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Chemo- and Regioselectivity-Tunable Pd-Catalyzed Allylic Alkylation of Imines

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Supporting Information

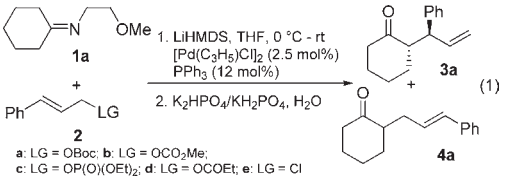
ABSTRACT: α-Carbanions of cyclic and acyclic imines have been successfully applied as nucleophiles in the Pd-catalyzed allylic alkylation reaction. Tuning of chemo- and regioselectivity has been realized by using *t*-BuOK/THF and LDA/toluene to give branched and linear products, respectively, with high regio- and diastereoselectivities. A plausible mechanism is proposed on the basis of the experimental results and DFT calculations.

The palladium-catalyzed allylic alkylation reaction is not only one of the most thoroughly studied transition-metal-catalyzed reactions but also one of the most useful reactions in organic synthesis.[1] While great achievements have been made, some challenging issues remain to be addressed. One is the regioselectivity of the reaction with monosubstituted allyl substrates. In most cases, especially in the reactions using carbon nucleophiles, linear products are obtained when Pd catalysts are used.[1] Branched products have been provided in only a few examples, such as in alkylations using catalysts with well-designed ligands[2,3] or substrates with directing groups[4] and in the decarboxylative alkylation of heteroaromatic alkanes.[5] Branched products have also been obtained in reactions using N-nucleophiles, including unprotected aziridines,[6a−c] hydrazine, and hydroxylamine.[6d] Another issue is the limitation of carbanion nucleophiles. For a long time, carbon nucleophiles have been limited to "soft" or stabilized carbanions. Although some enolates from ketones and carboxylic acid derivatives have been used successfully as nucleophiles,[2c,7,8] exploration of new types of "hard" carbanions as nucleophiles is still one of the main subjects in studies of Pd-catalyzed allylic alkylation reactions.[7n]

Recently, our group realized the regio- and enantioselective Pd-catalyzed allylic alkylation of monosubstituted allyl substrates[2] and also developed acyclic ketone enolates as well as α-carbanions of acyclic amides as nucleophiles.[2c,8] In this communication, we report that α-carbanions of cyclic and acyclic aliphatic imines are also suitable nucleophiles for the reaction[9] and that a dramatic tuning of regioselectivity can be achieved. A plausible mechanism to rationalize the experimental observations is proposed on the basis of density functional theory (DFT) calculations and further experiments.

Initially, the reaction of imine **1a** and cinnamyl *tert*-butyl carbonate **2a** in the presence of $[Pd(C_3H_5)Cl]_2/PPh_3$ and LiHMDS was examined (eq 1). Allylated products **3a** and **4a** were obtained in a ratio of 36:64 with a total yield of 60% after the hydrolysis of allylated imine. The dr of **3a** was determined to be 6:1. The prototypical reaction was investigated to optimize the reaction conditions (Table 1).

The experimental data imply that the base has a significant influence on the regiochemistry. The linear product **4a** was the major product using LiHMDS (entry 1). To our surprise, the branched product **3a** became predominant when NaHMDS or KHMDS was the base (entries 2 and 3). Moreover, when *t*-BuONa and *t*-BuOK were used, the **3a**/**4a** ratio sharply increased to 98:2 and 99:1, respectively, with sustained high diastereoselectivity of **3a** (entries 4 and 5). Next, a survey of different leaving groups revealed that Cl was the best choice, as cinnamyl chloride (**2e**) gave good yield and diastereoselectivity (entry 9 vs entries 5−8). The yield increased further when $(p\text{-}MeOC_6H_4)_3P$ was the ligand and 1.5 equiv of imine **1a** was used (entry 10). A control experiment showed that no desired allylation products were formed in the absence of Pd catalyst (data not shown).



After obtaining good conditions for the branched product (conditions A), we turned our attention to improving the selectivity for the linear product. Solvent optimization experiments showed that using toluene as the solvent significantly promoted the linear product but decreased the yield with LiHMDS as the base [entry 1 vs entry 12; for more data, see Table 2 in the Supporting Information (SI)]. To improve the yield, other lithium bases were examined. The use of lithium diisopropylamide (LDA) as the base appeared to give a good yield (77%) while the selectivity for the linear product remained high (8:92) (entry 14). Thus, the favorable conditions were identified for the selective formation of the linear product (conditions B).

The scope of this regioselectivity-tunable reaction was then investigated using conditions A and B. As shown in Table 2, both cyclic and acyclic aliphatic imines were suitable nucleophile precursors, providing the corresponding products in high yields. Using conditions A, excellent regio- and diastereoselectivities were realized for all of the reactions of imines **1** with **2e** and cinnamyl chlorides **2f**−**j** having an electron-withdrawing or electron-donating group on the phenyl ring. Branched products **3** were accompanied by yields of <2% for linear products **4** (entries 1−13). In addition, excellent diastereoselectivities were obtained except for entry 2, where a lower

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Table 1. Optimization of the Conditions for the Pd-Catalyzed Reaction of 1a with 2[a]

entry	base	2	% yield[b]	3a/4a[c]	3a anti/syn[c]
1	LiHMDS	**2a**	60	36/64	6/1
2	NaHMDS	**2a**	25	78/22	7/1
3	KHMDS	**2a**	12	68/32	7/1
4	*t*-BuONa	**2a**	26	98/2	9/1
5	*t*-BuOK	**2a**	51	99/1	7/1
6	*t*-BuOK	**2b**	60	98/2	7/1
7	*t*-BuOK	**2c**	64	98/2	24/1
8	*t*-BuOK	**2d**	17	95/5	13/1
9	*t*-BuOK	**2e**	70	99/1	32/1
10[d]	*t*-BuOK	**2e**	88	99/1	24/1
11[e]	*t*-BuOK	**2a**	48	95/5	4/1
12[e]	LiHMDS	**2a**	29	7/93	–
13[e]	*s*-BuLi	**2a**	61	12/88	–
14[e]	LDA	**2a**	77	8/92	–

[a] **1a**/$[Pd(C_3H_5)Cl]_2$/PPh_3/Base/**2a** molar ratio = 100/2.5/12/110/110. [b] Isolated yields. [c] Determined by ^1H NMR analysis. [d] P(*p*-$MeOC_6H_4)_3$ was the ligand; **1a**/$[Pd(C_3H_5)Cl]_2$/ligand/*t*-BuOK/**2e** molar ratio = 150/2.5/12/150/100. [e] Toluene was used as the solvent instead of THF.

anti/syn ratio of 7/1 was found. When unsymmetrical imine **1f** derived from 2-butanone was used as the substrate, two branched allylic products were obtained in yields of 32 and 28% (entry 6). Notably, aldimines **1g** and **1h** were also suitable substrates, providing the desired products with high selectivity (entries 7 and 8). However, no desired products were obtained when alkyl-substituted allyl substrates (e.g., crotyl chloride) were used with *t*-BuOK as the base (data not shown). X-ray structure analysis of the allyl product from the reaction of **1a** with **2h** confirmed its anti stereochemistry.

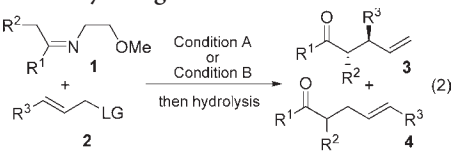
When conditions B were used, the reactions of imines **1** with cinnamyl *tert*-butyl carbonate **2a** all provided linear products **4** predominantly, with **4**/**3** ratios of 88−92:8−12 (entries 14−17).

The mechanism for the formation of linear products with Pd catalysts has been well-documented.[1]Thus, our focus was to probe the mechanistic features leading to the surprising branched product using both experimental and theoretical studies. Imine **1i** from cyclohexanone with an *N*-*n*-butyl substituent was synthesized and tested. The reaction using conditions A predominantly gave the branched product **3a**, with a **3a**/**4a** ratio of 95:5 and dr of 5:1 for **3a**. The linear product **4a** was the major product (**3a**/**4a** = 13:87) under conditions B. These results indicate that the regiochemistry is not determined by the methoxy group in imine **1a**.[4]

As shown in Scheme 1, it is possible that the reaction of the imine with *t*-BuOK produces an aza-allyl anion, which can serve as an N-nucleophile to produce an *N*-alkyl-*N*-allyl enamine intermediate. This intermediate may undergo a [3,3′] rearrangement followed by hydrolysis to afford the branched product.[5] With LDA as the base, the hard acid Li^+ should bind tightly to the N of the aza-allylic anion, promoting normal C-alkylation to afford the linear product.[10]

In order to test the above hypothesis, *N*-alkyl-*N*-allyl enamine **5** was prepared and examined under various reaction conditions. As shown in eq 3, no desired rearrangement product was detected. Thus, a direct [3,3′]-aza-Cope rearrangement of an *N*-alkyl-*N*-allyl enamine to form the branched product is ruled out.

Table 2. Pd-Catalyzed Regioselective Allylic Alkylation of Imines 1 with Allyl Reagents 2

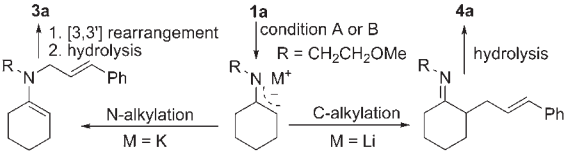


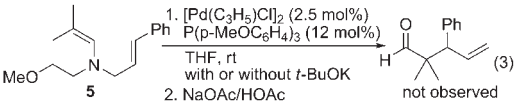
2a. R^3 = C_6H_5, LG = OBoc **2h**. R^3 = *p*-BrC_6H_4, LG = Cl
2e. R^3 = C_6H_5, LG = Cl **2i**. R^3 = *p*-MeC_6H_4, LG = Cl
2f. R^3 = *p*-FC_6H_4, LG = Cl **2j**. R^3 = *p*-$MeOC_6H_4$, LG = Cl
2g. R^3 = *p*-ClC_6H_4, LG = Cl

entry	1; R^1, R^2	2	conditions[a]	% yield[b]	3/4[c]	3 anti/syn[c]
1	**1a**; $(CH_2)_4$	**2e**	A	88	>98/2	24/1
2	**1b**; $(CH_2)_5$	**2e**	A	61	>98/2	7/1
3[d]	**1c**; Me, H	**2e**	A	51	>98/2	–
4	**1d**; Et, Me	**2e**	A	75	>98/2	11/1
5	**1e**; Pr, Et	**2e**	A	74	>98/2	11/1
6	**1f**; Me, Me	**2e**	A	60[e]	>98/2	13/1
7[d]	**1g**; H, Me_2	**2e**	A	46	>98/2	–
8[d]	**1h**; H, Et	**2e**	A	43[f]	>98/2	>50/1
9	**1a**	**2f**	A	82	>98/2	12/1
10	**1a**	**2g**	A	68	>98/2	24/1
11	**1a**	**2h**	A	55	>98/2	32/1
12	**1a**	**2i**	A	79	>98/2	16/1
13	**1a**	**2j**	A	69	>98/2	>50/1
14	**1a**	**2a**	B	77	8/92	–
15	**1b**	**2a**	B	64	8/92	–
16	**1d**	**2a**	B	88	12/88	–
17	**1e**	**2a**	B	90	9/91	–

[a] Conditions A: THF solvent at rt; **1**/$[Pd(C_3H_5)Cl]_2$/P(*p*-$MeOC_6H_4)_3$/*t*-BuOK/cinnamyl chloride molar ratio = 150/2.5/12/150/100. Conditions B: toluene solvent at 0 °C; **1**/$[Pd(C_3H_5)Cl]_2$/PPh_3/LDA/**2a** molar ratio = 120/2.5/12/120/100. [b] Isolated yields. [c] Determined by ^1H NMR analysis. [d] 2 equiv of imine and 2 equiv of *t*-BuONa were used. [e] The ratio of α- to α′-allylated products was 1:1.1. [f] Yield after reduction with $NaBH_4$.

Scheme 1. Plausible Mechanism for Tuning of the Regioselectivity between Conditions A and B





On the basis of recent literature on metal-mediated allyl−allyl coupling reactions,[11] we propose a Pd-mediated [3,3′]-reductive elimination to rationalize the formation of the branched product when Na/K bases are used. In this mechanism, there must be a critical transmetalation between the Pd−allyl complex **CP**, which is obtained in the last oxidative addition step, and the metal−imine anion to generate **Int-A** or **Int-B** (see Scheme 2).

DFT calculations using the Gaussian 03 program were carried out to explore the proposed mechanism.[12] As shown in Scheme 2,

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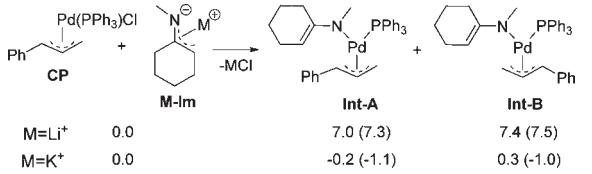
Scheme 2. Calculated Reaction Free Energies (kcal/mol) for the Transmetalation between CP and M-Im (M^+ = Li^+, K^+)[a]



[a] Values in parentheses are relative free energies without solvent effects.

the **CP** + **M-Im** is set to be the free energy zero point. The formation of **Int-A** and **Int-B** is accompanied by the formation of LiCl and KCl for M=Li^+ and K^+, respectively. The transmetalation reaction[13] between **CP** and **M-Im** is favorable if the metal ion is the soft acid K^+. **Int-A** and **Int-B** have similar stabilities. On the other hand, when the counterion is the hard acid Li^+, the reaction is unfavorable. As shown in parentheses, the calculated reaction free energies are similar without solvent effects (see SI Table 3 for details). Thus, the transmetalation reaction for M^+ = K^+ is >7.0 kcal/mol more favorable than that for M^+ = Li^+, mainly because of the stronger binding of Li^+ in **M-Im**. Thus, it is concluded that the transmetalation reaction can easily be achieved for M^+ = K^+. For Li^+, the equilibrium is less favorable.

Further calculations for the K^+ counterion case (Figure 1) indicated that the η^3-intermediate **Int-A** can easily rearrange into the more stable η^1-intermediate **CP-A**, which can undergo a very facile [3,3′]-reductive elimination to give the branched product **Pro-A**. On the other hand, the [3,3′]-reductive elimination transition state (**TS-B**) that leads to the linear product **Pro-B** has a much higher activation energy. Thus, this mechanism correctly rationalizes the high selectivity for the formation of the branched product with K^+ as the counterion.

The structures of **TS-A** and **TS-B** are shown in Figure 2. Both transition structures have a planar coordination at the Pd center. **TS-A** has the C···C bond formation at the reactive C1 center, and the seven-membered-ring geometry has no serious distortion. However, **TS-B** has a highly distorted geometry, as indicated by the large N−Pd−C angle of 142°. This occurs because the C3 center is less reactive in the C···C bond formation, as indicated by the relatively strong C3−Pd bond, and largely contributes to the high instability of **TS-B**. In addition, **TS-B** also suffers from steric interactions between the Ph group on the allyl and the bulky phosphine ligand.

The above mechanism is called an inner-sphere attack mechanism. We also calculated an outer-sphere attack mechanism (or ionic mechanism) for the K^+ case.[14] As shown in **TS-C** and **TS-D** (Figure 2), the imine anion attacks the Pd-coordinated allyl without coordinating to Pd. Both transition structures have a concerted C···N and C···C bond formation. **TS-C** and **TS-D** are calculated to be much less stable than **TS-A**. In addition, **TS-D**, which leads to the formation of the linear product, is calculated to be more stable than **TS-C** leading to the branched product by ∼1.8 kcal/mol (including solvent effects). The destabilization of **TS-C** is mainly due to serious steric interactions between the phenyl substituent on the allyl and the incoming cyclohexene ring, as indicated by two short H···C distances (∼2.67 and 2.60 Å). Thus, the outer-sphere mechanism not only has a higher activation energy than the inner-sphere mechanism but also gives the wrong (linear) product.

Finally, the deuterated, optically active allyl compound (*S*)-(*Z*)-**6** was used to probe the mechanistic features further

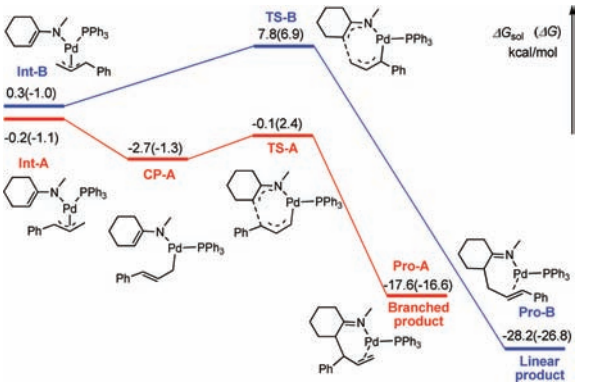


Figure 1. Predicted free-energy profiles for the mechanisms leading to branched and linear products under conditions A. Values in parentheses are relative free energies without solvent effects.

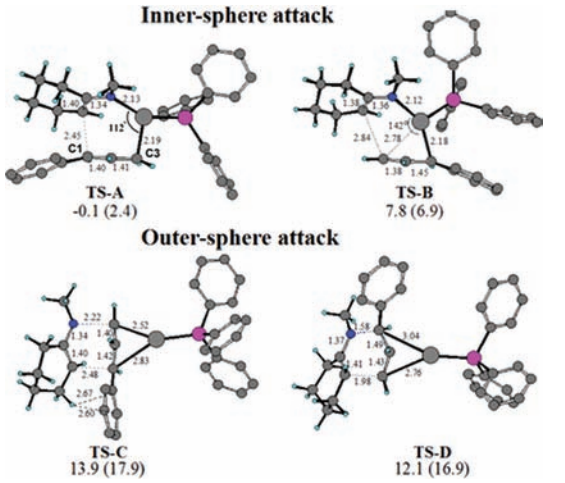


Figure 2. Structures and relative free energies of the transition states for the inner-sphere (**TS-A** and **TS-B**) and outer-sphere (**TS-C** and **TS-D**) mechanisms. H atoms on phenyl groups have been omitted for clarity. Values in parentheses are relative free energies without solvent effects.

(Scheme 3). According to the widely accepted reaction mechanism, (*S*,*S*)-(*Z*)-**7** and/or (*R*,*R*)-(*E*)-**7** should be produced if the nucleophile attacks the palladium of the allyl complex (inner-sphere attack mechanism), while (*S*,*S*)-(*E*)-**7** and/or (*R*,*R*)-(*Z*)-**7** should be the products when the nucleophile attacks the carbon of the allyl complex directly (outer-sphere mechanism)[1,15] (Scheme 3). When deuterated (*S*)-(*Z*)-**6** was reacted with **1a** under conditions A, "racemic" products **7** were obtained in 23% yield as a 1:1 mixture of *E* and *Z* isomers with a B/L ratio of 98:2 and an anti/syn ratio of 10:1. Both enantiomers were obtained by chiral HPLC separation, and their absolute configurations were determined to be (*S*,*S*)-(*Z*)-**7** and (*R*,*R*)-(*E*)-**7** by comparison of the signs of their optical rotation with that of nondeuterated (*R*,*R*)-**3a**, whose absolute configuration was assigned by X-ray analysis of a single crystal obtained from chiral HPLC separation, reduction, and esterification of (+)-**3a** (Scheme 4; also see the SI). These results confirm our Pd-mediated [3,3′]-reductive elimination mechanism.

In summary, α-carbanions of imines have been successfully applied as nucleophiles in the Pd-catalyzed allylic alkylation reaction. Tuning of chemo- and regio-selectivity has been realized by using bases with different counterions. When the soft-acid counterion Na^+ or K^+ is used, the branched product is obtained. If the hard-acid ion

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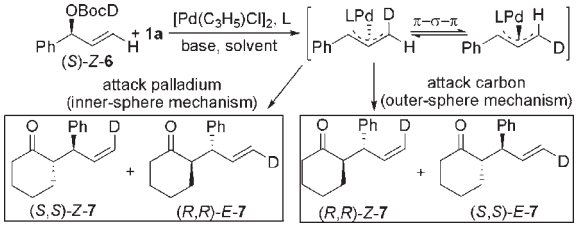
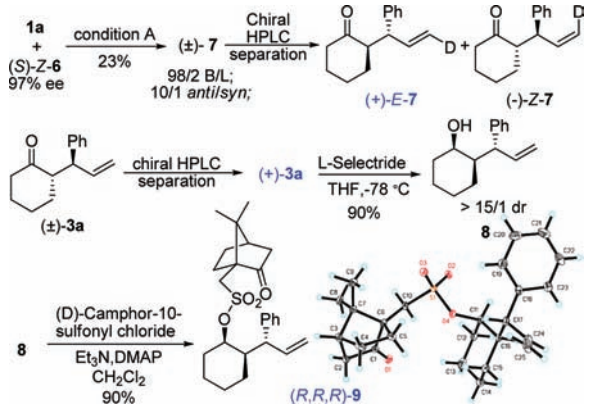
Scheme 3. Formation of Stereospecific Products in the Reaction of Imine 1a with (*S*)-(*Z*)-6 via Outer- and Inner-Sphere Attack Mechanisms



Scheme 4. Stereochemistry Study of the Reaction



Li^+ is used, the linear product is produced. A novel mechanism involving a transmetalation and a Pd-mediated [3,3′]-reductive elimination has been proposed to rationalize the formation of the branched product using Na^+ or K^+ as the counterion. The mechanism is supported by DFT calculations and a stereochemistry study of the reaction. This simple protocol for controlling the regioselectivity in Pd-catalyzed allylic alkylation reactions should have wide potential applications in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures, additional experimental and computational results, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) For reviews, see: (a) Pfaltz, A.; Lautens, M. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Vol. 2, p 833. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (c) Lu, Z.; Ma, S. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 258.

(2) (a) You, S.-L.; Zhu, X.-Z.; Luo, Y.-M.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, *123*, 7471. (b) Zheng, W.-H.; Sun, N.; Hou, X.-L. *Org. Lett.* **2005**, *7*, 5151. (c) Zheng, W.-H.; Zheng, B.-H.; Zhang, Y.; Hou, X.-L. *J. Am. Chem. Soc.* **2007**, *129*, 7718. (d) Chen, J.-P.; Ding, C.-H.; Liu, W.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2010**, *132*, 15493.

(3) (a) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *Chem. Commun.* **1997**, 561. (b) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 1681. (c) Prétôt, R.; Pfaltz, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 323. (d) Hilgraf, R.; Pfaltz, A. *Synlett* **1999**, 1814.

(4) (a) Trost, B. M.; Bunt, R. C.; Lemoine, R. C.; Calkins, T. L. *J. Am. Chem. Soc.* **2000**, *122*, 5968. (b) Itami, K.; Koike, T.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2001**, *123*, 6957. (c) Krafft, M. E.; Sugiura, M.; Abboud, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 9174. (d) Cook, G. R.; Yu, H.; Sankaranarayanan, S.; Shanker, P. S. *J. Am. Chem. Soc.* **2003**, *125*, 5115.

(5) Waetzig, S. R.; Tunge, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 4138.

(6) (a) Watson, I. D. G.; Styler, S. A.; Yudin, A. K. *J. Am. Chem. Soc.* **2004**, *126*, 5086. (b) Watson, I. D. G.; Yudin, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 17516. (c) Dubovyk, I.; Watson, I. D. G.; Yudin, A. K. *J. Am. Chem. Soc.* **2007**, *129*, 14172. (d) Johns, A. M.; Liu, Z.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2007**, *46*, 7259.

(7) For examples, see: (a) Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **1999**, *121*, 6759. (b) Trost, B. M.; Schroeder, G. M. *Chem.—Eur. J.* **2005**, *11*, 174. (c) Braun, M.; Laicher, F.; Meier, T. *Angew. Chem., Int. Ed.***2000**, *39*, 3494. (d) Kazmaier, U. *Curr. Org. Chem.* **2003**, *7*, 317. (e) Weiss, T. D.; Helmchen, G.; Kazmaier, U. *Chem. Commun.* **2002**, 1270. (f) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044. (g) Burger, E. C.; Tunge, J. A. *Org. Lett.* **2004**, *6*, 4113. (h) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846. (i) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180. (j) Braun, M.; Meier, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 6952. (k) Braun, M.; Meier, T. *Synlett* **2006**, 661. (l) Bélanger, É.; Cantin, K.; Messe, O.; Tremblay, M.; Paquin, J.-F. *J. Am. Chem. Soc.* **2007**, *129*, 1034. (m) Trost, B. M.; Xu, J.; Reichle, M. *J. Am. Chem. Soc.* **2007**, *129*, 282. (n) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 14092.

(8) (a) Yan, X.-X.; Liang, C.-G.; Zhang, Y.; Hong, W.; Cao, B.-X.; Dai, L.-X.; Hou, X.-L. *Angew. Chem., Int. Ed.* **2005**, *44*, 6544. (b) Zhang, K.; Peng, Q.; Hou, X.-L.; Wu, Y.-D. *Angew. Chem., Int. Ed.* **2008**, *47*, 1741.

(9) Hiroi, K.; Abe, J.; Suya, K.; Sato, S.; Koyama, T. *J. Org. Chem.* **1994**, *59*, 203.

(10) Reutov, O. A.; Kurts, A. L. *Russ. Chem. Rev.* **1977**, *46*, 1040.

(11) (a) Méndez, M.; Cuerva, J. M.; Gómez-Bengoa, E.; Cárdenas, D. J.; Echavarren, A. M. *Chem.—Eur. J.* **2002**, *8*, 3620. (b) Keith, J. A.; Behenna, D. C.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Oxgaard, J.; Stoltz, B. M.; Goddard, W. A., III. *J. Am. Chem. Soc.* **2007**, *129*, 11876. (c) Sherden, N. H.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6840. (d) Luzung, M. R.; Lewis, C. A.; Baran, P. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 7025. (e) Zhang, P.; Brozek, L. A.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 10686.

(12) Geometries were fully optimized with the DFT method of B3LYP using the 6-31G* basis set (the LAN2LDZ basis set for Pd) (BS1). Vibrational frequency calculations were carried out at the same level to obtain free energy corrections. The energies were further estimated using a larger 6-311+G** basis set (BS2) by single point calculations. Solvent effect of THF was estimated by the IEFPCM method. All presented values are relative free energies (kcal/mol) based on the calculated BS2 energies with BS1 free energy corrections. For full reference of Gaussian 03 and detailed calculation procedures, see the SI.

(13) We studied the transmetalation reactions in Scheme 2 using different counteranions as well as other possible transmetalation processes. The calculated equilibrium energies were similar to those with one PPh_3 ligand and different counteranions (Cl^- and OCO_2Me^-) and solvents (toluene and THF). For details, see section 6-1 in the SI.

(14) The inner-sphere and outer-sphere attacks involving two PPh_3 ligands were also explored through calculations. These possible TSs were less stable than that with one PPh_3 ligand. For details, see section 6-1 in the SI.

(15) (a) Braun, M.; Meier, T. *Synlett* **2005**, 2968. (b) Braun, M.; Meier, T.; Laicher, F.; Meletis, P.; Fidan, M. *Adv. Synth. Catal.* **2008**, *350*, 303.