not separated from some of the side products of similar low polarity, yields for coupling of the vinyl tosylates of entries 5–7 with *p*-tolyl Grignard were estimated by GC to range from 70 to 80%.

The coupling of alkenyl tosylates with aliphatic Grignard reagents was also accomplished with catalysts generated from the hindered Josiphos ligands. In all

cases of the coupling of alkenyl tosylates with alkylmagnesium halides we tested, catalysts generated from phenyl ligand **1** formed the coupled product in higher yield than catalysts generated from cyclohexyl ligand **2**. Depending on the degree of steric hindrance, the reaction proceeded quickly at room temperature (Table 3, entries 4–6) or required heating (Table 3, entry 7). The less substituted vinyl tosylate in entry 5 of Table 3, however, reacted in lower yield than the more substituted vinyl tosylates. Hydrodesulfonylation apparently competed with substitution and diminished the yield. Styrene was detected by GC-MS, and the evolution of a gas from the reaction mixture, presumably isobutene, was observed.

Conclusion

We have shown that catalysts containing strongly electron-donating and sterically hindered bisphosphines of the Josiphos class allow for Kumada couplings to be conducted with aryl and vinyl tosylates. Previous couplings of aryl and vinyl sulfonates have been conducted predominantly with triflates, but we show that the less expensive and more easily handled tosylates can also react under mild conditions. The Kumada couplings of tosylates catalyzed by a combination of a Pd(0) precursor and the Josiphos ligands generates biaryl and styrenyl

(47) Brummond, K. M.; Gesenberg, K. D.; Kent, J. L.; Kerekes, A. D. *Tetrahedron Lett.* **1998**, *39*, 8613.

compounds in good to excellent yields, often at room temperature. An equimolar ratio of vinyl or aryl tosylate and Grignard reagent is sufficient for many cross-couplings with activated, deactivated, and certain sterically hindered substrates. Furthermore, we conducted successfully the first alkylations of electron-rich aryl and vinyl tosylates.

The Kumada coupling has advantages and disadvantages, relative to other types of couplings. The Kumada coupling requires no synthesis of boronic acids or organotin reagents, but they occur with less functional group tolerance than Suzuki or Stille reactions. Thus, we are also seeking conditions to couple aryl tosylates with organozinc reagents or organoboron reagents with catalysts bearing the Josiphos ligands. At the same time, we are seeking systems that will further improve the turnover numbers of the coupling of Grignard reagents and that will exploit the chirality of the Josiphos ligand for enantioselective couplings.

Experimental Section

General Procedure 1: Coupling of Aryl Tosylates with Arylmagnesium Bromides. The reaction conditions and average yields for each reaction are shown in Table 1. A typical procedure is given for entry 1.

4-Methoxy-4'-methylbiphenyl.⁴⁸ Into a small vial were placed 7.2 mg of Pd(P(*o*-tol)₃)₂ (0.010 mmol), 5.4 mg of **1** (0.010 mmol), and 278 mg of 4-MeOC₆H₄OTs (1.00 mmol). The solids were dissolved in 3 mL of toluene. With a syringe, 1.1 mL of a 1.0 M solution of *p*-tolylmagnesium bromide (1.10 mmol) in diethyl ether was added to the well-stirred solution at room temperature. The vial was closed, and the solution was stirred at room temperature in the glovebox for 4 h. The resulting orange suspension was removed from the glovebox, hydrolyzed with 1.0 M HCl, and extracted three times with dichloromethane. The combined organic layers were washed with brine, dried over MgSO₄, and filtered. After evaporation of the

solvent, the crude product was purified using flash column chromatography (silica gel, hexanes, ethyl acetate 95:5) to give 164.6 mg (83%) of 4-methoxy-4'-methylbiphenyl: ¹H NMR (CDCl₃) δ 2.41 (s, 3H), 3.87 (s, 3H), 7.00 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.54 (d, *J* = 8.8 Hz, 2H); ¹³C NMR (CDCl₃) δ 21.5, 55.8, 114.6, 127.0, 128.4, 129.9, 134.2, 136.8, 138.4, 159.4.

General Procedure 2: Coupling of Aryl Tosylates with Alkenyl- and Alkylmagnesium Halides and Coupling of Alkenyl Tosylates with Aryl- and Alkylmagnesium Halides. The reaction conditions and average yields for each reaction are shown in Tables 2 and 3. A typical procedure is given for Table 2, entry 1.

1-Methoxy-4-(2-methylpropenyl)benzene.⁴⁹ Into a small vial were placed 3.6 mg of Pd(P(*o*-tol)₃)₂ (0.0050 mmol), 2.8 mg of **2** (0.0050 mmol), and 139 mg of 4-MeOC₆H₄OTs (0.500 mmol). The solids were dissolved in 1.5 mL of toluene. With a syringe, 1.1 mL of a 0.5 M solution of 2-methylpropenylmagnesium bromide (0.55 mmol) in tetrahydrofuran was added to the well-stirred solution at room temperature. The vial was sealed with a poly(tetrafluoroethylene) septum, removed from the glovebox, and stirred at 80 °C for 4 h.

The resulting orange to brown suspension was diluted in 100 mL of hexanes and filtered. After evaporation of the solvent, the crude product was purified using flash column chromatography (silica gel, hexanes, ethyl acetate 99:1) to give 71 mg (87%) of 1-methoxy-4-(2-methylpropenyl)benzene: ¹H NMR (CDCl₃) δ 1.86 (d, *J* = 1.3 Hz, 1H), 1.90 (d, 1.3 Hz, 1H), 3.82 (s, 3H), 6.23 (broad, 1H), 6.88 (d, 8.5 Hz, 2H), 7.18 (d, 8.5 Hz, 2H); ¹³C NMR (CDCl₃) δ 18.3, 25.8, 54.2, 112.4, 123.5, 127.6, 128.7, 130.3, 132.0, 132.9, 156.6.

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Supporting Information Available: Details of experimental procedures and characterization of all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO051394L

(49) Stratakis, M.; Hatzimarinaki, M.; Froudakis, G. E.; Orfanopoulos, M. *J. Org. Chem.* **2001**, *66*, 3682.

(48) Cho, C. H.; Yun, H. S.; Park, K. *J. Org. Chem.* **2003**, *68*, 3017.