to confirm the expected linear structure of the complex. Such selective measurements of intergroup separations of several nanometers should thus open up a new route for the structural determination of noncrystalline supramolecular assemblies.

Experimental Section

Synthesis and full characterization of ligand **2** is described in the Supporting Information.

EPR measurements: Four-pulse DEER time–domain signals were obtained with the sequence $(\pi/2)_{\nu 1}$–τ_1–$(\pi)_{\nu 1}$–t–$(\pi)_{\nu 2}$–$\tau_1+\tau_2$–t–$(\pi)_{\nu 1}$–τ_2–echo at a temperature of 15 K on a Bruker E 580 X-Band spectrometer. A Bruker Flexline split-ring resonator ER 4118X-MS3 was used with overcoupling to $Q \approx 100$. Pump pulses were generated by feeding the output of an HP8350B sweep oscillator to one microwave-pulse-forming unit of the spectrometer. All pulse lengths were 32 ns, the dwell time was 8 ns, and the fixed interpulse delays were $\tau_1 = 400$ ns and $\tau_2 = 1200$ ns (Figure 3a–c) or $\tau_2 = 2000$ ns (Figure 3d). Details are discussed in the Supporting Information.

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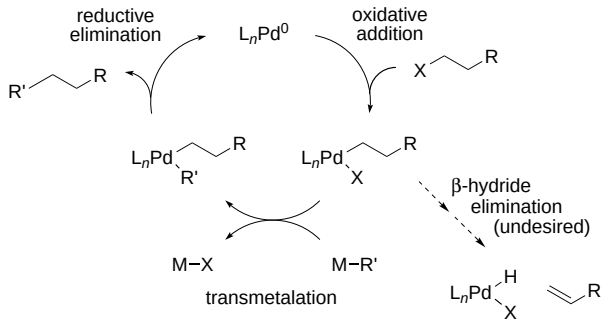
[14] A quantitative analysis of the orientation selection requires additional information on the experimental coordination geometry and the orientation of the copper *g* and hyperfine tensors with respect to the coordination polyhedron. This analysis is now underway.

Suzuki Cross-Couplings of Alkyl Tosylates that Possess β Hydrogen Atoms: Synthetic and Mechanistic Studies**

Matthew R. Netherton and Gregory C. Fu*

During the past few decades, remarkable progress has been reported in the development of mild and efficient nickel- and palladium-catalyzed protocols for carbon–carbon bond-forming reactions of electrophiles that contain C(sp^2)-X bonds (e.g., aryl and vinyl halides and sulfonates).[1] In contrast, general methods to cross-couple unactivated electrophiles that contain C(sp^3)-X bonds, especially when β hydrogen atoms are present in the molecule, are scarce, presumably because of slow oxidative addition and/or facile β-hydride elimination (Scheme 1).[2] In the case of alkyl halides, some advances have been described, specifically, examples of Suzuki cross-couplings of alkyl iodides, bromides, and chlorides,[3] Negishi reactions of alkyl iodides and bromides,[4] and Kumada couplings of alkyl bromides and a chloride.[5]



Scheme 1. Generalized mechanism for palladium-catalyzed cross-coupling reactions.

In contrast, to the best of our knowledge, at the time that we initiated our program in this area, there were no reports of palladium- or nickel-catalyzed cross-couplings of alkyl sulfonates. In the interim, however, Kambe and co-workers have described nickel-catalyzed Kumada couplings of two unfunctionalized alkyl tosylates.[5] In this communication, we establish that Pd/P*t*Bu_2Me can achieve Suzuki reactions of a range of functionalized alkyl sulfonates [Eq. (1); 9-BBN = 9-borabicyclo[3.3.1]nonane], and we report preliminary mechanistic studies of this new catalyst system.

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Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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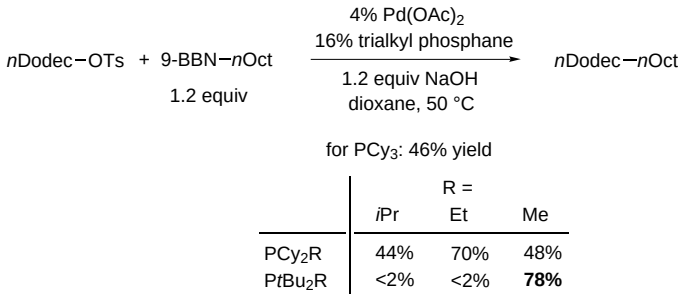
$$R_{alkyl}\text{–OTs} + \underset{1.2\ \text{equiv}}{\text{9-BBN–R'}} \xrightarrow[\text{1.2 equiv NaOH, dioxane, 50 °C}]{\text{4\% Pd(OAc)}_2,\ \text{16\% P}t\text{Bu}_2\text{Me}} R_{alkyl}\text{–R'} \qquad (1)$$

In our initial investigation of Suzuki couplings of alkyl sulfonates, we attempted to employ the catalysts that we had developed for reactions of alkyl bromides ($Pd(OAc)_2/PCy_3/K_3PO_4\cdot H_2O$/THF; Cy = cyclohexyl) and alkyl chlorides ($[Pd_2(dba)_3]/PCy_3/CsOH\cdot H_2O$/dioxane; dba = *trans*,*trans*-dibenzylidene acetone). Unfortunately, for the cross-coupling of *n*Dodec–OTs with 9-BBN–*n*Oct, these catalyst systems provide essentially none of the hoped-for eicosane (< 15 %).

After a considerable number of optimization experiments, we determined that $Pd(OAc)_2/PR_3$/NaOH/dioxane can furnish an appreciable quantity of the desired product. As illustrated in Scheme 2, this Suzuki reaction is remarkably sensitive to the structure of the trialkyl phosphane. Although PCy_3 and PCy_2iPr afford only modest yields of eicosane (ca.



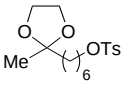
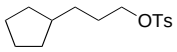
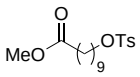
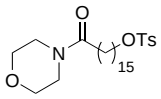
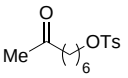
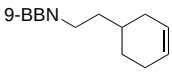
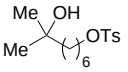
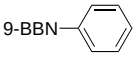
Scheme 2. Effect of the structure of the trialkyl phosphane on the yield of the Suzuki cross-coupling of an alkyl tosylate.

45 %), a slight decrease in the steric demand of *one* of the alkyl groups leads to a significantly more efficient reaction (70 % yield for PCy_2Et); interestingly, a further decrease in size results in a loss in yield (48 % for PCy_2Me). For di-*tert*-butyl-substituted trialkyl phosphanes, essentially none of the desired cross-coupling product is formed if the third substituent is either isopropyl or ethyl (< 2 %), but a good yield is obtained if it is methyl (78 %).[6]

Although we have not yet determined the origin of this striking dependence of reactivity on phosphane structure, we were pleased to discover that P*t*Bu$_2$Me,[7] which is commercially available, is an effective ligand for a range of palladium-catalyzed Suzuki cross-couplings of alkyl tosylates that bear β hydrogen atoms (Table 1).[8] The process tolerates a number of functional groups, including acetals and silyl ethers (entry 2), alkyl ethers (entry 3), esters (entry 4), tertiary amides (entry 5), ketones (entry 6), nitriles and olefins (entry 7), and tertiary alcohols (entry 8). Not only organoboron reagents that contain 9-BBN-C(sp^3) bonds, but also those with 9-BBN-C(sp^2) bonds can be employed (entry 8), and a double Suzuki coupling of a bis(tosylate) can be achieved (entry 9).[9,10]

Although we routinely conduct these cross-couplings at 50 °C, they can in fact be accomplished at room temperature, at the expense of a long reaction time (for the coupling

Table 1. Examples of Pd/P*t*Bu$_2$Me-catalyzed Suzuki cross-couplings of alkyl tosylates [see Eq. (1)].

Entry	R_{alkyl}–OTs	9-BBN–R′	Yield [%][a]
1	*n*Dodec–OTs	9-BBN–*n*Oct	80
2		9-BBN–$(CH_2)_{11}$OTES[b]	67
3		9-BBN–$(CH_2)_5$OBn	61[c]
4		9-BBN–$(CH_2)_5$OBn	60
5		9-BBN–*n*Oct	76
6		9-BBN–$(CH_2)_{11}$OTES[b]	55
7	NC$(CH_2)_8$–OTs		64
8			63
9[d]	TsO–$(CH_2)_{12}$–OTs	9-BBN–*n*Oct	73

[a] Yield of isolated product, average of two runs. [b] TES = triethylsilyl. [c] Isolated as 8-cyclopentyl-octan-1-ol (after hydrogenolysis). [d] 2.4 equiv of 9-BBN–R′, 8 % $Pd(OAc)_2$, 32 % P*t*Bu$_2$Me, and 2.4 equiv of NaOH were used.

illustrated in entry 1 of Table 1: 70 % yield after 7 days). This ability to couple an alkyl tosylate under mild conditions is noteworthy in view of the fact that aryl tosylates are generally not suitable substrates for palladium-catalyzed cross-couplings.[1]

We have recently described the use of phosphonium salts as air-stable substitutes for air-sensitive trialkyl phosphanes,[11] and we have demonstrated the interchangeability of these reagents for Pd/P*t*Bu$_2$Me-catalyzed Suzuki reactions of alkyl tosylates [Eq. (2) vs. entry 1 of Table 1].[12]

$$\underset{\text{1.2 equiv}}{\begin{matrix}n\text{Dodec–OTs}\\ +\\ \text{9-BBN–}n\text{Oct}\end{matrix}} \xrightarrow[\text{1.2 equiv NaOH, dioxane, 50 °C}]{\text{4\% Pd(OAc)}_2,\ \text{16\% [HP}t\text{Bu}_2\text{Me]BF}_4} \underset{\text{82\%}}{n\text{Dodec–}n\text{Oct}} \qquad (2)$$

We have begun to pursue mechanistic work on our Pd/P*t*Bu$_2$Me-based catalyst for cross-coupling alkyl tosylates and have focused on the stereochemistry of oxidative addition (i.e., inversion vs. retention).[13,14] As far as we are aware, this issue has not been addressed for any of the methods that have been described for coupling unactivated electrophiles that contain C(sp^3)-X bonds.[3–5] To gain insight into this stereochemical question, we treated diastereomerically pure tosylate **1**[15] with Pd/P*t*Bu$_2$Me, in the absence of an organoborane and NaOH, and examined the olefins that resulted from oxidative addition and then β-hydride elimination (Scheme 3).[16] On the basis of ^{1}H NMR analysis, we determined that oxidative addition occurs primarily with inversion

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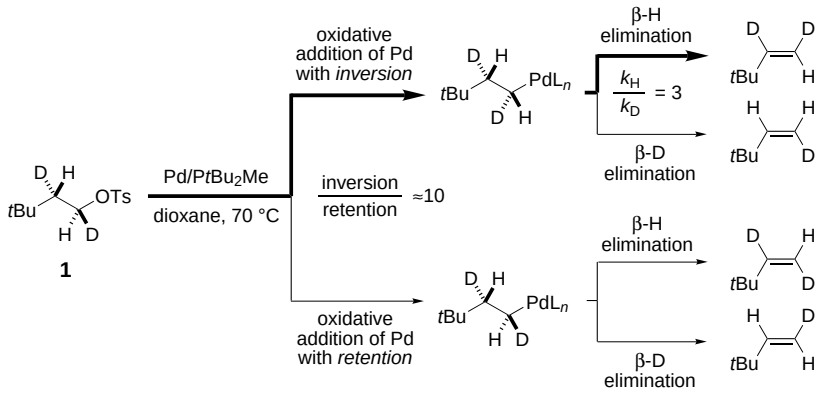
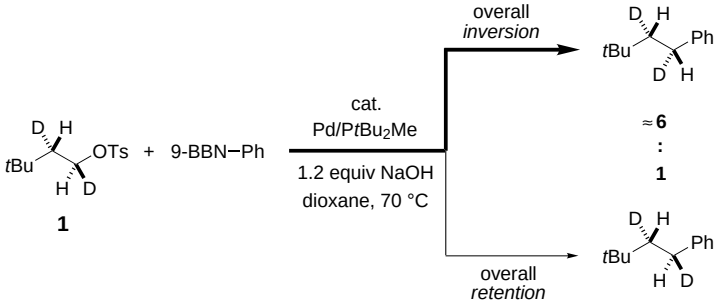


Scheme 3. Determination of the stereochemistry of oxidative addition of an alkyl tosylate to Pd/P*t*Bu$_2$Me.

of configuration (and that β-hydride elimination proceeds with 3:1 selectivity for H in preference to D).[17]

In a second investigation, we explored the stereochemical course of a Pd/P*t*Bu$_2$Me-catalyzed cross-coupling of tosylate **1** with an organoborane (Scheme 4). ^{1}H NMR analysis of the coupled product revealed that the Suzuki reaction occurs principally with inversion (ca. 6:1) at carbon.[17] Taken together, the studies outlined in Schemes 3 and 4 are consistent with predominant inversion of configuration during oxidative addition of the tosylate, along with (well-precedented) retention of configuration during reductive elimination.[14]



Scheme 4. Examination of the stereochemistry of a Pd/P*t*Bu$_2$Me-catalyzed Suzuki cross-coupling of an alkyl tosylate.

In summary, we have developed the first palladium- or nickel-catalyzed cross-coupling process that is effective for functionalized alkyl tosylates, specifically, a mild, Pd/P*t*Bu$_2$Me-based method for achieving Suzuki reactions. We have determined that, in contrast to couplings of alkyl bromides and chlorides, P*t*Bu$_2$Me (rather than PCy$_3$) is the ligand of choice for Suzuki reactions of tosylates. In initial mechanistic studies, we have established that alkyl tosylates oxidatively add to the catalyst with predominant inversion of configuration at carbon. Ongoing work is focused on expanding the scope of palladium-catalyzed cross-couplings of alkyl electrophiles (e.g., Stille reactions) and on enhancing our understanding of the origin of the exceptional reactivity of our catalyst system.

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[2] For overviews, see: a) T.-Y. Luh, M.-K. Leung, K.-T. Wong, *Chem. Rev.* **2000**, *100*, 3187–3204; b) D. J. Cárdenas, *Angew. Chem.* **1999**, *111*, 3201–3203; *Angew. Chem. Int. Ed.* **1999**, *38*, 3018–3020.

[3] Palladium-catalyzed Suzuki couplings: a) Alkyl iodides: T. Ishiyama, S. Abe, N. Miyaura, A. Suzuki, *Chem. Lett.* **1992**, 691–694; b) alkyl bromides: M. R. Netherton, C. Dai, K. Neuschütz, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 10099–10100; c) alkyl chlorides: J. H. Kirchhoff, C. Dai, G. C. Fu, *Angew. Chem.* **2002**, *114*, 2025–2027; *Angew. Chem. Int. Ed.* **2002**, *41*, 1945–1947.

[4] Nickel-catalyzed Negishi couplings: A. Devasagayaraj, T. Stüdemann, P. Knochel, *Angew. Chem.* **1995**, *107*, 2952–2954; *Angew. Chem. Int. Ed.* **1995**, *34*, 2723–2725; A. E. Jensen, P. Knochel, *J. Org. Chem.* **2002**, *67*, 79–85, and references therein.

[5] Nickel-catalyzed Kumada couplings: J. Terao, H. Watanabe, A. Ikumi, H. Kuniyasu, N. Kambe, *J. Am. Chem. Soc.* **2002**, *124*, 4222–4223.

[6] For the reactions outlined in Scheme 2, we observe an 11–36% yield of 1-dodecene (resulting from β-hydride elimination), with the balance of the material being unreacted tosylate or side products.

[7] a) For a discussion of the stereodynamics of P*t*Bu$_2$Me and related phosphanes, see: C. D. Rithner, C. H. Bushweller, *J. Am. Chem. Soc.* **1985**, *107*, 7823–7836; b) for a discussion of novel reactivity in the presence of P*t*Bu$_2$Me, see: D. Huang, W. E. Streib, O. Eisenstein, K. G. Caulton, *Angew. Chem.* **1997**, *109*, 2096–2098; *Angew. Chem. Int. Ed.* **1997**, *36*, 2004–2006; c) for a discussion of the steric differences between PCy$_3$ and P*t*Bu$_2$Me, see: C. Li, M. Ogasawara, S. P. Nolan, K. G. Caulton, *Organometallics* **1996**, *15*, 4900–4903.

[8] Notes: a) Under otherwise identical conditions, the use of: 1) bidentate electron-rich phosphanes, triaryl phosphanes, P*t*Bu$_2$H, OP*t*Bu$_2$H, and N-heterocyclic carbenes was not effective; 2) THF and other solvents furnished markedly lower yields; 3) PdCl$_2$, [*trans*-PdCl$_2$(NH$_3$)$_2$], [PdCl$_2$(cod)], and [{Pd(π-allyl)Cl}$_2$] were also effective, although [Pd$_2$(dba)$_3$] was not; b) under closely related conditions, the use of LiOH, K$_3$PO$_4$·H$_2$O, and KO*t*Bu led to decreased yields.

[9] Under the conditions described in Table 1, we have examined the Suzuki cross-coupling of 9-BBN–*n*Oct with two other alkyl sulfonates. For *n*Dodec–OMs, the desired product was generated in 51% yield; for *n*Dodec–OSO$_2$CH$_2$CF$_3$, no coupling was observed.

[10] We do not intend to suggest that achieving Suzuki cross-couplings of alkyl tosylates is now a solved problem. Although we believe that this Pd/P*t*Bu$_2$Me-based catalyst system represents significant progress, important challenges remain, including the coupling of more hindered reaction partners, as well as the coupling of boronic acids, neither of which proceed in appreciable yield under the conditions described in Table 1.

[11] M. R. Netherton, G. C. Fu, *Org. Lett.* **2001**, *3*, 4295–4298.

[12] [HP*t*Bu$_2$Me]BF$_4$ will be commercially available from Strem Chemicals (Dr. Mike Strem, personal communication).

[13] For a discussion of possible pathways (e.g., S$_N$2 or direct insertion), see: J. P. Collman, L. S. Hegedus, J. R. Norton, R. G. Finke, *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA, **1987**, chap. 5.

[14] For a review of oxidative addition and reductive elimination, including a discussion of stereochemical issues, see: J. K. Stille, *The Chemistry of the Metal-Carbon Bond, Vol. 2* (Eds.: F. R. Hartley, S. Patai), Wiley, New York, **1985**, chap. 9.

[15] For precedent for this approach, see: a) P. L. Bock, D. J. Boschetto, J. R. Rasmussen, J. P. Demers, G. M. Whitesides, *J. Am. Chem. Soc.* **1974**, *96*, 2814–2825; b) K. Matos, J. A. Soderquist, *J. Org. Chem.* **1998**, *63*, 461–470.

[16] We have also isolated and characterized the palladium-containing product of the reaction, [Pd(P*t*Bu$_2$Me)$_2$H(OTs)].

[17] We have confirmed these results by investigating the corresponding reaction of the diastereomer of tosylate **1**.

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